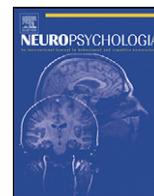




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Continuous theta-burst stimulation to primary motor cortex reduces the overproduction of forces following removal of visual feedback

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HIGHLIGHTS

- Force production calibrated with visual feedback is accurate.
- Forces produced exceed target values after visual feedback is removed.
- Self-produced proprioceptive feedback is thought to be attenuated.
- Motor cortical depression with TMS reduced the overproduction of forces.
- Suggests that TMS induced discrepancy between efference copy and motor command.

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ABSTRACT

Forward models, generated from the efference copies of motor commands, are thought to monitor the accuracy of ongoing movement. By comparing predicted with actual afferent information, forward models also aid in the differentiation of self-produced movements from externally generated ones. Many have proposed that a consequence of this comparison is attenuation of the predicted component of incoming sensory signals. Previous work from our laboratory has shown that following the removal of an external visual reference, discrete sequential forces exceed target values. Forces produced at the fingertip were perceived as weaker, which lead to a systematic, compensatory over-production of the magnitudes required. The relatively new repetitive TMS protocol of continuous theta-burst stimulation (cTBS) has been shown to reliably depress cortical excitability for a period following stimulation. If sensory attenuation mechanisms were responsible for the overproduction of forces found in our previous results, we hypothesized that reducing cortical excitability of M1 through application of cTBS would induce discrepancy between the efference copy generated and motor output produced. As a result, we expected the overproduction of forces following visual feedback removal would be reduced after receiving cTBS. Participants produced series of pinch grip forces in time to a metronome and to visually specified force magnitudes. Visual feedback of force output was extinguished 10 s into experimental trials and participants performed continued responses for the remaining 10 s. Results confirmed our hypothesis. Mean peak force and constant error were greater and more positive in the absence of visual feedback regardless of stimulation condition; however, the magnitude of increase was significantly reduced following cTBS compared with baseline and sham conditions. Variability was not differentially affected by stimulation condition, increasing only with removal of visual feedback contingent upon the larger forces produced in these trials. Our findings provide further evidence to support the idea that TBS may differentially affect motor output and efference copy generation.

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1. Introduction

It has been proposed that a function of corollary discharge from primary motor cortex (M1) is to aid in the generation of forward models of the sensory outcomes of that action (Bays,

Flanagan, & Wolpert, 2006; Bays, Wolpert, & Flanagan, 2005; Blakemore, Goodbody, & Wolpert, 1998; Blakemore, Wolpert, & Frith, 1998; Blakemore, Wolpert, & Frith, 2000; Shergill, Bays, Frith, & Wolpert, 2003; Shergill, Samson, Bays, Frith, & Wolpert, 2005; Voss, Bays, Rothwell, & Wolpert, 2007; Wolpert, 2007; Wolpert & Ghahramani, 2000). These predicted sensory outcomes are compared with incoming afferent information as a means to evaluate the success of movement execution and also to differentiate self-produced from externally sourced feedback (Bays et al., 2006, 2005; Blakemore, Goodbody, et al., 1998; Blakemore, Wolpert, et al., 1998;

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Blakemore et al., 2000; Shergill et al., 2003, 2005; Voss et al., 2007; Wolpert, 2007; Wolpert & Ghahramani, 2000). It is argued that this comparison process results in an attenuation of the predicted component of incoming sensory information (Bays et al., 2006, 2005; Blakemore, Goodbody, et al., 1998; Blakemore, Wolpert, et al., 1998; Blakemore et al., 2000; Shergill et al., 2003, 2005; Voss et al., 2007). Furthermore, this attenuation has been deemed responsible for the reduced perception of self-generated feedback compared with that from an external source (Bays et al., 2006, 2005; Blakemore, Goodbody, et al., 1998; Blakemore, Wolpert, et al., 1998; Blakemore et al., 2000; Shergill et al., 2003, 2005; Voss et al., 2007).

Previous work from our laboratory has found evidence for the abovementioned mechanism in the production of repetitive, discrete force pulses (Therrien & Balasubramaniam, 2010; Therrien, Lyons, & Balasubramaniam, 2010). Following removal of visual feedback of force output, force levels produced with each pulse were greater than target magnitudes produced when visual feedback was provided. Along with force magnitude, variability of the forces produced was also greater in these conditions. In the absence of an external reference, the forces produced were perceived as weaker leading to a systematic, compensatory over-production of the force magnitudes relative to the intended target. The results suggested that proprioceptive feedback alone was insufficient to guide the accurate production of target force magnitudes. In our task, visual feedback served to parameterize the proprioceptive system to ensure the appropriate production and scaling of force output.

Our experimental paradigm differs from those employed in previous studies of sensory attenuation mechanisms in that we do not make use of a purely externally generated stimulus. Previous literature discussing attenuated perception of self-produced feedback used forces or tactile stimuli that were applied either by the experimenters or with a robot arm (Bays et al., 2006, 2005; Blakemore, Goodbody, et al., 1998; Blakemore, Wolpert, et al., 1998; Blakemore et al., 2000; Shergill et al., 2003, 2005; Voss et al., 2007). The notion of visual feedback serving as an external reference in the calibration of proprioceptive feedback, however, has been noted in previous work (Streit, Shockley, Morris, & Riley, 2007; Streit, Shockley, & Riley, 2007; Withagen & Michaels, 2004, 2005). Studies of the size-weight illusion are perhaps the most common example, where the visually larger of two equally weighted objects is perceived as being lighter. Furthermore, studies of rod wielding paradigms have noted that manipulation of visual feedback can calibrate judgments of length using dynamic touch and also induce errors in perceptions of heaviness (Streit, Shockley, Morris, et al., 2007; Streit, Shockley, & Riley, 2007; Withagen & Michaels, 2004, 2005).

Transcranial magnetic stimulation (TMS) is an experimental technique that has grown in popularity over the last decade. While single pulses of TMS are useful in measuring corticospinal excitability, repetitive stimulation paradigms are used as a means to influence cortical excitability for periods of time following stimulation. The relatively new repetitive TMS protocol of continuous theta-burst stimulation (cTBS) has been shown to reliably depress cortical excitability for 20–60 min following stimulation (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Huang & Rothwell, 2004). A recent study by Voss et al. (2007) used cTBS to temporarily reduce excitability of the left M1 in a force matching task. Using a force transducer and torque motor, forces of known magnitude were generated on participants' right or left index fingers. Subjects were then asked to reproduce the force level they just experienced using the opposite index finger. Results showed that in pre-TBS sessions, participants consistently over-estimated the force levels experienced. Following cTBS, however, forces produced by the right index finger were much closer to the actual target values. The authors attributed these results to cTBS inducing a mismatch between the efference copy generated and the motor commands

sent to the finger, causing less attenuation of self-produced feedback.

If sensory attenuation mechanisms were responsible for the overproduction of forces noted in our own previous work (Therrien & Balasubramaniam, 2010; Therrien et al., 2010), it is possible that a reduction in cortical excitability of contralateral M1 could induce a similar reduction in positive force errors following removal of visual feedback. The objective of the present study was to investigate the effect of a 40 s train of cTBS (cTBS600) to M1 on the performance of our repetitive, discrete force production task. Application of cTBS600, was compared with baseline performance (no TMS) and a sham stimulation condition. We hypothesized that application of cTBS600 to the left hemisphere of M1, would induce discrepancy between the efference copy generated and motor output. As a result, we expected that the overproduction of force magnitudes following visual feedback removal would be reduced following cTBS600 stimulation, but persist in baseline and sham conditions.

2. Methods

2.1. Participants

Twelve participants volunteered for this study (6 male, mean age: 22.4 yrs). All participants were students at McMaster University and were right handed according to both self report as well as the Edinburgh Handedness Inventory (mean laterality index: 88.3; Oldfield, 1971). Participants reported no known neurological impairments or musculoskeletal impairments to the upper extremities. All had normal or corrected to normal vision at time of experimentation. All participants were screened by means of a standardized questionnaire to ensure compliance with safety standards regarding receipt of TMS (Wasserman, 1998). The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by Hamilton Health Sciences/McMaster University Faculty of Health Sciences Research Ethics Board.

2.2. Apparatus

We used the same apparatus from Therrien and Balasubramaniam (2010). A 6° of freedom load cell (ATI Nano 17) mounted on a vertical stainless steel t-stand was used to collect the force data. Forces were applied on the axis perpendicular to the gripping surface (z axis). The stand was fixed to the table surface in front of a 19 in., Viewsonic LCD flat panel computer monitor (refresh rate of 60 Hz), which provided participants' force contingent visual feedback. Force data were sampled at 1000 Hz with custom written Labview software (Labview 8.2, National Instruments). Load cells were calibrated with a factory generated 6 × 6 matrix describing the signal gain between voltage and resolved forces. This also allowed for correction of crosstalk between each measured force and moment arm. An AMTI amplifier was used to bolster voltage signals, which were then digitized with the National Instruments PCI-6220 DAQ. The ultimate resolution was 1/320 N in the z-axis. There was no hysteresis in the zero level of the resolved forces, which indicated no significant drift or offset in the force data associated with continued use of the device.

2.3. Experimental protocol

We used a modified version of the repetitive force production task developed for Therrien and Balasubramaniam (2010). Participants sat in a chair with their right forearm resting on adjustable arm rests on a table. They were positioned so they could comfortably reach the load cell and perform the pinch grip motion with the wrist in neutral position and no discomfort to the upper extremity. During the experiment, participants were presented with a visually specified target force of 16 N and were asked to match it by pinching the force transducer between the right thumb and index finger. The force target was presented as a column in a bar plot on the computer monitor, which was placed at a comfortable distance in front of the participant. Vertical axis labels gave participants additional information about the absolute magnitude of force. A second adjacent column represented participants' force output. Its height was contingent upon the force produced with each pinch on the load cell. The system gain was set so that a 1 N force caused a 1 cm increase in the height of the second column.

Participants were instructed to match the target force magnitude by modulating the force level produced with each pinch on the load cell. The movement rate was specified with an auditory metronome set at 2 Hz (500 ms intervals between sounds). Participants were to time each pinch with the sound of the metronome. All trials lasted 20 s. In experimental conditions (NVF), visual feedback of the target as well as the participants' current force output were removed after 10 s. Participants were asked to continue pinching the load cell, in time with the metronome, at

the same force level for the remainder of the trial. In control conditions (VF), visual force feedback remained present throughout the trial. Participants were given up to 5 practice trials with each condition prior to data collection in order to familiarize themselves with the task and experimental apparatus. During data collection all conditions were presented in a pseudo-randomized order with each condition being performed twice before beginning the sequence over. The protocol was split into three sessions each performed on different days. One session tested baseline performance of the task without TMS (BL). The second session had participants undergo 40 s of cTBS prior to completing the force production task (TBS). The third session involved a sham stimulation, where the active coil was placed away from the skull and a second, inactive coil was held over participants' heads (Sham). The order of these sessions was randomized and counterbalanced across participants. Ten repetitions of each condition were performed yielding a total of 60 trials per participant after the three stimulation conditions.

2.4. TMS procedure

Single pulses of focal TMS were delivered with a figure of eight coil (Magstim Comp., Oakville, ON; external diameter of each coil: 9 cm) and used to elicit motor evoked potentials (MEPs) in the first dorsal interosseous muscle (FDI) of the resting right hand. The coil was oriented tangential to the head, at an angle of approximately 45° from the anterior–posterior axis with the handle pointing to the posterior. MEPs were recorded using Ag/AgCl sintered electrodes placed over the FDI muscle belly and tendon, with the ground electrode placed on the Olecranon process of the elbow. The optimal stimulation site of the skull was determined as the cortical location where MEPs of 50 μ V in peak–peak amplitude could be evoked in 5/10 trials, with the lowest possible stimulator output. The position was marked using Brainsight software (Brainsight 2.1.4, Rogue Research, Montreal, Canada) to allow for accurate repositioning throughout the experimental sessions.

Once the optimal stimulation site was determined, participants were asked to perform three maximum voluntary contractions (MVC) of the FDI muscle, by pinching a handheld force gauge (Baseline Evaluation Instruments 12-0235, White Plains, NY) between the right thumb and index finger. Experimental MVC was taken as the average of the three trials. Single pulses of TMS were then delivered while participants held isometric contractions at 20% of their MVC (visual feedback was provided to ensure accurate force output). Active motor threshold (AMT) was determined as the lowest stimulator intensity sufficient to produce MEPs greater than 200 μ V above background EMG in at least 5/10 trials.

Continuous theta-burst stimulation (cTBS) was used for the repetitive stimulation phase of the experiment. cTBS involves continuous trains of pulses delivered in bursts of three at 50 Hz (20 ms between pulses) with a burst frequency of 5 Hz (200 ms between bursts; Huang et al., 2005; Huang and Rothwell, 2004). cTBS was delivered at 80% of AMT for a duration 40 s (a total of 600 pulses). This protocol is known as cTBS600 and depresses M1 cortical excitability in the stimulated area for up to 60 min following stimulation (Huang et al., 2005). Determination of the optimal cortical stimulation site and AMT remained the same in sham stimulation sessions. Repetitive stimulation, however, was performed with a second inactive coil placed over the participants' skull while the active coil was placed behind and oriented away from the head. This served to minimize perceived changes in location of the stimulator sounds between TBS and Sham conditions. Both TBS and Sham sessions were separated by at least 24 h to ensure that participants received no more than 800 TMS pulses per day, conforming to previously determined safety guidelines (Wasserman, 1998).

2.5. Data analysis

Force data were stored separately for offline analysis. A custom script in MATLABTM extracted the peak force magnitude produced with each pinch on the load cell as well as the sample iteration and time at which they occurred. From these data, trial means were computed. The mean force produced was determined as the mean peak force produced in each trial. Variability was quantified using measures of coefficient of variation (CV). Errors in force output were analyzed using measurements of constant error. Lastly, the force series produced in NVF trials was broken down into mean peak force values for two trials phases: before feedback removal ($t=0-10$ s) and after feedback removal ($t=11-20$ s). As participants were not informed of condition prior to each trial, only data from the continuation phase was used for analysis (i.e. $t=10-20$ s). Means were calculated across 10 repetitions per condition as well as across the 12 participants.

2.6. Statistical analysis

SPSS software (SPSS 16.0, Chicago, IL) was used to conduct separate analysis of variance (ANOVA) with repeated measures for each dependent variable. Forces produced as well as their variability were assessed using factors of stimulation condition (BL, Sham, TBS) and visual feedback condition (VF, NVF). ANOVA with repeated measures was also used to compare mean peak forces in the two phases of the NVF trials with factors trial phase ($t=0-10$ s, $t=11-20$ s) and stimulation condition (BL, Sham, TBS). Post-hoc means comparisons were performed using Tukey's HSD.

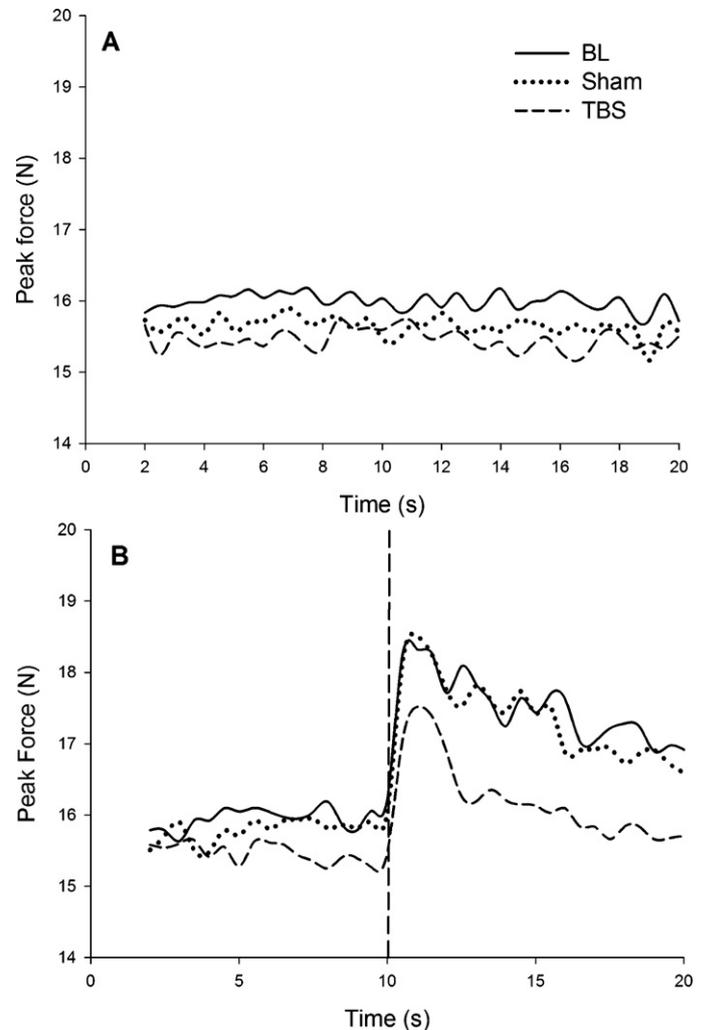


Fig. 1. The force time series produced in VF trials (A) and NVF (B) of the three stimulation conditions grand averaged across participants. The vertical dashed line denoted the time at which visual feedback was removed in NVF trials.

3. Results

The average force–time series obtained from our data can be seen in Fig. 1. Force–time series from VF trials are plotted in Fig. 1A and series from NVF trials are plotted in Fig. 1B. Analysis of mean peak force yielded a significant interaction among factors stimulation condition and visual feedback condition ($F(2,22)=3.573$, $p<.05$, Fig. 2A). Tukey's HSD tests showed that mean peak force was greater in NVF trials regardless of stimulation condition ($p<.01$). Post hoc means comparisons further revealed the interaction to be driven by the mean peak force in the NVF trials of the TBS condition, which was significantly lower than that produced in the BL and Sham conditions ($p<.01$).

The ANOVA for peak force coefficient of variation yielded a significant main effect for visual feedback condition ($F(1,11)=65.571$, $p<.001$, Fig. 2B). Variability of the forces produced was greater in the absence of visual feedback.

Analysis of constant error produced a significant interaction among factors stimulation condition and visual feedback condition ($F(2,22)=3.575$, $p<.05$, Fig. 2C). Tukey's HSD tests revealed a general effect where errors were greater and more positive in the absence of visual feedback ($p's<.01$). Post hoc means comparisons also revealed the interaction to be driven by a significantly lower constant error in the NVF trials of the TBS condition, compared to errors produced in the BL and Sham conditions ($p's<.01$).

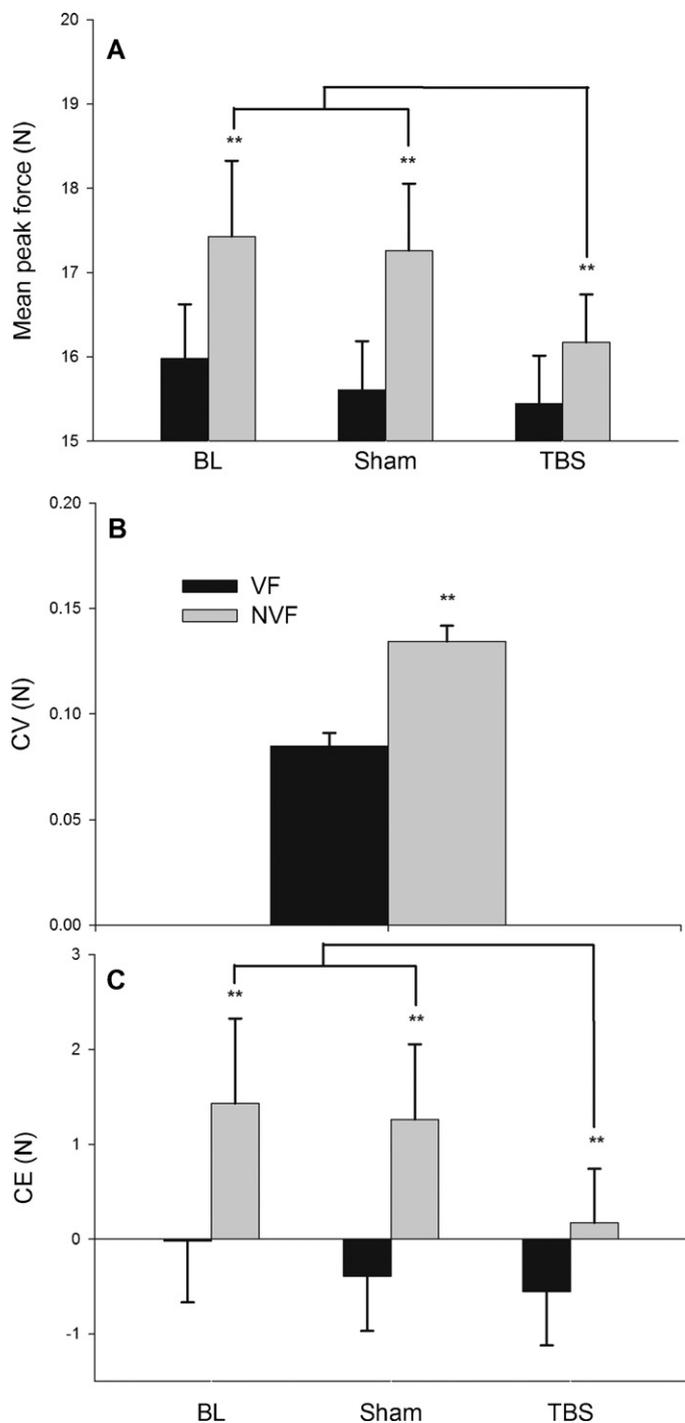


Fig. 2. (A) Interaction among factors visual feedback and stimulation condition for mean peak force. (B) Main effect of visual feedback for measures of coefficient of variation. (C) Interaction among factors visual feedback and stimulation condition for measures of constant error. In all cases, asterisks and connecting lines denote reliable pairwise comparisons, significant at $p < .01$.

Analysis of the mean peak forces produced in the two phases of NVF trials (before and after visual feedback removal) produced an interaction among factors trial phase and stimulation condition that neared significance ($F(2,22) = 3.222, p = .059$, Fig. 3A). Mean force did not appear to differ across stimulation condition in the period prior to visual feedback removal. Following feedback removal, however, a trend was present where mean peak force was lower only in the TBS condition. The mean difference in force produced over these two phases also yielded a main effect for stim-

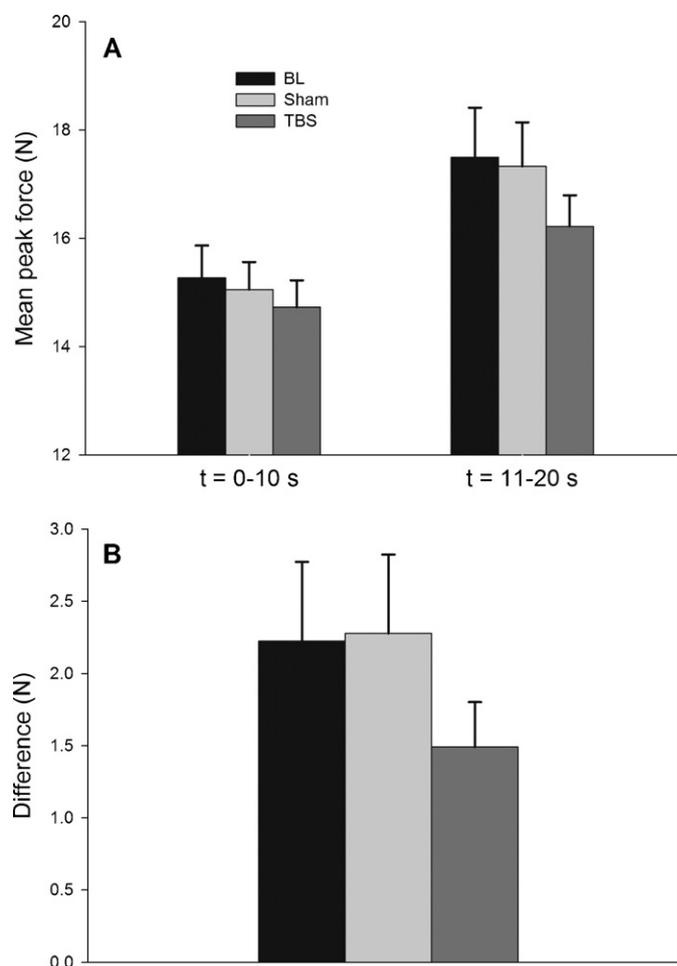


Fig. 3. NVF trials were divided into two phases corresponding to the period of time prior to visual feedback removal ($t = 0-10$ s) and the period of time from feedback removal to the end of the trial ($t = 11-20$ s). (A) Non-significant interaction among factors trial phase and stimulation condition for mean peak force ($p = .059$). (B) Non-significant main effect for stimulation condition on the difference between mean peak forces produced in the two phases of NVF trials ($p = .059$).

ulation condition that neared significance ($F(2,22) = 3.222, p = .059$, Fig. 3B). Once again a trend is present where the difference in mean peak force produced over the two trial phases was lower for the TBS condition, relative to BL and Sham.

4. Discussion

The objective of the present study was to determine whether application of a 40 s train of cTBS (cTBS600) to the FDI area of left M1 would influence the production of repetitive discrete pinch grip forces by the right hand. Based on our previous work, participants produce force magnitudes that exceed target values in the absence of visual feedback of force output. These results have been interpreted in the context of sensory attenuation mechanisms whereby self-produced forces are perceived as weaker, leading to a systematic overproduction of force magnitudes. Sensory attenuation mechanisms make use of forward models generated from efference copies of motor commands sent from M1. Voss et al. (2007) found that reducing excitability of M1, using cTBS, improved participants' force matching ability. The results were attributed to cTBS reducing the degree of sensory attenuation by inducing discrepancy between the efference copy and motor output. If attenuation of self-produced feedback was responsible for our previous results,

we expected to see a reduction in the force overproduction effect in cTBS600 trials relative to baseline and sham conditions.

In accordance with our previous work, mean peak force produced, variability and constant error were all greater and more positive in the absence of visual feedback regardless of stimulation condition. Variability was not differentially affected by stimulation session. The overall increase in measures of CV associated with NVF trials, likely reflected signal-dependent noise contingent upon the larger forces produced (Wolpert & Ghahramani, 2000). Interestingly the degree of increase in mean peak force was reduced following receipt of cTBS600. Analysis of constant error reflected these results showing a reduction in positive error in NVF trials of the TBS condition. Furthermore, examination of the two phases of NVF trials revealed a trend where prior to visual feedback removal, mean peak force did not differ between stimulation conditions. While all conditions showed an increase in force output after visual feedback was removed, this increase was proportionately lower after application of cTBS600.

Overall, the present results support our hypothesis that cTBS600 to M1 would differentially affect force production relative to Sham and BL conditions. The findings also add strength to the notion that the force overproduction effect noted in our previous work may, at least in part, be the result of sensory attenuation mechanisms (Therrien & Balasubramaniam, 2010; Therrien et al., 2010). As was suggested by Voss et al. (2007), it is possible that reducing excitability in the FDI area of left M1 caused divergence between the efference copy generated and the motor output produced. As a result, following removal of visual feedback of force output, there was less overlap between predicted and actual feedback leading to a lesser degree of attenuation. Following the mechanism proposed in our previous work, less attenuation lead to a decrease in the degree of overproduction of forces.

We controlled for non-specific effects of receiving TMS by including a sham stimulation condition. In these sessions, participants underwent the same procedures to locate optimal stimulation sites and determine active motor threshold. The repetitive stimulation was delivered by orienting the active coil away from the participant's head and placing a second inactive coil over the determined stimulation site. Participants did not report any perceived differences between the Sham and TBS conditions; however, it was only in the TBS condition that M1 excitability was altered. That mean peak force and constant error results were not significantly different between Sham and BL, but were significantly different in the TBS condition confirmed that the effects observed were the result of cTBS600 influence on motor cortical excitability.

One question that remains unclear from our data concerns the precise mechanism that gave rise to the incongruity between efference copy and motor output. As was suggested by Voss et al. (2007), cTBS must differentially influence the populations of neurons that generate these two products of neuronal processing. Di Lazzaro et al. (2008) found that unlike other transcranial magnetic stimulation protocols, cTBS did not change the overall excitability of corticospinal neurons. Instead it influenced cortical circuitry by altering the excitability of intracortical interneurons in M1 (Di Lazzaro et al., 2008; Huang et al., 2005). A possible explanation for our results then, is that motor cortical depression through cTBS may have stimulated changes in the processing of efference copy signals.

It has also been shown that repetitive TMS can influence a wider cortical area than just the stimulation site. Previous neuroimaging work has found that repetitive TMS to left M1 activated a network of areas outside the stimulation location, including dorsal and ventral premotor cortices (dPMC, vPMC), supplementary motor area (SMA) and contralateral (right) cerebellum (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004; Okabe et al., 2003; Siebner et al., 2000). The cerebellum has been proposed as a likely site for

the comparison between predicted sensory feedback from the forward model and actual incoming afferent information arising from movement execution (Blakemore, Wolpert, et al., 1998). Alternatively, Chronicle and Glover (2003) proposed that efference copies may be generated in areas upstream of M1, like premotor cortex. It is, therefore, also possible that sensory attenuation mechanisms could have been manipulated by spreading activation to cerebellar and premotor areas.

Interesting to note, however, was the slight reduction in force output following receipt of TBS even when visual feedback was presented. Although this difference was not statistically significant, it may provide some support for the role of M1 in the encoding of force as was originally proposed by Evarts (1968). It remains a possibility then, that M1 stimulation in our experiment could have induced discrepancy between efference copy and motor command by influencing force output directly.

The present study only tested performance of the limb contralateral to the stimulation site. Many studies have shown that repetitive TMS protocols also induce activity in the contralateral hemisphere of M1 and can modulate excitability of ipsilateral fibres in the corticospinal tract (Chen, Yung, & Li, 2003; Cincotta et al., 2006; Siebner et al., 2000; Trompetto et al., 2004). It would be interesting to expand upon the findings of the present study by including analysis of the performance of the hand ipsilateral to the stimulated hemisphere of M1.

In summary the primary finding of this study was that reducing excitability of M1 neurons, through application of cTBS600, produced a reduction in the overproduction of forces following removal of visual feedback. Force output in NVF trials was not significantly different in BL and Sham conditions; with both showing a greater magnitude of positive errors in force compared to TBS trials. These results add strength to our conclusion that the overproduction of forces seen in our previous work is the result of sensory attenuation mechanisms affecting perceptions of self-produced feedback. cTBS600 stimulation served to disrupt sensory attenuation processes by creating incongruity between predicted and actual afferent information. While the exact mechanism of this influence remains uncertain, our results add to those of Voss et al. (2007) showing that cTBS differentially affects the populations of neurons that produce the efference copy and those that generate motor output. Furthermore, we also provide yet another example of the utility of repetitive TMS protocols in studying the effects of virtual lesions to M1 on the performance of behavioural tasks.

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