

Continuous theta-burst stimulation to primary motor cortex reveals asymmetric compensation for sensory attenuation in bimanual repetitive force production

Amanda S. Therrien, James Lyons and Ramesh Balasubramaniam

J Neurophysiol 110:872-882, 2013. First published 15 May 2013;
doi: 10.1152/jn.00988.2012

You might find this additional info useful...

This article cites 37 articles, 8 of which you can access for free at:
<http://jn.physiology.org/content/110/4/872.full#ref-list-1>

Updated information and services including high resolution figures, can be found at:
<http://jn.physiology.org/content/110/4/872.full>

Additional material and information about *Journal of Neurophysiology* can be found at:
<http://www.the-aps.org/publications/jn>

This information is current as of September 4, 2013.

Continuous theta-burst stimulation to primary motor cortex reveals asymmetric compensation for sensory attenuation in bimanual repetitive force production

Amanda S. Therrien,¹ James Lyons,¹ and Ramesh Balasubramaniam^{1,2}

¹Sensorimotor Neuroscience Laboratory, McMaster University, Hamilton, Ontario, Canada; and ²University of California, Merced, California

Submitted 13 November 2012; accepted in final form 14 May 2013

Therrien AS, Lyons J, Balasubramaniam R. Continuous theta-burst stimulation to primary motor cortex reveals asymmetric compensation for sensory attenuation in bimanual repetitive force production. *J Neurophysiol* 110: 872–882, 2013. First published May 15, 2013; doi:10.1152/jn.00988.2012.—Studies of fingertip force production have shown that self-produced forces are perceived as weaker than externally generated forces. This is due to mechanisms of sensory reafference where the comparison between predicted and actual sensory feedback results in attenuated perceptions of self-generated forces. Without an external reference to calibrate attenuated performance judgments, a compensatory overproduction of force is exhibited. It remains unclear whether the force overproduction seen in the absence of visual reference stimuli differs when forces are produced bimanually. We studied performance of two versions of a bimanual sequential force production task compared with each hand performing the task unimanually. When the task goal was shared, force series produced by each hand in bimanual conditions were found to be uncorrelated. When the bimanual task required each hand to reach a target force level, we found asymmetries in the degree of force overproduction between the hands following visual feedback removal. Unilateral continuous theta-burst stimulation of the left primary motor cortex yielded a selective reduction of force overproduction in the hand contralateral to stimulation by disrupting sensory reafference processes. While variability was lower in bimanual trials when the task goal was shared, this influence of hand condition disappeared when the target force level was to be reached by each hand simultaneously. Our findings strengthen the notion that force control in bimanual action is less tightly coupled than other mechanisms of bimanual motor control and show that this effector specificity may be extended to the processing and compensation for mechanisms of sensory reafference.

bimanual control; repetitive forces; sensory attenuation; sensory reafference; transcranial magnetic stimulation

PREVIOUS WORK FROM OUR LABORATORY has shown that in the absence of a visual reference, self-generated, discrete, repetitive force pulses tend to exceed target magnitudes (Therrien and Balasubramaniam 2010; Therrien et al. 2011). This phenomenon of force overproduction has been attributed to mechanisms of sensory reafference affecting perceptions of self-produced, somatosensory feedback (Therrien et al. 2011). Specifically, it has been proposed that corollary discharge from the primary motor cortex (M1) is used in the generation of forward models of the sensory outcomes of a given motor act (Bays et al. 2005, 2006; Blakemore et al. 1998a, 1998b; Shergill et al.

2003; Voss et al. 2007; Wolpert and Ghahramani 2000). These sensory predictions are compared with incoming afferent information as a means of evaluating the accuracy of motor execution as well as to establish agency over self-generated movements (Bays et al. 2005, 2006; Blakemore et al. 1998a, 1998b; Shergill et al. 2003; Voss et al. 2007; Wolpert and Ghahramani 2000). This comparison process is thought to result in attenuation of the predicted component of incoming afferent information, reducing the salience of self-generated sensory feedback (Bays et al. 2005, 2006; Blakemore et al. 1998a, 1998b; Shergill et al. 2003; Voss et al. 2007). In the case of fingertip force production, self-produced forces are perceived as being weaker. Without visual reference stimuli to calibrate somatosensory performance judgments, participants exhibit a systematic overproduction of force to compensate.

Our previous work has examined only unimanual sequential fingertip forces. It remains unclear whether the systematic force overproduction seen in the absence of visual reference stimuli differs when forces are produced in a bimanual context. While strong coupling has been found between the limbs in studies of bimanual motor timing, the control of force in bimanual tasks seems to be less tightly coupled. Studies of both continuous isometric and repetitive force production have reported similar force output errors between unimanual and bimanual conditions (Davis 2007; Inui and Hatta 2002). In addition, Inui and Hatta (2002) provided unilateral visual feedback of either the dominant or nondominant hand in a bimanual repetitive force production task and found that removal of these reference stimuli induced asymmetric effects on the force output of the two hands. Specifically, feedback of the dominant hand resulted in similar force output for the two limbs, but nondominant limb feedback resulted in asymmetric performance variability. Together, these results suggest that mechanisms compensating for visual feedback manipulations may operate independently for each limb in cases of bimanual force production.

In our task, comparison of the force overproduction effect between unimanual and bimanual contexts could provide insight into the nature of sensory reafference processing. If sensory reafference mechanisms function in an effector-specific manner, each limb in a bimanual force production task should exhibit the force overproduction phenomenon, perhaps to differing extents, and show little correlation, or coupling, between the hands. Conversely, if these mechanisms encode context-specific information about the limbs in a bimanual task, some degree of coupling, or synergistic correlation, be-

Address for reprint requests and other correspondence: A. S. Therrien, Sensorimotor Neuroscience Laboratory, McMaster Univ., 1280 Main St. West, Hamilton, ON L8S 2K1, Canada (e-mail: therrias@mcmaster.ca).

tween them might be expected, similar to what has been found in previous studies of oscillatory multifinger force production (Latash et al. 2001; Scholz et al. 2002). In our task, this coupling could differentially influence the force overproduction exhibited after removal of visual feedback. Here we focus on a bimanual extension of the sequential force production task employed by Therrien and Balasubramaniam (2010). Our objective was to test the hypothesis that if the forces produced by the two limbs in a bimanual context are controlled asymmetrically as previous literature suggests, then sensory reafference signals may also be processed asymmetrically for each limb in a bimanual force production task.

METHODS

Ethics Statement

The McMaster University Research Ethics Board and the Hamilton Health Sciences/McMaster University Faculty of Health Sciences Research Ethics Board approved the experimental protocols presented here. All participants provided informed consent prior to participation.

Experimental Apparatus

Force data were collected with two 6 degrees of freedom load cells (ATI Nano 17) mounted on vertical stainless steel t-stands. Forces were applied on the axes perpendicular to the gripping surface (z -axes) of each transducer. The stands were placed in parallel, ~22 cm apart, and fixed to the table surface in front of a 19-in. Viewsonic LCD flat-panel computer monitor (refresh rate of 60 Hz) that provided participants' force-contingent visual feedback. Force data were sampled at 1,000 Hz with custom-written LabVIEW software (LabVIEW 8.2, National Instruments). A factory-generated 6×6 matrix, describing the signal gain between voltage and resolved forces, was used to calibrate each load cell. This calibration matrix also allowed for correction of cross talk between measured forces and moment arms. An AMTI amplifier was used to bolster voltage signals, which were then digitized with the National Instruments PCI-6220 DAQ. The ultimate resolution of each transducer 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.

Bimanual Sequential Force Production Task

Participants sat in a chair with both forearms resting on adjustable armrests, located in front of each force transducer, on a table surface. They were positioned so they could comfortably reach each load cell with the appropriate arm and perform the pinch grip motion with the wrists in neutral position. During each experiment, participants were presented with a visually specified target force level, of either 8 N or 16 N, in the form of a column in a bar plot. They were asked to match this force level by repetitively pinching either one or both of the load cells between the thumb and index finger of the right hand only (UR), the left hand only (UL), or both hands simultaneously (Bi). Participants were to synchronize their pinch rate with an auditory metronome set to 2 Hz (corresponding to 500 ms between sounds), which remained present throughout each trial. Each pinch of the load cell modulated the height of a second column, adjacent to the target column, on the bar plot in a manner contingent upon the force level produced. The goal of the task was to match the height of the target column with the second column, by modulating the force level produced with each pinch of the load cell. The system gain was set so that a 1-N increase in force produced a 1-cm increase in the height of the second column.

All trials lasted 20 s. In experimental conditions (NV), visual feedback of the target as well as participants' current force output were removed after 10 s. In these conditions, participants were asked to continue repetitively pinching the load cell in time with the metronome and at the same force level for the remainder of the trial. In control conditions (V), visual force feedback remained present throughout the trial. In all experiments, participants were given up to five practice trials with each condition prior to data collection in order to familiarize themselves with the task and experimental apparatus. Participants were instructed as to which hand(s) (UR, UL, Bi) to use prior to the start of each trial but were not informed of the experimental condition (8 N or 16 N, V or NV).

Experiment 1: bimanual shared goal task. Right-handed volunteers ($n = 10$, 5 men, 5 women; mean age: 24.6 yr; mean Edinburgh Handedness Inventory laterality index: 73.3; Oldfield 1971) performed the bimanual sequential force production task. The UL and UR hand conditions involved performing the pinch grip motion only on the left or right load cell with the corresponding hand. In these trials, the total force visible on the screen corresponded to the force output of the active hand. In the Bi condition, participants produced pinch grip forces on both the right and left force transducers with the corresponding hands. The visual display of the total force produced in Bi trials corresponded to the summed output forces of the two hands. Trial conditions were presented in a randomized order with five repetitions of each trial type. For 3 hand conditions (UL, UR, Bi), 2 force target force levels (8 N, 16 N), and 2 visual feedback conditions (V, NV), this yielded a total of 60 trials per participant.

Experiment 2: bimanual independent goal task. Without specific force targets for each hand in the Bi condition of *experiment 1*, analysis of any force overproduction by each hand in NV trials was limited. To better analyze the force overproduction effect in each hand in the bimanual sequential force production task, a second group of right-handed volunteers ($n = 12$, 6 men, 6 women; 22.1 ± 3.7 yr; mean Edinburgh Handedness Inventory Laterality Index: 82.5; Oldfield 1971) were recruited to perform a variant of the protocol employed in *experiment 1*. In this task, the UR and UL hand conditions involved producing pinch grip forces with the right or left hand only. In the Bi trials, however, the target force level was to be reached with each hand simultaneously rather than being shared across the two effectors. In this version of the bimanual sequential force production task the visual feedback was structured such that a single force target of 16 N was presented as the center column of a three-column bar plot on the computer monitor. The two remaining columns represented participants' force output. These were located on either side of the center target column and directly in front of the corresponding load cell. The height of these columns was contingent upon the force produced with each pinch of the corresponding load cell. This meant that the leftmost column of the visual display corresponded to the left transducer and represented the force output of the left hand. The rightmost column of the visual display corresponded to the right transducer and represented the force output of the right hand. The height of the center target column remained fixed at 16 N throughout the experiment. Forces were analyzed for four hand conditions (UR, UL, BiR, BiL) and two visual feedback conditions (V, NV). Six repetitions were performed for each condition, yielding 36 trials per participant.

Experiment 3: unilateral transcranial magnetic stimulation in the bimanual independent goal task. In Therrien et al. (2011) we used continuous theta-burst stimulation (cTBS) to reduce the excitability of left M1 and found that this resulted in a systematic reduction in the force overproduction exhibited by the contralateral hand in NV trials by inducing discrepancy between efference copy and motor output signals. The idea behind the present experiment was to test whether perturbing one hemisphere of M1 would induce an effector-specific modulation of the force overproduction effect in the bimanual repetitive force production task. The same group of volunteers from *experiment 2* participated in two additional testing sessions in which

they performed the same bimanual force production task as *experiment 2* after receiving either real or sham cTBS.

Transcranial magnetic stimulation procedures. A figure of eight coil (Magstim, Oakville, ON, Canada; external diameter of each coil: 9 cm) was placed tangential to the head, at an angle of $\sim 45^\circ$ from the anterior-posterior midline, with the handle pointing to the posterior. The coil was used to deliver single pulses of focal transcranial magnetic stimulation (TMS) over left motor cortex and elicit motor evoked potentials (MEPs) in the first dorsal interosseous muscle (FDI) of the resting right hand. MEPs were recorded by electromyography (EMG). Ag/AgCl sintered electrodes were placed over the FDI muscle, in belly-tendon configuration, with a ground electrode placed on the olecranon process of the elbow. The site for repetitive stimulation was determined as the cortical location where MEPs of 50 μ V in peak-peak amplitude could be evoked in at least 50% of trials with the lowest stimulator output. This optimal stimulation site was recorded with Brainsight software (Brainsight 2.1.4, Rogue Research, Montreal, QC, Canada) to allow for precise repositioning of the coil throughout both TBS and sham stimulation sessions.

After the optimal stimulation site was determined, participants performed two or three maximum voluntary contractions (MVCs) 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. Final MVC was taken as the average of these trials. To determine active motor threshold (AMT), single pulses of TMS were delivered while participants held isometric contractions at 20% of their MVC. A dial on the force gauge provided visual feedback to ensure that an accurate force level was attained. AMT was determined to be the lowest stimulator intensity sufficient to produce MEPs $>200 \mu$ V above background EMG in at least 50% of trials.

As in Therrien et al. (2011), cTBS was used for the repetitive stimulation phase of the experiment. In cTBS, continuous trains of TMS are 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 an intensity of 80% AMT for a duration of 40 s (to yield a total of 600 pulses). This protocol, termed cTBS600, is known to depress cortical excitability in the stimulated region for up to 60 min after stimulation (Huang et al. 2005). For the sham stimulation sessions, the same procedures outlined above were used to determine the optimal stimulation site and AMT. Unbeknownst to participants, however, repetitive stimulation was performed with a second inactive coil placed over the participant's skull while the active coil was moved behind and oriented away from the head. Both TBS and sham stimulation sessions were separated by a minimum of 24 h to ensure compliance with previously determined safety guidelines (Wasserman 1998).

Data Analysis

Force data were stored separately for off-line analysis. A custom-written script in MATLAB was used to extract the peak force magnitude produced with each pinch of the load cell as well as the corresponding sample iteration and the trial time at which the peak occurred. Trial means were calculated from these data. To prevent contamination from transient behavior as participants adjusted to each new trial, the first 2 s of data (corresponding to the first 4 peak forces) was discarded from each trial. Mean force was defined as the mean peak force produced in each trial. Variability of each trial was quantified with coefficients of variation (CV). Only continuation phase data ($t = 11$ – 20 s) were used for these analyses, i.e., after the feedback was removed in NV trials. Pearson product-moment correlations were performed for the detrended force series produced by each hand in the bimanual conditions of all three experiments. In *experiments 2* and *3*, the force errors produced by each hand when visual feedback was removed were quantified relative to the mean force level produced by participants prior to feedback removal. Trials were separated into mean peak force values for two trial phases:

before feedback removal ($t = 2$ – 10 s) and after feedback removal ($t = 11$ – 20 s). The difference between the mean force levels produced in these two trial phases was taken as a measurement of the average change in force level over the course of the two trial phases. This method of quantifying force errors was chosen over measures relative to the target force magnitude only (i.e., constant error) to account for differing baseline levels of force output that were exhibited by participants even when visual force feedback was provided. All means were calculated across condition repetitions as well as across study participants.

Statistical Analysis

Separate analyses of variance (ANOVAs) with repeated measures were calculated for each dependent variable with SPSS software (SPSS 16.0, Chicago, IL). In *experiment 1* the forces produced and the associated variability were assessed with factors of hand condition (UR, UL, Bi), target force level (8 N, 16 N), and visual feedback condition (V, NV). In *experiment 2*, the forces produced, the associated variability, and the change in force level over the two trial halves were assessed with factors of hand condition (UR, UL, BiR, BiL) and visual feedback condition (V, NV). The same analysis was performed for *experiment 3*, but with an additional factor of stimulation condition (sham, TBS). Post hoc means comparisons were performed with Tukey's honestly significant difference (HSD).

RESULTS

The goal of *experiment 1* was to assess the differences between sequential force pulses produced either unimanually by the right or left hand or bimanually through shared effort by the two hands together. Force-time series for the 16-N target force magnitude can be seen in Fig. 1. Grand mean data from the two unimanual and the overall bimanual (combined output of the two hands) conditions are plotted in Fig. 1, *A* and *B*. Force series produced by each hand of a representative subject in the bimanual condition of *experiment 1* are shown in Fig. 1, *C* and *D*. Representative subject data were chosen over grand mean data because of high variability from shifts in how forces were distributed over the two hands in this condition. Analysis of mean peak force produced a main effect of target force magnitude, which indicated that participants successfully produced two significantly different force levels corresponding to the 8 and 16 N force target conditions [$F(1,9) = 674.045$, $P < 0.001$]. Mean peak forces were slightly above the target magnitudes but were comparable across participants (9.0 N and 16.7 N for the 8 and 16 N force target conditions, respectively). An interaction among the factors hand condition, force target magnitude, and visual feedback condition was significant [$F(2,18) = 3.624$, $P < 0.05$; Fig. 2A], with post hoc means comparisons revealing it to be driven by significantly greater forces produced in the absence of visual feedback in all conditions, except when the target force magnitude was 16 N and forces were produced unimanually by the left hand. Post hoc analysis also revealed an interesting effect where the mean peak force produced in NV trials of the bimanual hand condition exceeded the mean peak force produced in the NV trials of the unimanual conditions. This difference between the bimanual and both unimanual hand conditions was significant for the 16-N target force magnitude but only reached significance between the bimanual and unimanual left hand conditions for the 8-N target force magnitude.

Analysis of peak force CV also yielded a significant interaction between the factors hand condition, force target magni-

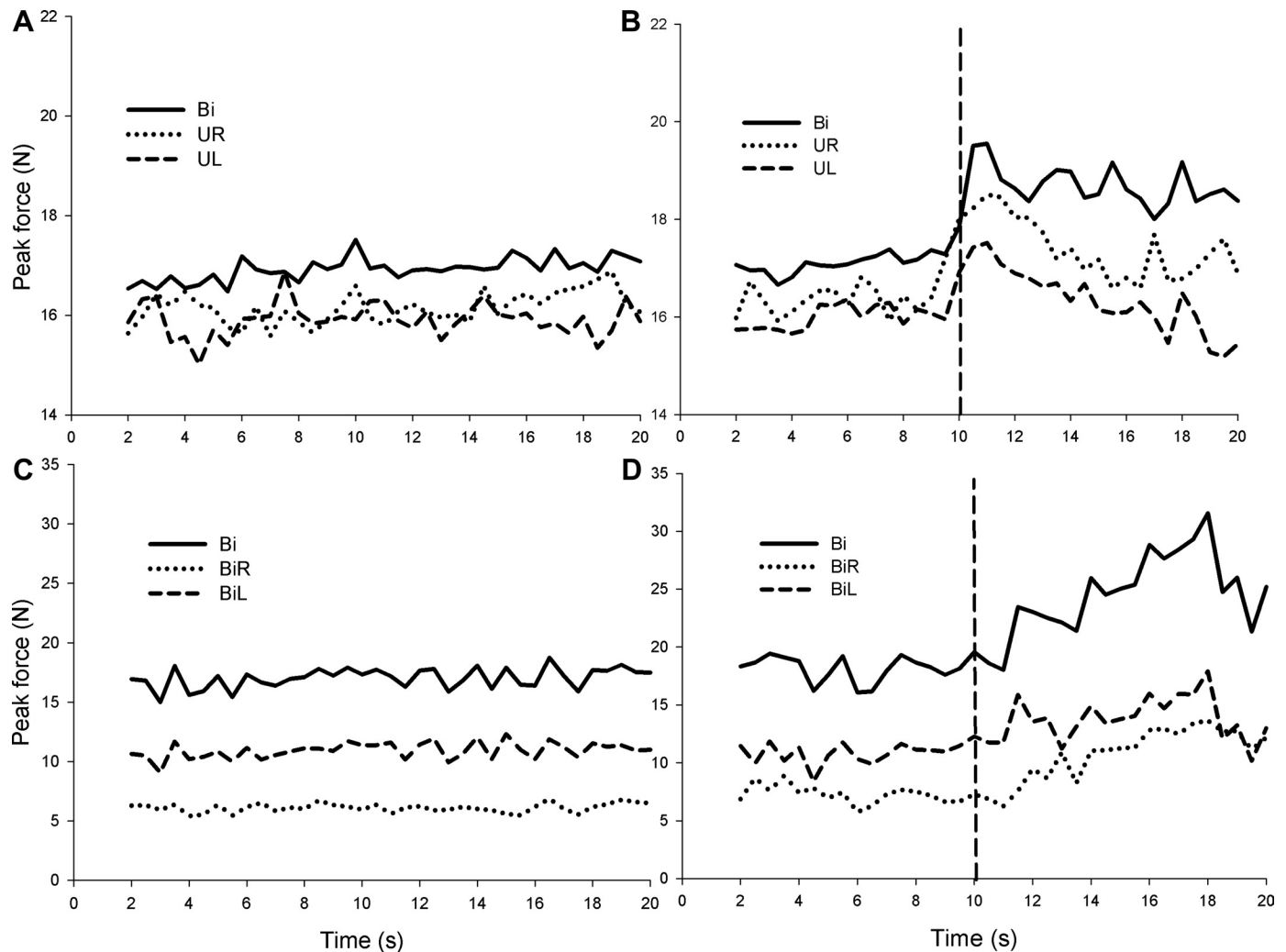


Fig. 1. Force-time series produced with a 16-N target force magnitude in the 2 unimanual and the shared-goal bimanual hand conditions of *experiment 1*. Mean force-time series are plotted for conditions in which visual feedback of force output remained present throughout (A) and in which feedback was removed (B). Because of high variability from shifts in force distribution by the 2 hands in the shared-goal bimanual task, rather than mean data, force output data from each hand in these conditions are plotted from a representative subject in C (conditions in which visual feedback remained present throughout the trial) and D (conditions in which visual feedback was removed). Vertical dashed lines represent the time at which visual feedback was removed. Bi, bimanual; U, unimanual; R, right hand; L, left hand.

tude, and visual feedback condition [$F(2,18) = 7.645$, $P < 0.01$; Fig. 2B]. Post hoc means comparisons revealed peak force variability to be larger in the absence of visual feedback regardless of target force or hand condition. Post hoc analysis also revealed an interesting pattern where force variability in the bimanual hand condition was lower compared with forces produced unimanually, despite the tendency for greater mean peak force in this hand condition. Force variability in the bimanual hand condition for the 8-N target force magnitude was significantly reduced compared with both unimanual right and unimanual left hand conditions. This reduction only reached significance between the bimanual and unimanual left conditions for the 16-N target force magnitude.

The bimanual task in this experiment involved the target force magnitude being reached through the summed output of the two hands. As participants were not instructed as to a specific strategy to use when dividing the target force magnitude between the two hands, analysis of any force overproduction by each hand in NV trials of this hand condition was limited. Pearson product-moment correlations were performed

comparing the detrended force series produced by each hand in the bimanual hand condition; the results of this analysis can be seen in Table 1. When visual feedback was present, the forces produced by each hand showed weak negative correlations that failed to reach significance. When visual feedback was removed, the force series showed smaller correlations that were weakly positive for the 8-N target force magnitude and approached zero for the 16-N target force magnitude. Thus it seemed that the force output of the two hands showed no significant synergistic correlation when producing a shared force bimanually; however, whether this was due to each hand expressing the force overproduction phenomenon independently remained unclear.

In *experiment 2* the force task in the bimanual hand condition was modified to better analyze the force output behavior of each hand when visual feedback was removed. Instead of reaching the force target through the combined effort of the two hands, the goal of the bimanual task in this experiment was to attain the target force level simultaneously with both hands. Grand mean force-time series obtained from our data can be

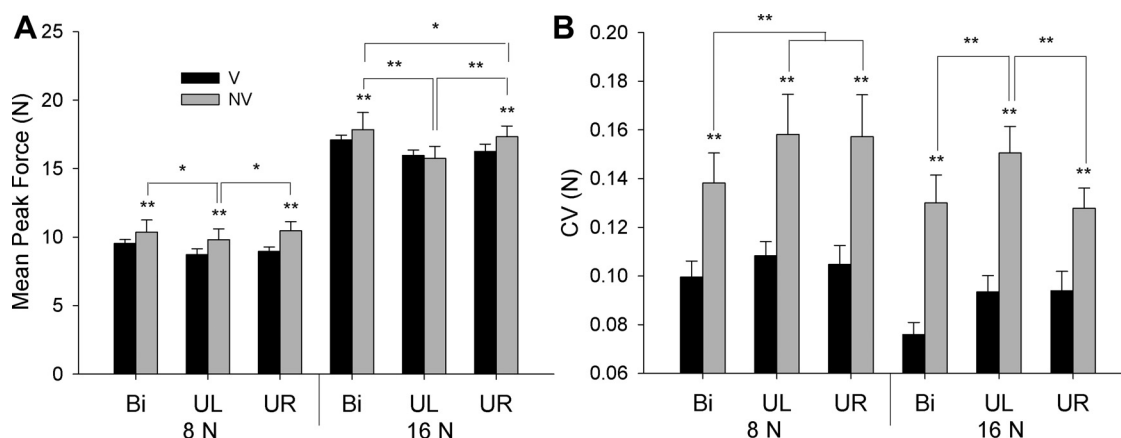


Fig. 2. Significant interactions among factors target force magnitude, hand condition, and visual feedback condition for mean peak force (A) and peak force coefficient of variation (CV, B) in *experiment 1*. Asterisks and connecting lines denote reliable pairwise means comparisons: * $P < 0.05$, ** $P < 0.01$. V, visual feedback present; NV, visual feedback removed.

seen in Fig. 3. The force-time series from the unimanual hand conditions are plotted in Fig. 3A, while the force-time series from the bimanual hand conditions are shown in Fig. 3B. Clear differences were present in the performance of the two hands for both the unimanual and bimanual hand conditions. The left hand consistently produced larger forces than the right, even when visual feedback was present. Upon removal of visual feedback, both hands produced positive force errors. While the magnitude of these errors was similar when both hands acted unimanually, the errors were greater and more positive for the right hand in the bimanual hand condition. A significant interaction among factors of hand and visual feedback condition for mean peak force mirrored these results [$F(3,33) = 6.315$, $P < 0.01$; Fig. 4A]. Post hoc means comparisons revealed mean peak forces produced in the absence of visual feedback to be greater in all conditions except when the left hand was acting in the bimanual task. The right hand produced lower mean peak forces than the left hand when visual feedback was present, and this difference was significant for the bimanual hand condition. Pairwise means comparisons also revealed that mean peak forces produced by each hand in the absence of visual feedback were greater in unimanual hand conditions than when the hands produced forces bimanually.

Analysis of the mean change in force level over the course of a trial revealed a similar pattern of results. A significant interaction between factors of hand and visual feedback condition showed that positive force errors were displayed for all conditions except when the left hand acted in the bimanual task [$F(3,33) = 6.753$, $P < 0.01$; Fig. 4B]. Independent-samples *t*-tests were used to compare means obtained for conditions where visual feedback was present against zero. No significant

differences were obtained ($P > 0.05$), demonstrating that the biases in force output seen in these conditions in Fig. 4A were consistent throughout the trial. While the degree of force overproduction exhibited by the two hands in NV trials was

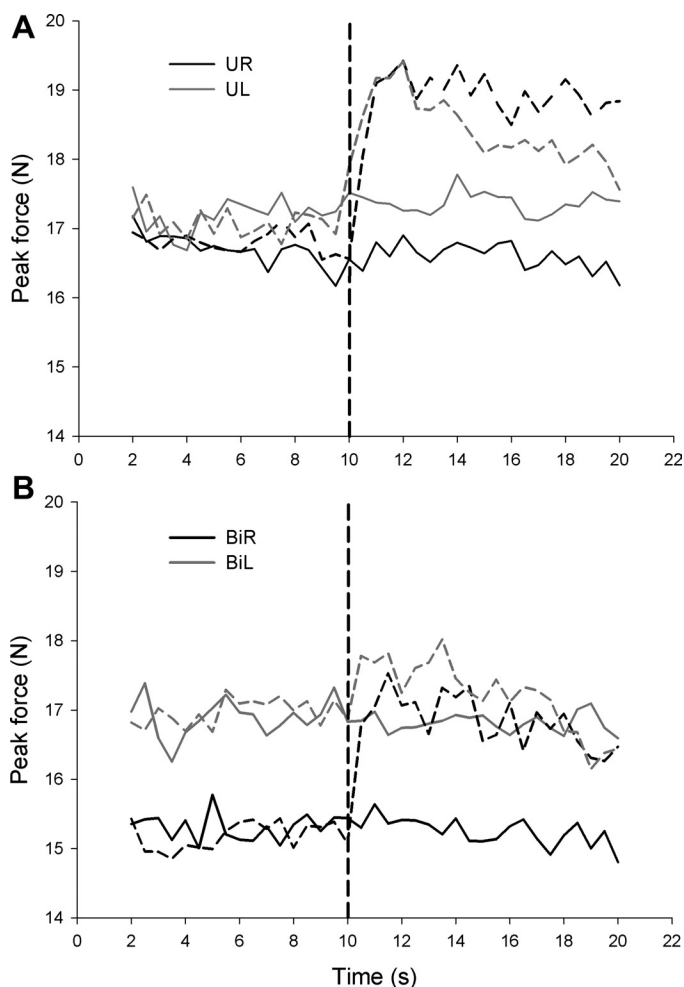


Fig. 3. Mean force-time series produced in the 2 unimanual (A) and the 2 bimanual (B) hand conditions of *experiment 2*. Solid lines represent conditions in which visual feedback of force output remained present throughout the trial. Dashed lines represent conditions in which visual feedback was removed. Vertical dashed lines denote the time at which visual feedback was removed.

Table 1. Pearson product-moment correlation coefficients between force series produced by right and left hands in bimanual hand condition of *experiment 1*

Visual Feedback	Target Force Magnitude	
	8 N	16 N
V	-0.353	-0.123
NV	0.405	-0.061

$n = 10$ for all analyses. V, visual feedback present; NV, visual feedback removed.

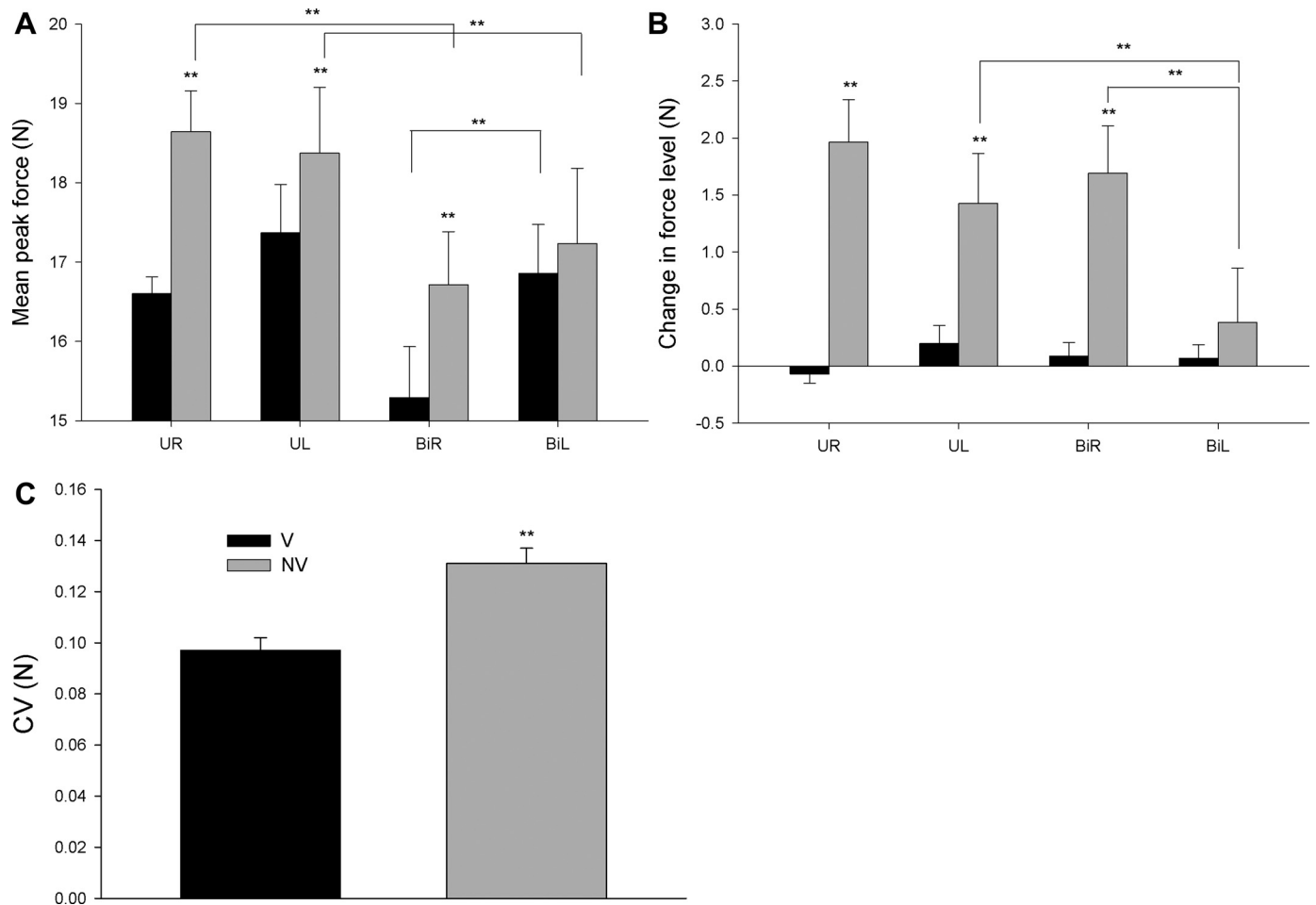


Fig. 4. *A* and *B*: significant interactions among factors hand condition and visual feedback condition for mean peak force (*A*) and mean change in force level over the course of a trial (*B*) for *experiment 2*. *C*: significant main effect of visual feedback condition for peak force CV in *experiment 2*. Asterisks and connecting lines denote reliable pairwise means comparisons: $**P < 0.01$.

similar in unimanual conditions, post hoc means comparisons revealed significant differences between them in the bimanual hand condition. Pairwise means comparisons also showed within-hand differences between the unimanual and bimanual contexts of the task. The mean change in force output seen when visual feedback was removed did not change for the right hand across unimanual and bimanual contexts; however, the degree of force overproduction exhibited by the left hand after visual feedback removal was significantly reduced when the limb acted in a bimanual task.

Analysis of peak force CV yielded only one significant main effect of visual feedback condition [$F(1,11) = 34.792$, $P < 0.001$; Fig. 4C] in which variability was greater in absence of visual feedback. As in *experiment 1*, correlational analysis was performed on the detrended force series produced by each hand in the bimanual condition to assess coupling between the limbs in these trials. The results of this analysis can be seen in Table 2. Correlation coefficients were again weakly negative when visual feedback was present but became smaller when it was removed, although values failed to reach significance in either condition.

Taken together, the results of this experiment suggest that, while the variability of the forces produced did not differ as a function of hand condition, expression of the force overproduction effect noted in our previous work did differ between

unimanual and bimanual contexts as well as between hands within the bimanual task. Nonsignificant correlations again suggested independent action by each hand in the bimanual task; however, it still remained unclear whether the difference in overproduction errors exhibited by each hand in NV trials of this condition were rooted in asymmetric processing of reafferent feedback from the self-generated force pulses. We sought to investigate this question in *experiment 3*.

In *experiment 3* we used a 40-s train of cTBS to the FDI area of left M1 to induce a period of unilateral cortical depression. In Therrien et al. (2011) we used this TMS protocol on a unimanual sequential force production task and found it to

Table 2. Pearson product-moment correlation coefficients between force series produced by right and left hands in bimanual hand conditions of *experiments 2* and *3*

Visual Feedback	Experiment 2	Experiment 3 Stimulation Condition	
		Sham	TBS
V	-0.505	-0.323	0.212
NV	-0.122	-0.171	0.491

$n = 12$ for all analyses. TBS, theta-burst stimulation.; Sham, sham stimulation.

result in significant reductions in the degree of force overproduction seen after removal of visual feedback. This result was attributed to a TMS-induced discrepancy between sensory predictions and actual afferent feedback resulting in reduced attenuation of self-generated somatosensory feedback. The goal of the present experiment was to investigate whether a unilateral perturbation to this mechanism would result in differential effects for the unimanual and bimanual force production tasks used in *experiment 2*. The mean force-time series obtained from our data in *experiment 3* are plotted in Fig. 5. Data from the UR and UL hand conditions can be seen in Fig. 5, *A* and *B*, respectively. Data from the BiR and BiL hand conditions can be seen in Fig. 5, *C* and *D*, respectively. Clear differences can again be seen in the performance of the two hands. As in *experiment 2*, the left hand was biased to produce greater forces than the right hand, even when visual feedback was present. Upon removal of visual feedback, both hands produced positive force errors in unimanual conditions (although this effect is more pronounced in the right hand), but only the right hand showed the force overproduction phenomenon in the bimanual condition. Interestingly, after receipt of cTBS, the magnitude of these force errors by the right hand (contralateral to the stimulation site) is selectively reduced.

Repeated-measures ANOVA for mean peak force yielded a significant interaction among factors of stimulation session, hand condition, and visual feedback condition that showed a similar pattern of results [$F(3,33) = 3.258$, $P < 0.05$; Fig. 6*A*]. Post hoc means comparisons revealed that mean peak forces produced in the absence of visual feedback were consistently greater than those produced when it was present in all conditions except when the left hand acted in the bimanual task. There was also a nonsignificant trend for the left hand to produce greater forces than the right when visual feedback was present. Furthermore, an additional effect was present where the degree of force overproduction in NV trials was selectively reduced for the right hand in both the unimanual and bimanual hand conditions after receipt of cTBS.

Analysis of the mean change in force level produced over the course of a trial also yielded a significant interaction among factors stimulation session, hand condition, and visual feedback condition [$F(3,33) = 3.422$, $P < 0.05$; Fig. 6*B*]. Significant positive force errors were seen in the absence of visual feedback for all conditions except when the left hand acted in the bimanual hand condition. *t*-Tests comparing the change in force level in conditions where visual feedback was present to zero again revealed no significant differences ($P > 0.05$).

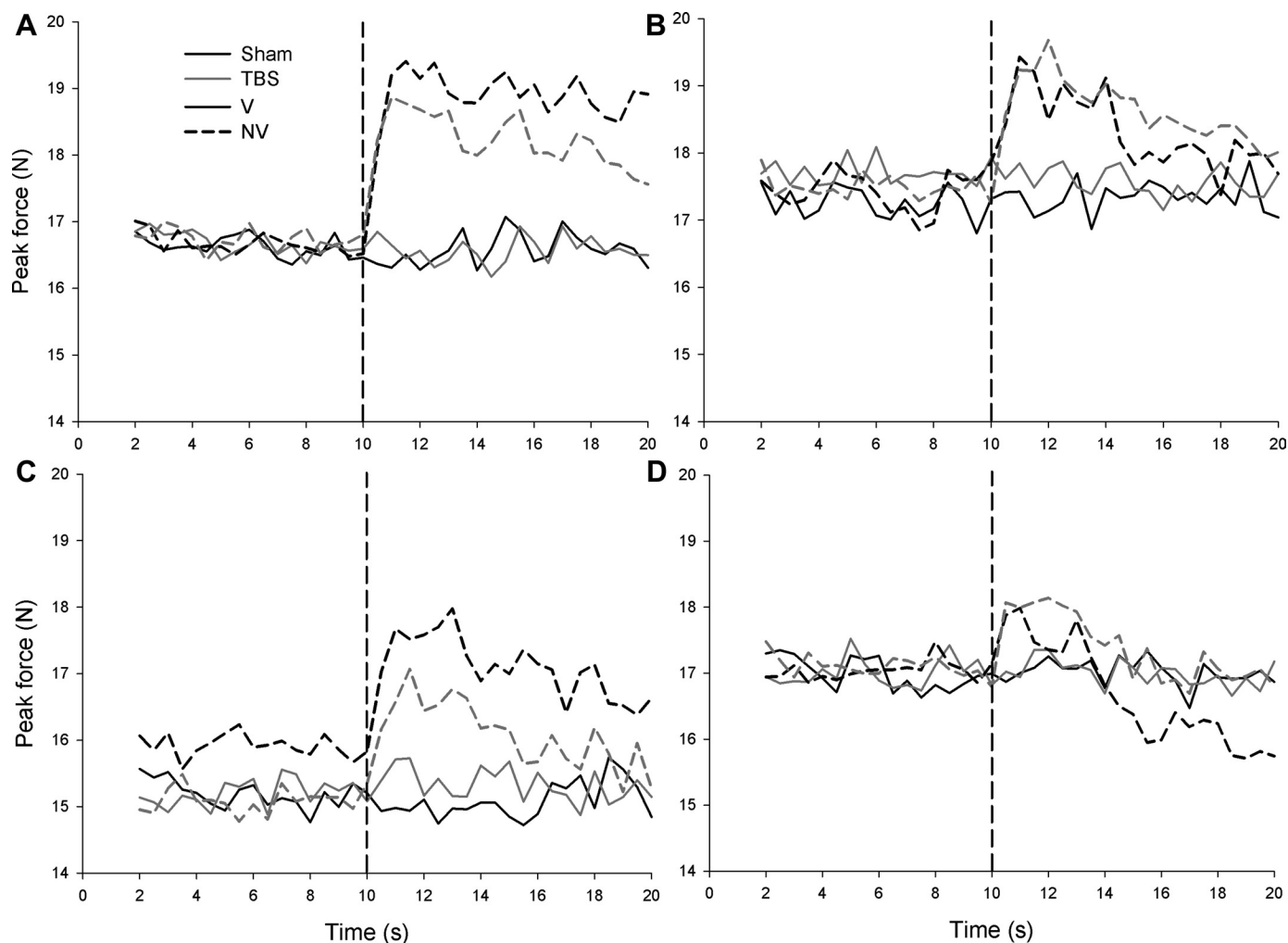


Fig. 5. Mean force-time series produced in the unimanual right (*A*), unimanual left (*B*), bimanual right (*C*), and bimanual left (*D*) hand conditions of *experiment 3*. Solid lines represent conditions in which visual feedback remained present throughout the trial (V). Dashed lines represent conditions in which visual feedback was removed (NV). Vertical dashed lines denote the time at which visual feedback was removed. TBS, theta-burst stimulation; Sham, sham stimulation.

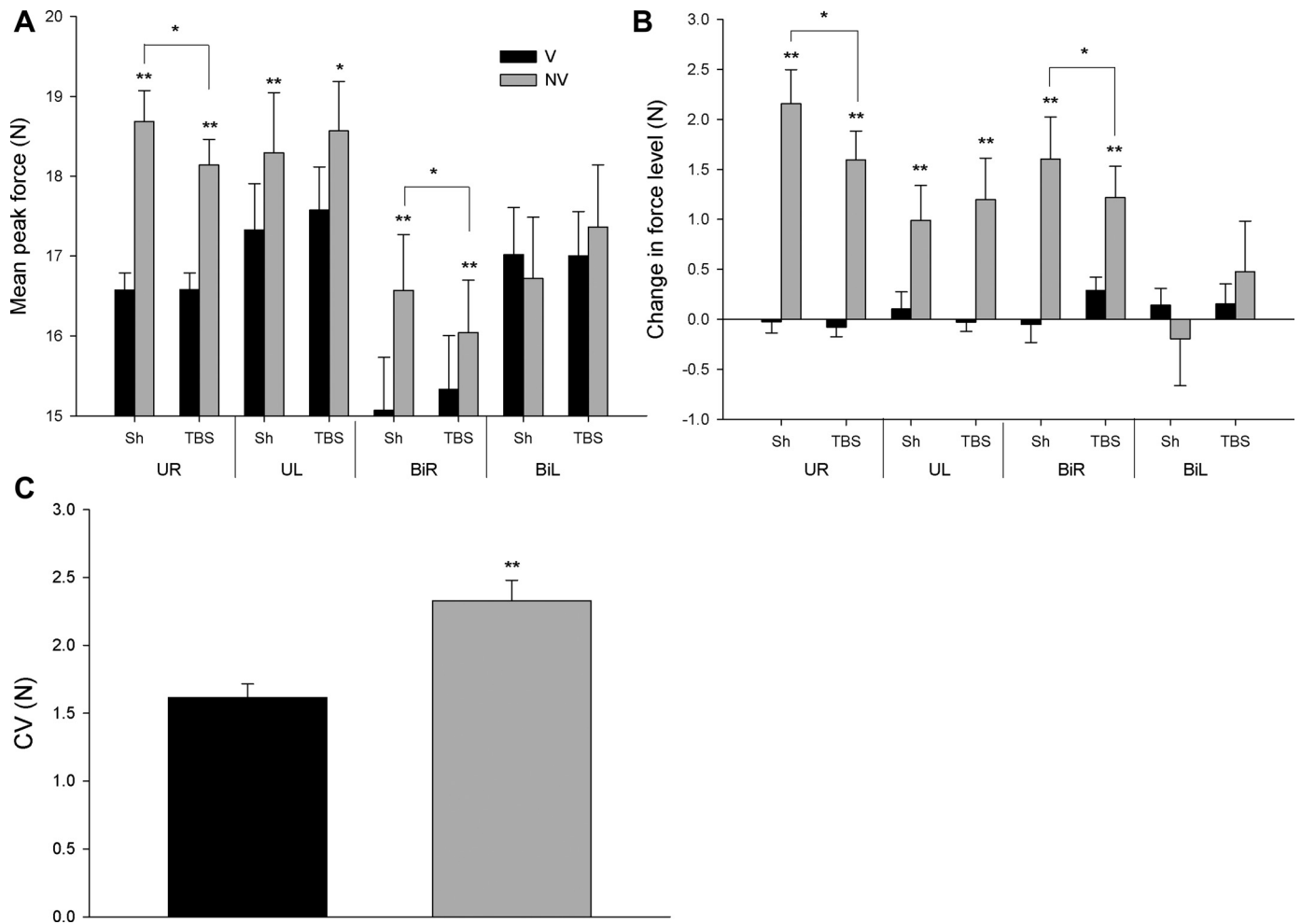


Fig. 6. *A* and *B*: significant interactions among factors stimulation session, hand condition, and visual feedback condition for mean peak force (*A*) and mean change in force level over the course of a trial (*B*) in *experiment 3*. *C*: significant main effect of visual feedback condition on peak force CV in *experiment 3*. Asterisks denote reliable pairwise means comparisons: * $P < 0.05$, ** $P < 0.01$.

While there was a trend for the left hand to show reduced force overproduction errors when acting in the bimanual compared with the unimanual condition, this failed to reach significance. Similar to the mean peak force results, positive force errors produced in the absence of visual feedback were reduced for the right hand in both the unimanual and bimanual hand conditions after receipt of cTBS. Together these results suggest that unilateral cTBS influenced the processing of reafferent feedback selectively for the hand contralateral to stimulation. Analysis of peak force CV yielded only a single main effect of visual feedback condition [$F(1,11) = 95.367$, $P < 0.001$; Fig. 6C], suggesting that force variability was not differentially affected by either hand condition or the stimulation sessions of our task. This is in line with previous results (Therrien et al. 2011).

Pearson product-moment correlations performed on the detrended force series produced by each hand in the bimanual task can be seen in Table 2. As in the previous experiments, correlation coefficients did not reach significance for either visual feedback condition or stimulation session, suggesting a lack of coupling between the hands overall. Interestingly, while correlations were weakly negative in the sham stimulation session, becoming less correlated in NV trials, correlation coefficients were weakly positive after receipt of cTBS and

became slightly stronger after visual feedback withdrawal. Together, the results of *experiment 3* suggest that unilateral cTBS influenced the processing of reafferent feedback from self-produced forces in our task, and this influence was selective for the limb contralateral to stimulation.

DISCUSSION

Our goal was to investigate the processing of reafferent feedback in a bimanual sequential force production task. Two groups of volunteers participated in either a task in which the bimanual hand condition required a target force magnitude to be achieved through the shared output of both hands or a task in which each hand was to produce the same target force magnitude simultaneously. In both, the bimanual production of force was compared with conditions in which each hand performed the sequential force production task unimanually. In *experiment 1* we found that forces tended to exceed target magnitudes in the absence of visual feedback; however, this was less reliable for the left hand. In addition, the forces produced bimanually in this condition did not simply show a pattern of results consistent with the combination of the behavior exhibited in the unimanual hand conditions. With the larger target force magnitude, forces produced in the bimanual

hand condition without visual feedback tended to exceed the forces produced by either hand unimanually without visual feedback. With the smaller target force magnitude, this was not the case. After visual feedback removal, forces produced bimanually were similar to those produced by the dominant, right, hand acting in a unimanual task. Without specific force targets for each hand in the bimanual task, any investigation into the force overproduction phenomenon in this condition was limited. Correlational analyses performed for the force series produced by the two hands in bimanual trials yielded no significant results, indicating a lack of significant coupling between the limbs in this condition overall. Interestingly, though, correlation coefficients were weakly negative when visual feedback was present but became smaller and more positive when it was removed. These results suggested the presence of some synergistic covariation (Latash et al. 2001; Scholz et al. 2002) that was reduced upon removal of visual feedback. Despite this reduced coupling, variability of the force series was lower in bimanual trials after removal of visual feedback.

In *experiment 2* we showed that when the target force magnitude was specified for each hand in a bimanual task, the force overproduction phenomenon did not occur equally for both. When acting in a unimanual task, forces produced by both the right and left hands exceeded target magnitudes after removal of visual feedback. When acting bimanually, however, force overproduction was only seen reliably in the dominant hand. Unlike in *experiment 1*, variability was not differentially affected by hand condition, suggesting that when the two hands act bimanually to produce independent force targets variability of the forces produced is comparable to unimanual tasks. *Experiment 3* replicated the differences in expression of the force overproduction phenomenon between the right and left hands in bimanual, compared with unimanual, trials. Interestingly, a period of unilateral motor cortical depression, induced by application cTBS600, resulted in a reduction of positive errors in force output following visual feedback removal that was selective for the hand contralateral to stimulation. Variability of the forces produced was significantly influenced neither by hand condition nor by stimulation session—a result that was in line with *experiment 2* as well as our previous work (Therrien et al. 2011).

Overall, the results of this study support our hypothesis that sensory reafference signals may be processed asymmetrically (and possibly separately) for each limb in a bimanual force production task. A lack of significant correlation between the hands in bimanual trials of *experiment 1* suggested independent control, rather than synergistic covariation, of the hands after removal of visual feedback of force output. *Experiments 2* and *3* further investigated this hypothesized asymmetric control and found that while force overproduction was consistently exhibited by the right hand after feedback removal, the effect was less reliable for the left hand in bimanual conditions. Our study participant pools were strongly right handed (values greater than +40 on the Edinburgh Handedness Inventory indicate right hand dominance; Oldfield 1971). It is possible that the observed asymmetry in force overproduction was due to strength differences between the dominant and nondominant limbs; however, in that case, one would have expected reduced force overproduction by the left hand when it acted unimanually as well. Both neurophysiological and neuroimaging stud-

ies have routinely shown that strongly right-handed individuals have better-developed efferent and afferent connections with their dominant side (Bernard et al. 2011; Dassonville et al. 1997; Siebner et al. 2002). An alternative possibility is that forward model predictions may be more precise for the dominant limb in this population. Following the mechanism proposed in our earlier work (Therrien et al. 2011), in the absence of visual feedback more precise sensory predictions would result in increased overlap with actual somatosensory feedback stemming from motor execution. This would lead to an augmented degree of sensory attenuation, which would in turn amplify the degree of compensatory overproduction of force by the right hand in bimanual tasks.

The notion of asymmetric processing of reafferent feedback is further supported by the observation that the effect of unilateral cTBS was selective to the hand contralateral to stimulation for both unimanual and bimanual hand conditions. The unimanual results are in line with our previous experiment (Therrien et al. 2011) and strengthen the notion that reducing excitability in the FDI area of M1, through application of cTBS, may have induced discrepancy between predicted and actual sensory feedback. After removal of visual reference stimuli, there was reduced overlap between these two signals, which led to reduced sensory attenuation and, in turn, to a decrease in the degree of force overproduction following stimulation. Additionally, the bimanual results suggest possible effector specificity in sensory prediction signals. One would expect context-specific forward models to contain sensory predictions averaged over the two limbs in a bimanual task. Unilaterally perturbing one hemisphere would induce a global mismatch with incoming afferent feedback, and such error signals would likely result in global updates to subsequent motor commands that would have affected the behavior of both limbs after stimulation.

It is important to note that, as in our previous study, our data do not provide any information regarding the mechanism that gave rise to a discrepancy between the sensory predictions generated and motor output produced. It is possible that application of cTBS induced changes in the processing of efference copy signals by altering the excitability of intracortical interneurons (Di Lazzaro et al. 2008). The cerebellum has been suggested as the neural locus for a forward model comparator (Blakemore et al. 1998b), and there exists evidence that efference copies may be generated upstream of M1 (Chronicle and Glover 2003). Spreading activation to any of these areas could have also disrupted sensory attenuation mechanisms in our task (Bestmann et al. 2004; Okabe et al. 2003; Siebner et al. 2000).

In addition to comparisons between the behavior of each hand in a bimanual sequential force production task, our study involved investigation of two kinds of bimanual tasks: one in which the goal force was to be achieved through the shared output of the two hands and one in which the two hands were to each produce the target force concurrently. Analysis of any differences between the magnitudes of forces produced by the two hands when the task goal was shared, versus not shared, was limited because of a lack of prescribed force sharing strategy in *experiment 1*. Measures of force variability, however, revealed differences between the two bimanual tasks. In the shared-goal task, a trend was present for variability to be reduced in the bimanual compared with unimanual hand conditions. This was interesting, as similar reductions in variability

in the absence of feedback have been noted in studies of motor timing (Drewing and Aschersleben 2003; Helmuth and Ivry 1996; Kelso et al. 1979). However, when the bimanual task was altered so that the goal was no longer shared, this effect of hand condition on force variability disappeared. Both bimanual tasks employed here involved a shared temporal goal between the hands. Our finding of changes in force variability between the two tasks suggests that something unique occurred when this shared temporal goal was paired with a shared force level goal that served to stabilize the forces produced, despite the positive errors and overall lack of coupling they exhibited. While negative covariation between the hands has been seen consistently in studies of motor timing and temporal coordination, one might wonder why the control of force level would reveal such capacity for independence. There are hemispheric asymmetries in the processing of somatosensory feedback (Goble and Brown 2007; Goble et al. 2005, 2006). Furthermore, it has been proposed that this asymmetry in somatosensory processing has led to distinct specializations in motor performance between the limbs (Sainburg 2002). That negative covariation has been found in previous studies of bimanual motor timing does not run counter to this hypothesis, as bimanual tasks often involve a shared goal; therefore, temporal coordination between independent actions of the two hands is necessary for accurate task execution. Rather, findings of asymmetry between the hands during control of bimanual forces and similarity between the two hands during the control of bimanual movement timing suggest that these two aspects of motor control may be specified at different levels of motor program generation (Ivry 1986).

The present study is the first, to our knowledge, to examine compensation for attenuated reafferent feedback from self-produced forces in a bimanual task. While our results are preliminary, the effects of sensory reafference on bimanual motor output warrant further study. First, examination of the data in all three of the present experiments reveals a trend for a gradual decrease in force output as trials progressed after visual feedback withdrawal that was present in all hand conditions, although this was least marked when the right hand acted unimanually. Decays in force output following visual feedback removal have been noted in studies of unimanual and bimanual production of isometric forces and have been attributed to the decay of visuomotor memory of the target force level (Davis 2007; Vaillancourt and Russell 2002). It is possible that a similar process may be at work in our task. Future study of this slow decay, perhaps in longer trials, and potential differences between the right and left hands in its expression may provide further insight into the nature of asymmetric processing of reafferent feedback between dominant and non-dominant hemispheres. Second, with respect to the TMS manipulation of *experiment 3*, the present study involved only unilateral stimulation of left M1. Given the anatomical and physiological asymmetries between dominant and nondominant hemispheres of right-handed individuals (Bernard et al. 2011; Dassonville et al. 1997; Siebner et al. 2002), it would be interesting to expand upon the present findings to investigate the effects of stimulation to the contralateral hemisphere of M1.

In summary, previous studies of unimanual sequential forces have shown that the magnitudes produced tend to exceed target values in the absence of visual feedback of force output. This has been attributed to compensation for the sensory attenuation

that results from the reafferent processing of self-generated somatosensory feedback. In the present study we examined this effect in two bimanual extensions of the sequential force production task. Differences in expression of the force overproduction phenomenon between unimanual and bimanual tasks could provide insight into the effector specificity or context specificity of sensory prediction signals. Results showed that unimanual sequential forces produced after visual feedback removal exceeded target values for both limbs. Forces produced bimanually, however, did not show the same symmetric overproduction. Indeed, unilaterally depressing excitability in one hemisphere of M1 to disrupt sensory prediction processes induced behavioral alterations selectively for the hand contralateral to stimulation. Overall our findings fall in line with previous literature suggesting that the control of force by the two hands in a bimanual task may be less tightly coupled than other mechanisms of motor control. The present results also add to this literature by showing that the asymmetric control of bimanual force may also extend to the processing of reafferent somatosensory feedback and compensation for the resulting attenuation of its salience.

ACKNOWLEDGMENTS

We thank all members of the Sensorimotor Neuroscience and Motor Behavior Laboratories at McMaster University for helpful discussions and two anonymous reviewers for their comments.

GRANTS

This work was supported by an National Sciences and Engineering Research Council (NSERC) Doctoral Scholarship awarded to A. S. Therrien and NSERC Discovery and Research Tools & Instruments Grants awarded to R. Balasubramaniam.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: A.S.T. and R.B. conception and design of research; A.S.T. performed experiments; A.S.T. analyzed data; A.S.T. interpreted results of experiments; A.S.T. prepared figures; A.S.T. drafted manuscript; A.S.T., J.L., and R.B. edited and revised manuscript; A.S.T., J.L., and R.B. approved final version of manuscript.

REFERENCES

- Bays PM, Flanagan JR, Wolpert DM. Attenuation of self-generated tactile sensations is predictive, not postdictive. *PLoS Biol* 4: e28, 2006.
- Bays PM, Wolpert DM, Flanagan JR. Perception of the consequences of self-action is temporally tuned and event driven. *Curr Biol* 15: 1125–1128, 2005.
- Bernard JA, Taylor SF, Seidler RD. Handedness, dexterity, and motor cortical representations. *J Neurophysiol* 105: 88–99, 2011.
- Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur J Neurosci* 19: 1950–1962, 2004.
- Blakemore SJ, Goodbody SJ, Wolpert DM. Predicting the consequences of our own actions: the role of sensorimotor context estimation. *J Neurosci* 18: 7511–7518, 1998a.
- Blakemore SJ, Wolpert DM, Frith CD. Central cancellation of self-produced tickle sensation. *Nat Neurosci* 1: 635–640, 1998b.
- Chen J, Lin Y, Shan D, Wu Z, Hallett M, Liao K. Effect of transcranial magnetic stimulation on bimanual movements. *J Neurophysiol* 93: 53–63, 2005.

- Chronicle E, Glover J.** A ticklish question: does magnetic stimulation of the primary motor cortex give rise to an "efference copy"? *Cortex* 39: 105–110, 2003.
- Cincotta M, Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Inghilleri M, Berardelli A.** Modulatory effects of high-frequency repetitive transcranial magnetic stimulation on the ipsilateral silent period. *Exp Brain Res* 171: 490–496, 2006.
- Dassonville P, Zhu XH, Uurbil K, Kim SG, Ashe J.** Functional activation in motor cortex reflects the direction and the degree of handedness. *Proc Natl Acad Sci USA* 94: 14015–14018, 1997.
- Davis NJ.** Memory and coordination in bimanual isometric finger force production. *Exp Brain Res* 182: 137–142, 2007.
- Di Lazzaro V, Pilato F, Dileone M, Profice P, Oliviero A, Mazzone P, Insola A, Ranieri F, Megalio M, Tonali PA, Rothwell JC.** The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. *J Physiol* 586: 3871–3879, 2008.
- Drewing K, Aschersleben G.** Reduced timing variability during bimanual coupling: a role for sensory information. *Q J Exp Psychol A* 56: 329–350, 2003.
- Goble DJ, Brown SH.** Task-dependent asymmetries in the utilization of proprioceptive feedback for goal-directed movement. *Exp Brain Res* 180: 693–704, 2007.
- Goble DJ, Lewis CA, Brown SH.** Upper limb asymmetries in the utilization of proprioceptive feedback. *Exp Brain Res* 168: 307–311, 2006.
- Goble DJ, Lewis CA, Hurvitz EA, Brown SH.** Development of upper limb proprioceptive accuracy in children and adolescents. *Hum Mov Sci* 24: 155–170, 2005.
- Helmuth LL, Ivry RB.** When two hands are better than one: reduced timing variability during bimanual movements. *J Exp Psychol Hum Percept Perform* 22: 278–293, 1996.
- Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC.** Theta burst stimulation of the human motor cortex. *Neuron* 45: 201–206, 2005.
- Huang YZ, Rothwell JC.** The effect of short-duration bursts of high-frequency, low-intensity transcranial magnetic stimulation on the human motor cortex. *Clin Neurophysiol* 115: 1069–1075, 2004.
- Inui N, Hattori H.** Asymmetric control of force and symmetric control of timing in bimanual finger tapping. *Hum Mov Sci* 21: 131–146, 2002.
- Ivry RB.** Force and timing components of the motor program. *J Mot Behav* 18: 449–474, 1986.
- Kelso JA, Southard DL, Goodman D.** On the nature of human interlimb coordination. *Science* 203: 1029–1031, 1979.
- Latash ML, Scholz JF, Danion F, Schöner G.** Structure of motor variability in marginally redundant multifinger force production tasks. *Exp Brain Res* 141: 153–165, 2001.
- Okabe S, Hanajima R, Ohnishi T, Nishikawa M, Imabayashi E, Takano H, Kawachi T, Matsuda H, Shio Y, Iwata NK, Furubayashi T, Terao Y, Ugawa Y.** Functional connectivity revealed by single-photon emission computed tomography (SPECT) during repetitive transcranial magnetic stimulation (rTMS) of the motor cortex. *Clin Neurophysiol* 114: 450–457, 2003.
- Oldfield RC.** The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9: 97–113, 1971.
- Sainburg RL.** Evidence for a dynamic-dominance hypothesis of handedness. *Exp Brain Res* 142: 241–258, 2002.
- Scholz JP, Danion F, Latash ML, Schöner G.** Understanding finger coordination through analysis of the structure of force variability. *Biol Cybern* 86: 29–39, 2002.
- Shergill SS, Bays PM, Frith CD, Wolpert DM.** Two eyes for an eye: the neuroscience of force escalation. *Science* 301: 187, 2003.
- Siebner HR, Peller M, Willech F, Minoshima S, Boecker H, Auer C, Drzezga A, Conrad B, Bartenstein P.** Lasting cortical activation after repetitive TMS of the motor cortex: a glucose metabolic study. *Neurology* 54: 956–963, 2000.
- Siebner HR, Limmer C, Peinemann A, Drzezga A, Bloem BR, Schwaiger M, Conrad B.** Long-term consequences of switching handedness: a positron emission tomography study on handwriting in "converted" left-handers. *J Neurosci* 22: 2816–2825, 2002.
- Therrien AS, Balasubramaniam R.** Timing and visual feedback constraints on repetitive finger force production. *Exp Brain Res* 201: 673–679, 2010.
- Therrien AS, Richardson BA, Balasubramaniam R.** Continuous theta-burst stimulation to primary motor cortex reduces the overproduction of forces following removal of visual feedback. *Neuropsychologia* 49: 2941–2946, 2011.
- Vaillancourt DE, Russell DM.** Temporal capacity of short-term visuomotor memory in continuous force production. *Exp Brain Res* 145: 275–285, 2002.
- Vorberg D, Hambach R.** Timing of two-handed rhythmic performance. *Ann NY Acad Sci* 423: 390–406, 1984.
- Voss M, Bays PM, Rothwell JC, Wolpert DM.** An improvement in perception of self-generated tactile stimuli following theta-burst stimulation of primary motor cortex. *Neuropsychologia* 45: 2712–2717, 2007.
- Wassermann EM.** Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol* 108: 1–16, 1998.
- Wolpert DM, Ghahramani Z.** Computational principles of movement neuroscience. *Nat Neurosci* 3: 1212–1217, 2000.