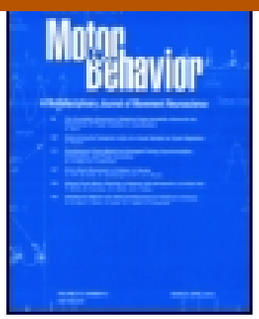

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RESEARCH ARTICLE

Interindividual Variability in Use-Dependent Plasticity Following Visuomotor Learning: The Effect of Handedness and Muscle Trained

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ABSTRACT. Motor learning has been linked with increases in corticospinal excitability (CSE). However, the robustness of this link is unclear. In this study, changes in CSE associated with learning a visuomotor tracking task were mapped using transcranial magnetic stimulation (TMS). TMS maps were obtained before and after training with the first dorsal interosseous (FDI) of the dominant and nondominant hand, and for a distal (FDI) and proximal (biceps brachii) muscle. Tracking performance improved following 20 min of visuomotor training, while map area was unaffected. Large individual differences were observed with 18%–36% of the participants revealing an increase in TMS map area. This result highlights the complex relationship between motor learning and use-dependent plasticity of the motor cortex.

Keywords: handedness, motor learning, motor mapping, plasticity, TMS

Introduction

Learning or relearning a motor skill has been linked with use-dependent plasticity in the human motor system (Butefisch et al., 2000; Plautz, Milliken, & Nudo, 2000; Sanes & Donoghue, 2000). Use-dependent plasticity can be explored by assessing changes in excitability of the corticospinal pathway, considered a marker of plasticity (Siebner & Rothwell, 2003). Transcranial magnetic stimulation (TMS) is often used to study changes in corticospinal excitability (CSE), e.g., by quantifying the peak-to-peak amplitude of the motor-evoked potential (MEP) elicited when stimulating the primary motor cortex (Barker, Jalinous, & Freeston, 1985; Rossini et al., 2015). Whereas early studies suggested a strong link between increases in CSE and improved motor performance following motor learning (Jensen, Marstrand, & Nielsen, 2005; Muellbacher, Ziemann, Boroojerdi, Cohen, & Hallett, 2001), more recently this relationship has been challenged and labelled as considerably variable across participants (Bologna et al., 2015; Vallence, Kurylowicz, & Ridding, 2013).

Variability in changes of MEP amplitude following motor learning may explain the equivocal results in the literature regarding changes in excitability following motor learning with (1) the dominant vs. the nondominant hand or (2) a proximal muscle vs. a distal muscle of the arm. The greatest changes in MEP amplitude following motor learning have been suggested for the dominant hand by some (Hammond & Vallence, 2006), but nondominant hand by others (Cirillo, Rogasch, & Semmler, 2010). Other researchers reported no difference in MEP facilitation between hands (Gallasch, Christova, Krenn, Kossev, & Rafolt, 2009; Garry, Kamen, & Nordstrom, 2004). Moreover, these studies have not found a consistent relationship between changes in motor performance and MEP amplitude. When comparing motor learning of a proximal and distal muscle, Krutky and Perreault (2007) reported a progressively smaller increase in MEP amplitude for a proximal wrist and upper arm muscle compared with a distal hand muscle. Yet, equivalent changes in TMS-evoked movement direction of the index finger, wrist, and elbow following training were observed. They reported small MEP changes following training the biceps muscle, which confirm findings by Ziemann, Muellbacher, Hallett, and Cohen (2001) who were first to report little to no change in MEP amplitude following training. In contrast, Jensen, Marstrand, and Nielsen (2005) reported a significant increase in biceps MEP amplitude following a visuomotor tracking learning.

These contradicting results raise questions about variability in use-dependent plasticity across different muscles in both the dominant and nondominant arm. The expression of changes in excitability has many determinants (Ridding & Ziemann, 2010), (e.g., age, attention, genetics, sex, time of the day, physical activity, and prior voluntary muscle activity) and is therefore variable across participants as some factors are difficult to control. To capture some of this variability, a recent trend has been to categorize participants as either responders or nonresponders to the training. Those participants for whom MEP amplitude increases are grouped together and categorized as responders, whereas those participants for whom MEP amplitude does not change or decreases are categorized as nonresponders (e.g.,

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Wiethoff, Hamada, & Rothwell, 2014). It is possible that a discrepancy in the number of responders and nonresponders is a major contributor to the conflicting results regarding changes in CSE and motor performance following learning with the dominant and nondominant hand or for different muscles in the arm.

Therefore, this study was designed to investigate use-dependent plasticity following a visuomotor tracking learning task with the dominant and nondominant hand; or distal vs. proximal muscle. We aimed to quantify the number of responders and nonresponders with regard to changes in CSE across all trained muscles. Changes in CSE are assessed using a novel TMS mapping technique (van de Ruit, Perenboom, & Grey, 2015), rather than averaging a set of single MEPs to quantify CSE by mean MEP amplitude. TMS maps allow one to draw the same conclusions as the more commonly used stimulus-response curve (Ridding & Rothwell, 1997), while providing the additional ability to expose uneven expansions of the cortical map or changes in the distribution of excitability which can otherwise not be detected. This study comprises two experiments. In the first experiment, the number of responders and nonresponders were studied by comparing learning with the dominant and nondominant hand, as quantified by changes in TMS map area. In the second experiment, the number of responders and nonresponders were studied by comparing learning with a proximal and distal muscle, as quantified by changes in TMS map area. Furthermore, in both studies we tested whether changes in TMS map area were related to changes in performance.

Methods

Participants

We conducted two experiments involving 40 healthy participants (Experiment 1: 20 participants—22 $\pm$ 3 y, range 18–29, 12 female; Experiment 2: 20 participants—22 $\pm$ 5 y, range 18–37, 13 female). The samples were independent, with different participants taking part in each experiment. All participants provided written informed consent before participating in the study. Participants were screened for contraindications to TMS using a modified version of the TMS adult safety questionnaire originally suggested by Keel, Smith, and Wassermann (2001), and handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the University of Birmingham's Science, Technology, Engineering and Mathematics ethics committee (ERN_11-0444), and all experiments were performed in accordance with the Declaration of Helsinki.

Electromyography

Bipolar surface electrodes (Blue Sensor N, Ambu, Denmark) were used to record the electromyographic (EMG) activity of the first dorsal interosseous (FDI) or biceps brachii (BB) with only one muscle recorded for each experimental session. All EMG signals were amplified (FDI: 1k; BB: 2k), band pass filtered (20–1000 Hz), and digitally sampled at 5 kHz to be stored for offline analysis.

Transcranial Magnetic Stimulation (TMS)

A custom-made polyurethane coated 90 mm figure-of-8 coil (type: batwing; type no. 15411) was used to deliver magnetic stimuli to the primary motor cortex using a Magstim Rapid^2 (Magstim Ltd, Dyfed, United Kingdom). The coil was held at 45° to the sagittal plane, with the handle in the posterior direction, to induce biphasic currents in the lateral-posterior to medial-anterior direction. The site evoking the largest MEPs, the "hotspot", was found by visual inspection of the EMG. Subsequently, resting motor threshold (RMT) was determined as the threshold intensity at which at least 5 out of 10 stimuli evoked MEPs when stimulating at the hotspot with a peak-to-peak amplitude $> 50\ \mu$V (Rossini et al., 1994). Coil position and orientation were monitored throughout the experiment using frameless stereotaxy (BrainSight 2, Rogue Research Inc, Montreal, Canada).

TMS Mapping

CSE was assessed using TMS maps acquired with a novel rapid mapping procedure that takes advantage of frameless stereotaxy together with a reduced interstimulus interval (van de Ruit, Perenboom, & Grey, 2015). After finding the motor hotspot and motor threshold of the muscle studied, a square 6 $\times$ 6 cm grid was positioned over the hemisphere studied. The grid was aligned such that the motor hotspot would be roughly central in the map to ensure full mapping of the cortical representation was possible. For each TMS map, 80 stimuli were delivered at 120% of RMT. Stimuli were applied at pseudorandom locations within the grid with each site receiving a single stimulus. It was ensured that each stimulus was delivered at a different location. The interstimuls interval (ISI) was set to 1.5 s as this frequency of stimulus delivery together with the small number of stimuli required for the protocol does not depress cortical excitability (Mathias, Barsi, van de Ruit, & Grey, 2014) as has been shown with longer protocols. To compare across different participants, MEPs were normalized before the maps were constructed (see Experimental Protocol for details).

Experimental Protocol

Experiment 1: Dominant vs. Nondominant Hand Training

In the first experiment, we compared the number of responders and nonresponders, quantified by changes in TMS map area, following visuomotor tracking learning for both the dominant and nondominant hands. Participants visited the lab twice, during which visuomotor tracking learning

was performed with either the FDI muscle of the dominant or nondominant hand. Sessions were separated by at least 7 days but performed at the same time of the day. The order in which training was performed with dominant and nondominant hand was counterbalanced across participants. Three TMS maps were acquired before and after the visuomotor tracking learning task. MEPs were normalized to the electrically evoked maximal M-wave (M_{max}) in order to compare across different participants. To obtain the M_{max}, a bipolar probe was used to stimulate the ulnar nerve at the level of the elbow using a constant current stimulator (Digitimer DS7A, Digitimer Ltd, Welwyn Garden City, UK).

The visuomotor tracking learning task used in this study is based on a method successfully applied by others (Jensen, Marstrand, & Nielsen, 2005; Perez, Lungholt, Nyborg, & Nielsen, 2004). Figure 1 shows the experimental setup for Experiment 1. Participants were seated comfortably, with a monitor in their direct line of sight. Participants were asked to rest the hand that was tested palm down on a table 20 cm in front of them. The distal phalanx of the index finger was lined up with a force transducer (NL 62–50 kg, Digitimer Ltd, Welwyn Garden City, UK). To ensure an isolated contraction of the FDI muscle, the wrist and other finger were immobilized using Velcro straps. The measured force exerted by FDI contraction (measured by the force transducer) was displayed as a circular cursor on the computer screen. The cursor moved automatically from the left to the right. Participants were able to control the movement of the cursor by activating and relaxing the FDI muscle. When contracting the FDI muscle the cursor moved to the top of the screen, while when relaxing the cursor moved to the bottom of the screen (based on design of Perez, Lungholt, Nyborg, & Nielsen, 2004). The force signal was high pass filtered by 30 Hz, amplified by 500–2 k and sampled at 4 kHz to be stored for offline analysis.

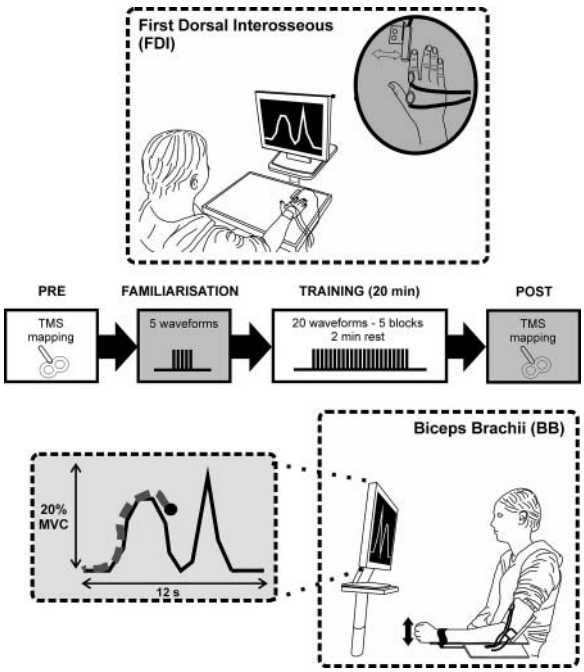

FIGURE 1. Experimental protocol and setup during the visuomotor tracking learning task. Participants were seated with a monitor in direct line of sight on which the waveforms were presented. The task was performed by either activating or relaxing the first dorsal interosseous muscle (FDI) (top panel) or biceps brachii (BB) muscle (bottom right panel). Training was performed for a total of 20 min (five blocks of 4 min) with 2 min rest between each block. TMS was used to probe changes in excitability using TMS mapping of the FDI or BB muscle before and after training.

Participants were presented with five different waveforms to familiarize them with the task. Each waveform was 12 s long, including a 1 s rest period at the start and end. The waveforms were scaled between 0% and 20% of the participants maximal voluntary contraction (MVC), determined before the start of the learning task. The familiarization period was followed by five training blocks consisting of 20 waveforms, making each training block take 4 min. After each training block, participants were allowed a 2-min break to minimize the possibility of muscle fatigue. The same waveforms were presented in each training block, although the order of presentation was randomized. Visual feedback of the absolute tracking error was provided after each waveform. The online feedback on performance served to keep participants motivated, to reduce their tracking error and to stabilize their attention.

Experiment 2: Distal vs. Proximal Muscle Training

In the second experiment, we compared variability in changes in TMS map area following visuomotor tracking learning for a proximal and distal muscle of the dominant arm. The setup and experiment were identical to that for the previous experiment except with visuomotor tracking performed with either the BB or FDI muscle of the dominant arm. Again, the order in which training was performed with proximal and distal muscle was counterbalanced across participants. As finding M_{max} in the proximal BB muscle was found too uncomfortable for the participants, MEPs for this experiment were normalized to the mean maximal MEP (MEP_{max}) amplitude in response to 10 stimuli at maximal stimulator output over the motor hotspot.

When visuomotor tracking learning performance of the BB muscle was tested, participants rested the dominant arm in a rig that held the arm with the elbow at approximately 120° and adjusted to a height that would prevent strain in the shoulder and neck (Figure 1: bottom). The arm was immobilized by a Velcro strap at the level of the wrist and just below the elbow. Participants were instructed to always keep the hand midway between pronation and supination with the thumb up. A torsion bar attached to the Velcro strap was used to record the forces exerted by a biceps contraction. During the learning task, participants repetitively

activated the BB muscle to track the presented waveforms. When training with the distal FDI muscle, the same procedures as in Experiment 1 were followed.

Data Analysis

Visuomotor Tracking Performance

Tracking performance was quantified by the root mean square (RMS) error between the target waveform and the tracked path. The effect of the training was examined by comparing the mean RMS error over all training blocks. A lower RMS would be indicative for increased performance and a decreased tracking error with respect to the target waveform.

TMS Maps

To create the TMS map, data were analyzed offline with a bespoke MATLAB script (MATLAB Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States). All stimuli positions were projected in a 2D plane. Accordingly, each position was matched with its corresponding MEP peak-to-peak (MEP_{pp}) value extracted from the EMG 20–50 ms after stimulation. All EMG recordings with a background EMG over 30 μV (peak-to-peak) in a window from 5 to 50 ms before stimulation were excluded.

Maps were quantified by the map area and center of gravity (COG). MEP_{pp} values were used to approximate a 6 × 6 cm grid composed of 2500 pixels using MATLAB's "gridfit" function (D'Errico, 2005). The number of pixels with an approximated MEP_{pp} amplitude greater than 10% of the maximum MEP_{pp} value (Uy, Ridding, & Miles, 2002) was calculated and expressed as total map area (in mm^2). If the 10% threshold was smaller than 100 μV peak-to-peak, 100 μV was taken as the threshold for calculating the area. The *x*- and *y*-coordinate of the COG was calculated from the MEP_{pp} amplitude and its position on the map, thus creating an amplitude weighted mean of the map. Full details of this process are described in van de Ruit, Perenboom, and Grey (2015).

To quantify changes in the position of the COG, the *x* and *y* components of the translation in COG were calculated by taking the difference in *x* and *y* position of the COG before and after the visuomotor tracking learning task (Δx and Δy). In this way a negative value would indicate a shift in anterior (x) or lateral (y) direction and a positive value a shift posteriorly (x) or medially (y).

The absolute displacement was calculated by taking the Euclidian distance (ED) between COG of the median TMS map before and after learning:

$$ED = \sqrt{\left(yCOG_{pre} - yCOG_{post}\right)^2 + \left(xCOG_{pre} - xCOG_{post}\right)^2}.$$

Statistical Analysis

Statistical testing was conducted with IBM SPSS Statistics 21. Tests were considered significant at $\alpha = 0.05$. The data were tested for normality (Shapiro-Wilk test), sphericity (Machly's test), and examined for significant outliers. When the assumption of covariance matrix circularity was violated a Geisser–Greenhouse adjustment was made (denoted by GG following the F test). Data are reported as mean ± 1 *SD* unless otherwise noted.

Learning

To examine visuomotor tracking learning performance during the training a three-way repeated measures analysis of variance (3w-rmANOVA) was used with factors MUSCLE (*left, right*) × BLOCK (*block 1–5*) × WAVEFORM (*Waveform 1–20*). This statistical analysis was performed on the tracking performance data (i.e. RMS errors). The factor WAVEFORM was included to test for heterogeneity in the difficulty of the waveforms.

TMS Maps

To assess learning induced changes in CSE the effect of learning on the TMS map area was studied. First, the map with the median map area of the three maps acquired before and after learning was selected. In case only two baseline measures were considered, for example, when data were missing for one map, the map with the lowest mean background EMG was used. Subsequently, the difference in map area between the pre- and postmeasurement was taken ($\Delta\text{area} = \text{area}_{POST} - \text{area}_{PRE}$). A negative Δarea would thereby indicate a decrease in map area, a positive Δarea an increase. The Δarea data were then tested for statistical significance with respect to the fixed value of 0 using a one sample t-test. A paired t-test was used to study any differences in learning induced changes in map area between the two muscles used in each experiment. The same analysis was performed for the translation of the COG (Δx and Δy).

To quantify the response rate to visuomotor tracking learning three groups of responders were defined. Baseline variance was calculated by calculating the difference of the median map with respect to the two other maps collected before training commenced. The standard deviation of the baseline variance of all participants was used to classify participants as either positive responders, nonresponders or negative responders. Participants were classified as positive responders if Δarea of the median map before and after learning > 1 *SD* of the baseline variance in map area. In contrast, negative responders were classed as participants with a decreased map area < –1 *SD* of baseline map variance. All other participants were classified as nonresponders.

Relationship between Motor Learning and Changes in Corticospinal Excitability

A linear regression was performed on the tracking performance data and changes in map area to determine if a greater improvement in tracking performance could predict the change in map area. To quantify the improvement in tracking performance the percentage improvement between different blocks was calculated. Based on the improvements in tracking performance over training blocks linear regression was performed between the improvement from block 1 to block 3, the early learning phase, and block 3 to block 5, the late learning stage, separately with the change in map area. Finally, the Pearson correlation was used to determine if there was any association between the changes in map area (Δarea) in the dominant vs. nondominant hand (Experiment 1) or the proximal vs. distal muscle (Experiment 2).

RESULTS

All participants that completed the study tolerated TMS well and none of the participants reported any muscle fatigue following visuomotor tracking learning. The data were normally distributed and had no significant outliers.

Experiment 1: Dominant vs. Nondominant Hand

In total 19 of the 20 recruited participants completed both sessions of the experiment. One participant did not attend the second experimental session and was removed from the study.

Visuomotor Tracking Learning

For analysis of the visuomotor tracking learning data, 17 of the 19 available data sets were included. Two data sets were omitted from processing due to errors with the force recordings.

All participants successfully completed 20 min of visuomotor tracking learning. Figure 2A displays tracking performance in the first and last block of training with the dominant hand for one single waveform. Here, tracking has become much more controlled following learning. Overall, a progressive decrease in tracking error over the five blocks for both the dominant and nondominant hand was found (Figure 2B). This was confirmed by the three-way repeated measures ANOVA (within factors: MUSCLE, BLOCK, and WAVEFORM), that showed a significant effect for BLOCK ($p = 0.03$). Bonferroni post hoc testing indicated significant differences between block 1 and 2 and block 1 and 3, but not any of the other blocks. Moreover, a significant main effect for WAVEFORM ($p < 0.01$) and BLOCK × WAVEFORM interaction was found ($p < 0.01$), indicating there was a different learning rate for the different waveforms, some being more difficult than others.

TMS Mapping

Analysis of the TMS map data was performed on 17 participants. Two data sets had to be discarded as a result of measurement noise in the MEP recordings, these data were not from the same two participants excluded for the visuomotor task. The maps included in the analysis for all sessions were constructed out of 66 ± 12 stimuli.

No significant difference was observed in RMT between the dominant (50% ± 7% MSO) and nondominant (49% ± 7% MSO) hand ($t(16) = 0.75$, $p = 0.47$). The standard deviation of the Δarea in the baseline recordings (with respect to the median map) was 343 mm^2 for the dominant hand and 330 mm^2 for the nondominant hand. Based on 1

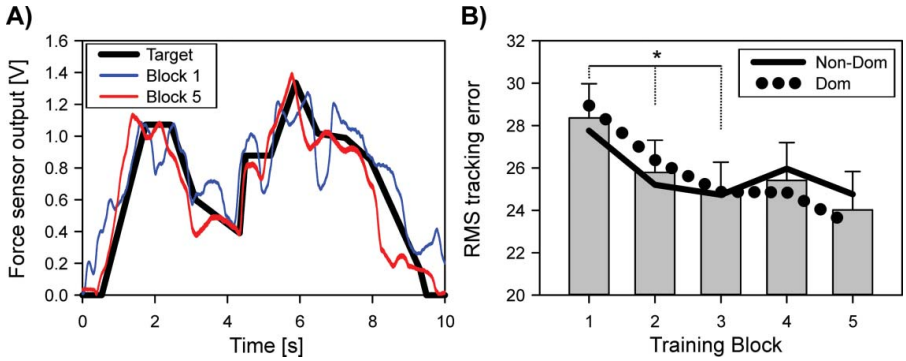

FIGURE 2. Effect of training a visuomotor tracking learning task with the FDI muscle of either the dominant and nondominant hand on tracking performance. (A) Example of a single waveform for which tracking performance improved from the first block (blue line) to last block (red line) with respect to the target waveform (black line). (B) Overall, tracking performance improved over the five training blocks (shaded bars), for either the dominant (solid line) or nondominant index finger (dotted line). Tracking performance significantly improved with training (*$p < 0.05$) from block 1 to 3, after which performance stabilized.

SD of the baseline Δarea, a positive responder was defined as Δarea > 343 mm^2 (dominant) or > 330 mm^2 (nondominant), negative responder if Δarea < –343 mm^2 (dominant) or < −330 mm^2 (nondominant) and else a nonresponder.

Figure 3 shows TMS maps before and after training for the dominant and nondominant hand. In this example, the map area increased for the dominant hand whereas there is no change in map area for the nondominant hand.

The maps provided are representative for the results, with some participants exhibiting an increase in map area following learning, for some participants map area remained the same and in others it decreased. The mixed response was accentuated by a nonsignificant effect for both the dominant and nondominant hand when comparing the difference in map area before and after training to 0 using a student t-test (dominant: $t(16) = 0.84$, $p = 0.41$; nondominant: $t(16) = 0.21$, $p = 0.84$) (Figure 4A). Moreover, a paired t-test indicated no difference in the response size between the two hands ($t(16) = 0.64$, $p = 0.54$). Classifying responders and nonresponders based on map area revealed six positive responders, nine nonresponders and two negative responders after training with the dominant hand. Three positive responders, eleven nonresponders and three negative responders were found following training with the nondominant hand.

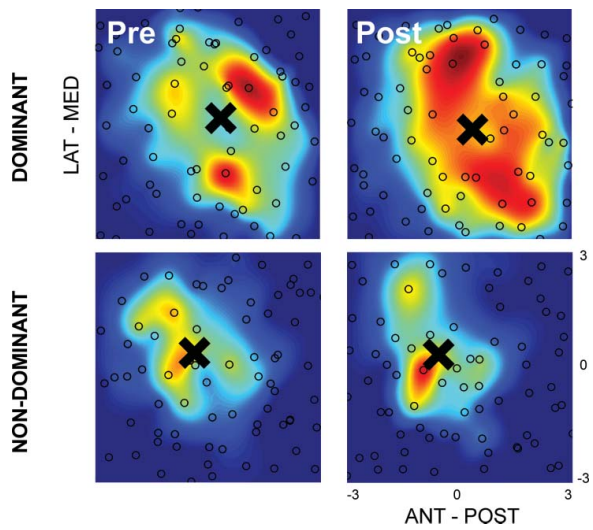

FIGURE 3. Individual examples of TMS maps before and after learning for both the dominant (top row) and nondominant hand (bottom row). In this case, the top row represents a positive responder (increase in map area), while the bottom row represents a nonresponder following the visuomotor tracking learning task. All black open circles represent one stimulation and the black cross (×) highlights the COG. Red indicates the biggest MEPs, in contrast to small or no MEPs which are indicated by blue.

Similarly no significant displacement of the COG was found for either the *x*- or *y*-coordinate in both hands (dominant—Δ*x*: $t(16) = 0.62$, $p = 0.54$; Δ*y*: $t(16) = 0.91$, $p = 0.38$; nondominant—Δ*x*: $t(16) = 0.50$, $p = 0.62$; Δ*y*: $t(16) = 1.63$, $p = 0.12$) (Figure 4B). The COG displacement following learning was for the dominant hand 5.5 ± 2.5 mm and the nondominant hand 5.6 ± 2.7 mm.

Relationship between Learning and Change in Map Area

As there was no significant improvement in performance during the training after block 3, the training data were split up by analyzing the improvement from block 1 to 3 and 3 to 5 separately (early and late learning). The relationship between the improvement in tracking performance and the change in map area was assessed using a linear regression (Figure 5A). For block 1–3 and both hands, improvement in tracking performance and change in MEP area tended to be positively correlated (dominant: $r = 0.09$; nondominant: $r = 0.20$); however, these regressions were nonsignificant (dominant: $p = 0.76$; nondominant: $p = 0.47$). In addition, the regression analysis for both hand and block 3–5 revealed no significance for either the dominant ($r = 0.03$, $p = 0.93$) or nondominant hand ($r = 0.41$, $p = 0.13$). Moreover, there was no association between changes in map area of the dominant and nondominant hand (Pearson correlation: $r = 0.31$, $p = 0.23$) (Figure 5B).

Experiment 2: Distal vs. Proximal Muscle

All 20 participants completed both sessions of the experiment.

Visuomotor Tracking Learning

For analysis of the visuomotor tracking learning data all data sets were included. All participants successfully completed the 20-min visuomotor tracking learning task. Figure 6A displays tracking performance in the first and last block of training for one single waveform when training with the BB, illustrating that tracking has become more accurate following learning. Overall, a progressive decrease in tracking error over the five blocks for both the distal and proximal muscle was found (Figure 6B). This was confirmed by the three-way repeated measures ANOVA (within factors: MUSCLE, BLOCK, and WAVEFORM), that showed a significant effect for BLOCK ($p = 0.04$). Bonferroni post hoc testing indicated significant differences between block 1 and 2 and block 1 and 3, but not any of the other blocks. Moreover, a significant main effect for WAVEFORM was found ($p < 0.01$), indicating some waveforms were more difficult than others.

TMS Mapping

Analysis of the TMS map data was performed on 17 participants. Two data sets had to be discarded as a result of

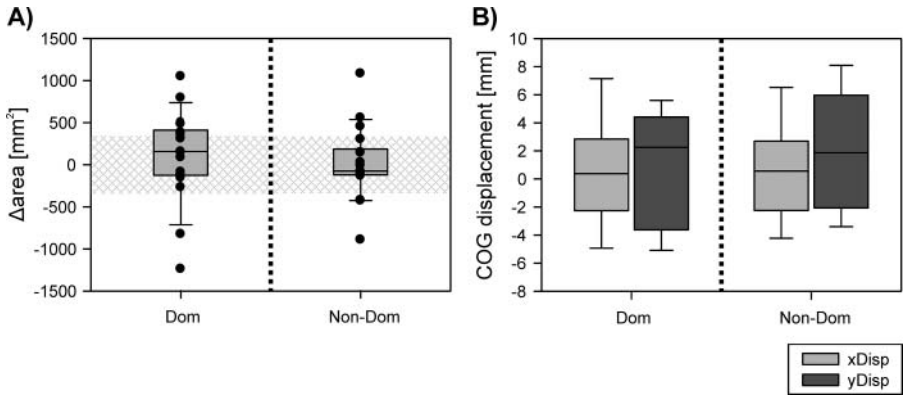

FIGURE 4. Effect of training a visuomotor tracking learning task with the FDI muscle of either the dominant or nondominant hand on TMS map area and COG. (A) Change in map area ($\Delta\text{area} = \text{area}_{POST} - \text{area}_{PRE}$) was not significantly different from 0 for either hand; however, there are great interindividual differences with some participants showing an increase, decrease, or no change in map area (black dots). Based on baseline variability of the map area, all participants with a change in map area within the range as marked by the shaded rectangle in the background were classified as nonresponders. (B) No change was found for either the displacement of the *x*- or *y*-coordinate of the COG for any hand.

technical difficulties. The maps included in the analysis for all sessions were constructed out of 73 ± 4 stimuli. MEP_{max}, used to normalize the MEPs, was on average 4.2 ± 2.3 mV (range: 1.5–9.8 mV) for FDI and 0.8 ± 0.7 mV (range: 0.1–1.7 mV) for BB.

There was a significantly higher RMT for the proximal (57% ± 10% MSO) compared with distal (44% ± 7% MSO) muscle ($t(16) = 4.8$, $p < 0.01$). The *SD* of the Δarea in the baseline recordings (with respect to the median map) was 239 mm^2 for the proximal muscle and 254 mm^2 for the distal muscle. Therefore, a participant was defined as a positive responder if Δarea $> 239\ mm^2$ (proximal) or $> 254\ mm^2$ (distal), negative responder if Δarea $< -239\ mm^2$ (proximal) or $< -254\ mm^2$ (distal) and else a nonresponder.

Figure 7 shows TMS maps before and after training for both muscles. In this example, the map area decreased for the distal muscle whereas an increase in map area for the proximal muscle is present.

The maps provided are representative for the results, with some participants exhibiting an increase in map area following learning, in some participants map area remained the same while in others it decreased. The mixed response was accentuated by a nonsignificant effect for both the proximal and distal muscles when comparing the difference in map area before and after training to 0 using a student t-test (distal: $t(16) = 1.04$, $p = 0.32$; proximal: $t(16) = 0.74$, $p = 0.47$) (Figure 8A).

Moreover, a paired t-test indicated no difference in the response size between the two muscles ($t(16) = -0.27$, $p = 0.79$). Classifying responders and nonresponders based on map area revealed six positive responders, eight nonresponders and three negative responders after training with the distal muscle. Five positive responders, seven nonresponders and five negative responders were found following training with the proximal muscle.

No significant displacement of the COG was found for the *x*-coordinate in the distal muscle and *x*-coordinate of the proximal muscle (distal—Δx: $t(16) = 0.20$, $p = 0.84$; Δy: $t(16) = -1.04$, $p = 0.31$; proximal—$t(16) = 0.14$, $p = 0.89$). However, a significant displacement in the COGs *y*-coordinate was found for the proximal muscle ($t(16) = 2.44$, $p = 0.03$) (Figure 8B). The COG displacement following learning was for the distal muscle was 4.1 ± 3.0 mm and the proximal muscle 3.8 ± 2.3 mm.

Relationship between Learning and Change in Map Area

As there was no significant improvement in performance during the training after block 3 the training data was split up by analyzing the improvement from block 1 to 3 and 3 to 5 separately (early and late learning). The relationship between the improvement in tracking performance and the change in map area was assessed using a linear regression (Figure 9A). For both the proximal and distal muscles, there was a poor relationship between performance improvement in block 1–3 and change in map area. Therefore, both regressions were found not to be statistically significant (proximal: $r = 0.36$, $p = 0.19$; distal: $r = 0.08$, $p = 0.78$). In addition, the regression analysis for both hand and block 3–5 revealed no significance for either the proximal ($r = 0.04$, $p = 0.89$) or distal muscle ($r = 0.21$, $p = 0.47$). There was no association between changes in map area of the proximal and distal muscle (Pearson correlation: $r = -0.04$, $p = 0.89$) (Figure 9B).

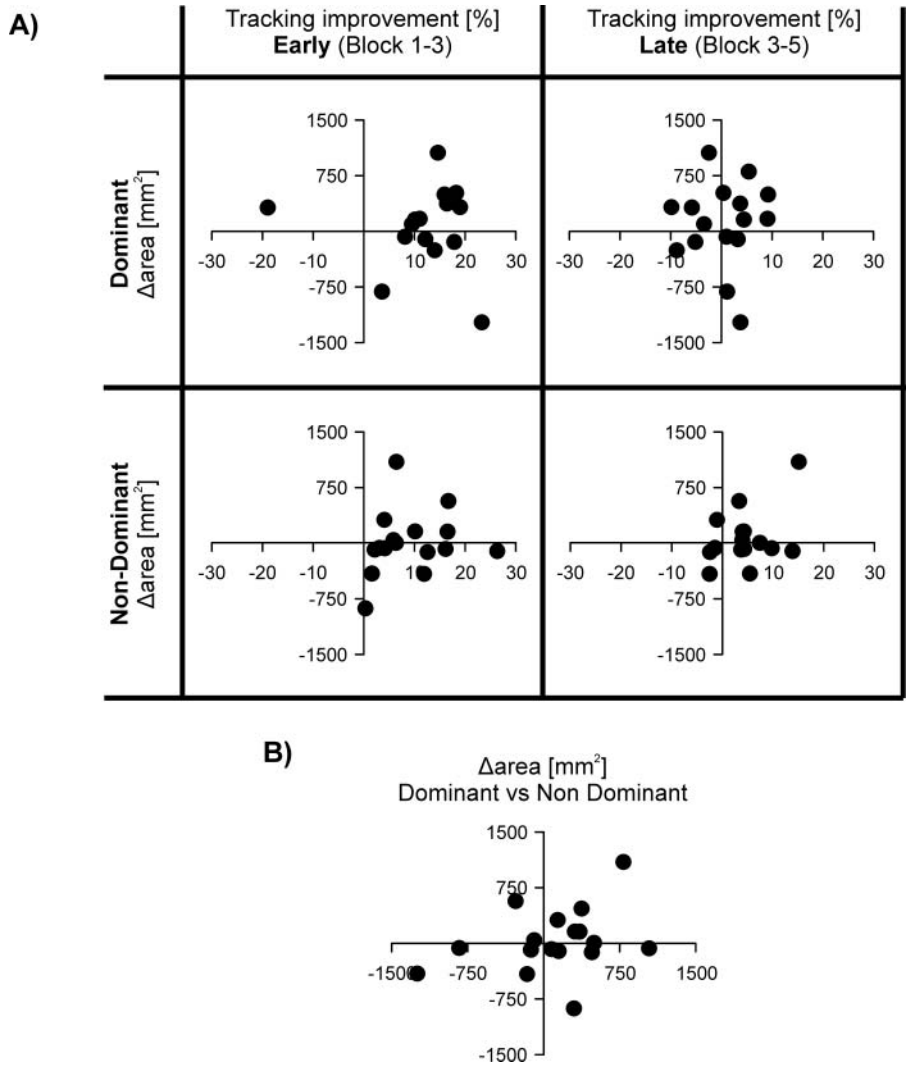

FIGURE 5. Results of the linear regression performed to investigate whether improvement in tracking performance could predict change in TMS map area. A correlation analysis was performed to find out if changes in map area of both hand are correlated. (A) Linear regressions were performed to see if the improvement in tracking error (expressed as % improvement) during either the early (block 1–3) or late (block 3–5) phase of training could predict change in map area, as overall performance was found to not improve significantly after block 3. The improvement in tracking error in either the early or late phase of motor learning could not predict change in map area for either the dominant or nondominant hand. (B) A correlation analysis revealed changes in map area for the dominant hand could not predict change in map area of the nondominant hand, or vice versa.

Discussion

This study investigated response variability in changes to CSE following a 20 min visuomotor tracking learning task performed either with the dominant or nondominant hand and with distal vs. proximal muscle in healthy participants. TMS mapping was used to explore changes in CSE, and the map area used to categorize participants as either responders or nonresponders. No significant group differences in map area were found between the dominant and nondominant hands or between proximal and distal muscles. This is in line with recent reports on response variability to various noninvasive brains stimulation protocols. Overall, only 18%–36% of the participants were classified as responders, revealing an increase in TMS map area following the visuomotor tracking learning task, despite all participants demonstrating a significant increase in tracking performance.

Response Variability

Anatomical and physiological differences between and within hemispheres (Hammond, 2002; Palmer & Ashby, 1992; Schambra et al., 2011; Serrien & Spape, 2009;

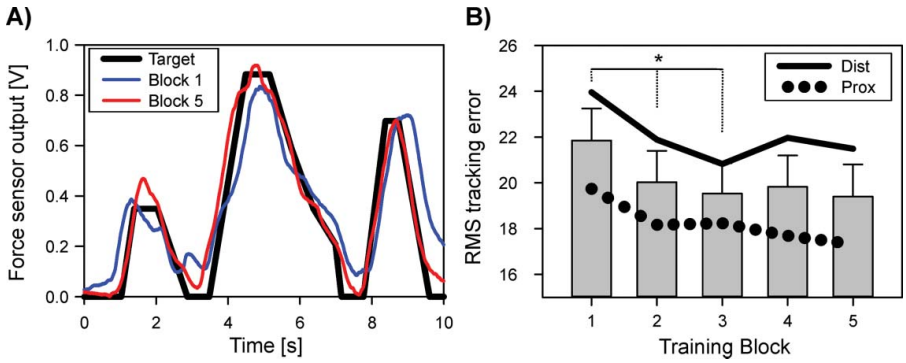

FIGURE 6. Effect of training a visuomotor tracking learning task with the distal FDI muscle or proximal BB muscle on tracking performance. (A) Example of a single waveform for which tracking performance improved from the first block (blue line) to last block (red line) with respect to the target waveform (black line). (B) Overall, tracking performance improved over the five training blocks (shaded bars), and for either the distal (solid line) or proximal muscle (dotted line). Tracking performance significantly improved with training ($*p < 0.05$) from block 1 to 3, after which performance stabilized.

Wassermann, Mcshane, Hallett, & Cohen, 1992) have been suggested to explain discrepancies in use-dependent plasticity when performing a motor learning task with either the dominant vs. nondominant hand or proximal vs. distal muscle (Cirillo, Rogasch, & Semmler, 2010; Krutky & Perreault, 2007). In this study, no significant changes in TMS map area following a challenging visuomotor tracking learning task were found for the dominant and nondominant hand using TMS mapping, despite an increase in visuomotor tracking performance for both. Nonetheless, a higher number of positive responders, participants with an increase in TMS map area, were found for the dominant hand (6) than the nondominant hand (3). Similarly, tracking performance improved significantly with no significant changes in TMS map area observed following learning with both the distal finger muscle (FDI) and proximal muscle (BB). An increased TMS map area was found for five participants when training the proximal muscle, and six participants when training the distal muscle.

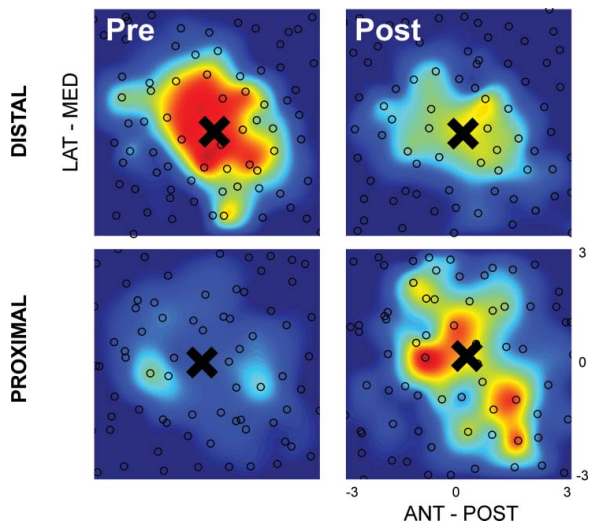

FIGURE 7. Individual examples of TMS maps before and after learning for both a distal muscle (top row) and a proximal muscle (bottom row). In this case, the top row represents a negative responder (decrease in map area), while the bottom row represents a positive responder following the visuomotor tracking learning task (increase in map area). All black open circles represent one stimulation and the black cross (×) highlights the COG. Red indicates big MEPs, in contrast to small MEPs which are indicated by blue.

There is ample evidence that not every participant will display similar responses to a noninvasive brain-stimulation protocol that aims to enhance or suppress CSE (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013; Lopez-Alonso, Cheeran, Rio-Rodriguez, & Fernandez-Del-Olmo, 2014; Muller-Dahlhaus, Orekhov, Liu, & Ziemann, 2008; Wiethoff, Hamada, & Rothwell, 2014). In fact, the predicted response only occurs for 1/3–2/3 of the healthy participants. Moreover, it was also recently shown that the response may not be consistent within participants across different testing sessions (Horvath, Vogrin, Carter, Cook, & Forte, 2016). This is not surprising given that, the response is mediated by numerous factors such as age, gender, attention, and history of synaptic activity (for review: Ridding & Ziemann, 2010). These factors likely also affect use-dependent plasticity, and yet very few motor learning studies report on interindividual variability. Only a study by Vallence, Kurylowicz, and Ridding (2013) demonstrates increased MEP amplitude in 75% of the participants following a ballistic thumb abduction task. Moreover, they did not observe associations between plasticity induced following motor learning or noninvasive brain stimulation protocols in the same participants. This signifies the importance

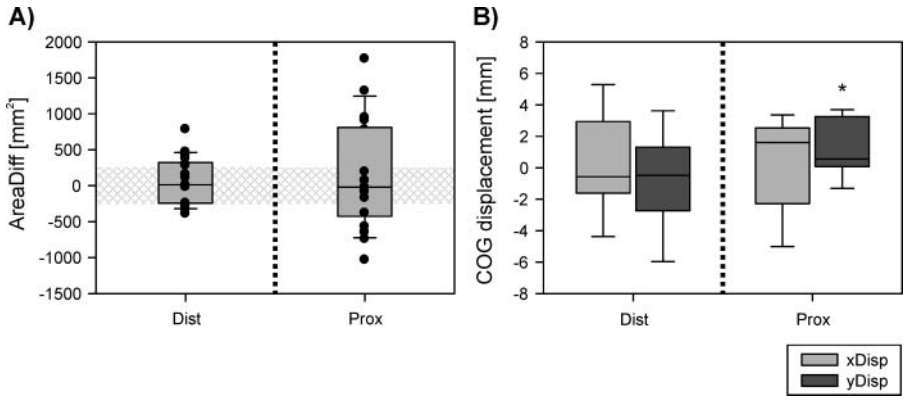

FIGURE 8. Effect of training a visuomotor tracking learning task with a distal (FDI) and proximal (BB) muscle on TMS map area and COG. (A) Change in map area (Δarea = area$_{POST}$ − area$_{PRE}$) was not significantly different from 0 for either muscle; however, there are great interindividual differences with some participants showing an increase, decrease, or no change in map area (black dots). Based on baseline variability of the map area, all participants with a change in map area within the range as marked by the shaded rectangle were classified as nonresponders. (B) No change was found in *x*-coordinate of the COG for any muscle, while a significant displacement of the *y*-coordinate for the proximal muscle was found but not the distal muscle.

of interindividual variability, as common mechanisms are thought to underlie both brain stimulation and use-dependent plasticity.

In this study, a homogenous group of young and active healthy participants (18–29 years) were recruited to the study and factors like attention en time of day tested were well controlled. The finding that despite these precautions to limit variability, fewer than 40% of the participants in the present study exhibited an increase in TMS map area following the visuomotor tracking learning task raises the question about the adequacy of training volume. Between 12 and 32 min of training has been performed (Jensen, Marstrand, & Nielsen, 2005; McAllister, Rothwell, & Ridding, 2011; Perez, Lungholt, Nyborg, & Nielsen, 2004; Willerslev-Olsen, Lundbye-Jensen, Petersen, & Nielsen, 2011) and linked with increases in MEP amplitude. In this study, training within a single session was limited to five blocks and a total of 20 min to prevent overlearning but allow us to quantify changes in TMS map area following the fast phase of learning (Floyer-Lea & Matthews, 2005; Luft & Buitrago, 2005). The significant improvement only up to block 3, matched the findings of Floyer-Lea and Matthews (2005) for single session learning but not those of Jensen, Marstrand, and Nielsen (2005), who reports continuous improvement over all blocks in the first training session. Our findings suggest there was no further improvement in performance after block 3, potentially as a result of a lack of focus or that the skill had been mastered. Overlearning was first reported by Muellbacher, Ziemann, Boroojerdi, Cohen, and Hallett (2001) who found that after an initial learning stage associated with rapid MEP facilitation, with further learning the MEP size returned to baseline. To ensure the great variety in changes in TMS map area following learning was not mediated by participants rate of learning a linear regression between the improvement in performance from block 3 to block 5 and the change in map area was performed. The regression was not significant, suggesting that improvement during the last training blocks could not predict the change in map area. However, with only this result and the fact that TMS map area was not measured after block 3 the possibility that overlearning has affected our results cannot be excluded.

An important additional factor mediating the effect of learning on changes in excitability is if the visuomotor tracking learning task sufficiently engages the primary motor cortex. Compared with a ballistic motor task, which involves primarily feedforward control, feedback control plays a critical role in a visuomotor tracking learning task. Baraduc, Lang, Rothwell, and Wolpert (2004) demonstrated that 1 Hz rTMS applied to the motor cortex can disrupt ballistic learning, but it does not disrupt learning of novel dynamics imposed by a force field, suggesting that the motor cortex is essential in ballistic learning, but it might be less engaged in more complex tasks. Evidence for widely distributed cortical activity during visuomotor tracking learning was also provided by Floyer-Lea and Matthews (2004). They reported learning associated changes in brain activity in prefrontal areas, supplementary- and premotor area, parietal areas, cerebellum and basal ganglia (Catalan, Honda, Weeks, Cohen, & Hallett, 1998; Hardwick, Rottschy, Miall, & Eickhoff, 2013; Mitz, Godschalk, & Wise, 1991; Wise, Moody, Blomstrom, & Mitz, 1998). In conclusion, in more complex learning tasks, learning-induced plasticity might rely more on other areas of the cortical network than the primary motor cortex, which we are unable to detect using TMS.

One may question whether the TMS mapping method applied in this study has affected the response rate. Few studies have used TMS mapping to explore changes in excitability following motor learning. The classic motor

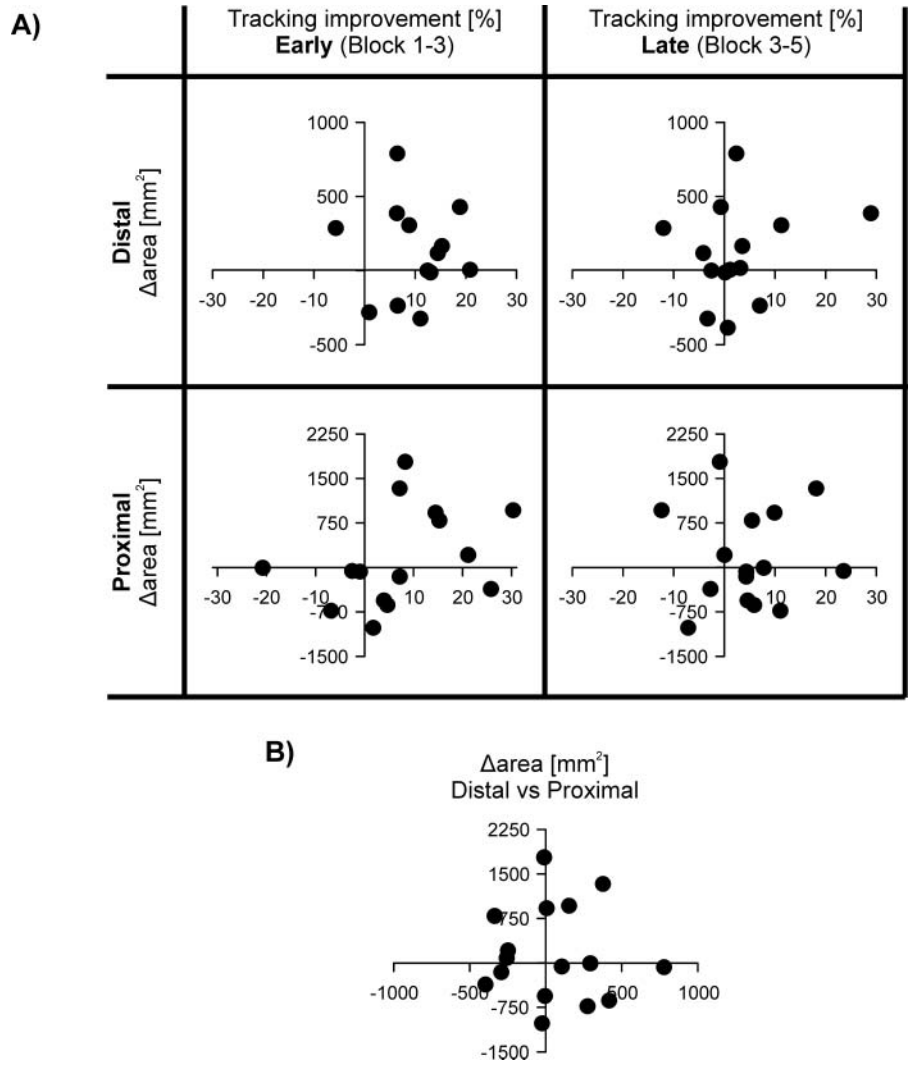

FIGURE 9. Results of the linear regression performed to investigate whether improvement in tracking performance could predict change in TMS map area. A correlation analysis was performed to find out if changes in map area of the proximal and distal muscle are correlated. (A) Linear regressions were performed to see if the improvement in tracking error (expressed as % improvement) during either the early (block 1–3) or late (block 3–5) phase of training could predict change in map area, as overall performance was found to not improve significantly after block 3. The improvement in tracking error in either the early or late phase of motor learning could not predict change in map area for either the dominant or nondominant hand. (B) A correlation analysis revealed change in map area for the dominant hand could not predict change in map area of the nondominant hand, or vice versa.

learning paper by Pascual-Leone et al. (1995) was the first to demonstrate increases in TMS map area following learning a complex motor task. The complexity and time consuming nature of the traditional mapping method reduces its sensitivity to detect changes in CSE. The used mapping method in this study allows obtaining all data within the same time window as during which, routinely, 20–30 MEPs are acquired to quantify CSE using the mean MEP amplitude. The cortical representation that the TMS map area reflects is affected by current spread of the magnetic stimulus (Thickbroom, Sammut, & Mastaglia, 1998). Thus, if cortical excitability is increased locally near the motor hotspot, reflected as an increase in MEP amplitude, this should also be detected in the TMS map as stimuli further away from the motor hotspot will also exceed stimulation threshold. At present, there is no reason to assume TMS mapping would provide different results than just using the mean MEP amplitude at the motor hotspot.

Mono- and biphasic TMS pulses result in different patterns of descending motor output (Di Lazzaro et al., 2001) and very recently this has been suggested to affect the TMS map (Stephani, Paulus, & Sommer, 2016). The use of novel controllable TMS stimulators have revealed that not only pulse waveform but also current direction and pulse duration determine the specific interneuronal circuitry activated (D'Ostilio et al., 2016; Goetz et al., 2016; Hannah &

Rothwell, 2017). This may affect both the neuroplastic response when TMS is employed to induce plasticity (Hannah, Rocchi, Tremblay, & Rothwell, 2016) and the specific circuitry assessed when TMS is used to probe changes in excitability (Sommer et al., 2006). Therefore, a limitation of our study results is that TMS mapping using monophasic TMS pulses with any current direction may reveal a different response rate than we have observed with the biphasic Magstim Rapid^2 TMS stimulator used in the present study.

Differences in Use-Dependent Plasticity across Muscles

The finding of no difference in change in TMS map area following learning with the dominant or nondominant hand is in line with the findings of Gallasch, Christova, Krenn, Kossev, and Rafolt (2009); Garry, Kamen, and Nordstrom (2004). They reported no difference in MEP amplitude following learning, suggesting similar capacity for use-dependent plasticity for both hemispheres. Both studies reported significant changes in performance for both hands following motor learning of a complex tasks (goal-directed movement task or Purdue pegboard task) (Gallasch, Christova, Krenn, Kossev, & Rafolt, 2009; Garry, Kamen, & Nordstrom, 2004). However, not all studies that compared use-dependent plasticity for the dominant and nondominant hand have come to a similar conclusion. Studies where a ballistic motor learning task was employed have produced much less clear results. While Cirillo, Rogasch, and Semmler (2010) found a greater improvement in thumb peak acceleration for the dominant hand, Ridding and Flavel (2006) report a larger improvement for the nondominant hand. These hemispheric differences in learning have been linked to a larger increase in MEP size in the nondominant hemisphere (Cirillo, Rogasch, & Semmler, 2010) or no difference in MEP changes when induced by paired associative stimulation (Ridding & Flavel, 2006). In another study, training a ballistic pinch movement led to similar behavioral gains but greater MEP changes for the dominant motor cortex (Hammond & Vallence, 2006). Different results may be explained by the discrepancy in learning task, being a simple ballistic motor task vs. complex goal-directed or visuomotor tracking learning task. Indeed, task complexity is linked with increased cortical activity (Datta, Harrison, & Stephens, 1989) for complex motor tasks. It may be concluded that is there is an asymmetry in use-dependent plasticity, this only holds for simple learning tasks.

Previous research has also suggested that the capacity of proximal and distal muscles to undergo use-dependent plasticity may be due to differences in task complexity. However, the present study does not support this view. Krutky and Perreault (2007) reported minimal change in peak acceleration following a ballistic motor learning task with the upper arm while Ziemann, Muellbacher, Hallett, and Cohen (2001) observed no change in performance at all. In both studies this was accompanied with minimal changes in MEP amplitude. In contrast, significant long-lasting changes in peak acceleration, movement direction, and MEP amplitude have been reported for the same task when the FDI muscle was tested (Krutky & Perreault, 2007; Muellbacher, Ziemann, Boroojerdi, Cohen, & Hallett, 2001). Krutky and Perreault (2007) explain their findings by evidence that proximal muscles have a smaller cortical representation and less monosynaptic connections than distal muscles (Palmer & Ashby, 1992; Penfield & Boldrey, 1937; Wassermann, Mcshane, Hallett, & Cohen, 1992). Whereas this might suggest there is minimal change in motor performance in proximal muscles compared with distal muscles following similar training, this is not supported by findings that significant improvement in motor performance occur in a force-field adaptation task (Shadmehr & Mussa-Ivaldi, 1994) and a similar visuomotor tracking learning task as performed here (Jensen, Marstrand, & Nielsen, 2005). The latter study also reported significant changes in MEP amplitude. Although difference in use-dependent plasticity between proximal and distal muscles may exist, this may only be important when training simple ballistic motor learning tasks.

Conclusion

This study highlighted variability of use-dependent plasticity for learning a visuomotor tracking learning task, with only 18%–36% of the participants showing an increased TMS map area despite significant tracking improvement. A dissociation exists between changes in TMS map area and improvement in tracking performance in both experiments, confirming other reports (Bologna et al., 2015; Delvendahl et al., 2011; Jung & Ziemann, 2009). In conclusion, this study highlights the complex relationship between different motor learning tasks and changes in TMS measures and the importance of considering response variability in use-dependent plasticity when investigating differences across muscles.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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