Differential plasticity of extensor and flexor motor cortex representations following visuomotor adaptation.

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Abstract

Representations within the primary motor cortex (M1) are capable of rapid functional changes following motor learning, known as use-dependent plasticity. GABAergic inhibition plays a role in use-dependent plasticity. Evidence suggests a different capacity for plasticity of distal and proximal upper limb muscle representations. However, it is unclear whether the motor cortical representations of forearm flexor and extensor muscles also have different capacities for plasticity. The current study used transcranial magnetic stimulation (TMS) to investigate motor cortex excitability and inhibition of forearm flexor and extensor representations before and after performance of a visuomotor adaptation task that primarily targeted flexors and extensors separately. There was a decrease in extensor and flexor motor-evoked potential (MEP) amplitude after performing the extensor adaptation, but no change in flexor and extensor MEP amplitude after performing the flexor adaptation. There was also a decrease in motor cortical inhibition in the extensor following extensor adaptation, but no change in motor cortical inhibition in the flexor muscle following flexor adaptation or either of the non-prime mover muscles. Findings suggest that the forearm extensor motor cortical representation exhibits plastic change following adaptive motor learning, and broadly support the distinct neural control of forearm flexor and extensor muscles.

Keywords: motor learning; motor cortex excitability; transcranial magnetic stimulation; intracortical inhibition; use-dependent plasticity.

Introduction

The ability to learn movements is crucial for effective human functioning. It is well-established that the primary motor cortex (M1)—the brain area responsible for execution of voluntary movement—plays a role in motor learning (Kawai et al. 2015; Sanes and Donoghue 2000). Specifically, a substantial body of evidence demonstrates that M1 representations undergo rapid plastic change following motor learning (Boroojerdi et al. 2001; Ljubisavljevic 2006), known as 'use-dependent plasticity' (Classen et al. 1998; Ljubisavljevic 2006).

Transcranial magnetic stimulation (TMS) has proven to be a valuable research tool for investigating use-dependent plasticity in M1 (Classen et al. 1998; Francois and Boyadjian 2006; Ljubisavljevic 2006; Reis et al. 2008). If a single TMS pulse, sufficiently intense to depolarise neurons, is delivered to the hand or arm area of M1, it will elicit a small twitch in the target muscle, known as the motor-evoked potential (MEP). The amplitude of the MEP reflects the excitability of the corticospinal pathway from the point of stimulation to the muscle from which the MEP is recorded; a change in corticospinal excitability (CSE) provides a marker of plasticity (Bestmann and Krakauer 2015; Francois and Boyadjian 2006; Rossini et al. 2015; Rothwell et al. 2009).

TMS has been used to investigate use-dependent learning. Muellbacher et al. (2001) used TMS to measure changes in MEP amplitude following a motor learning task in which participants were trained to make ballistic pinch movements using only the thumb and index finger. Peak force and peak acceleration of the ballistic pinch movements improved rapidly with training, and there was a significant increase in MEP amplitude after training compared to baseline (Muellbacher et al. 2001). This significant increase in MEP amplitude following motor training has been replicated with ballistic tasks involving other movements, including

thumb flexion and adduction (Butefisch et al. 2000), index finger flexion and extension (Bagce et al. 2013; Krutky and Perreault 2007), wrist flexion and extension (Ackerley et al. 2011; Krutky and Perreault 2007), and elbow flexion and extension (Krutky and Perreault 2007). Furthermore, the increase in MEP amplitude is evident in muscles that are engaged during motor training, but not surrounding muscles that are not engaged during motor training (Krutky and Perreault 2007; Muellbacher et al. 2001). These findings provide evidence of ballistic motor learning-induced plasticity in M1.

Evidence suggests that the capacity for use-dependent plasticity differs across major subdivisions of M1 upper-limb representations. Following ballistic motor training of finger, wrist and elbow joints, Krutky and Perreault (2007) found that there was a greater increase in MEP amplitude in muscles that result in movement of the fingers than the wrist or elbow, and a greater increase in MEP amplitude muscles that result in movement of the wrist than the elbow. Research into the functional organisation of M1 suggests that motor output from overlapping cortical sites converge onto individual muscles; additionally, motor output from any given cortical site diverges onto individual muscles with different “gains” depending on the final movement that is performed (Melgari et al. 2008; Schieber 2001; Suzuki et al. 2012). It is therefore plausible that the capacity for use-dependent plasticity might also differ between these unique muscle representations. Indeed, this suggestion has been tested in a study that required participants to perform a finger tracking task involving graded finger flexion and extension movements. In one condition, force resistance was applied to the extensor muscle during finger-tracking, thus, the extensor was the prime mover; in another condition, force resistance was applied to the flexor muscle, thus, the flexor was the prime mover. Results showed a significant increase in MEP amplitude in the flexor following training both when the flexor and extensor acted as the prime mover; in contrast there was no change in MEP amplitude in the extensor in either condition, that is, irrespective of whether

the flexor or the extensor acted as the prime mover during the task (Godfrey et al. 2013). This finding suggests that flexor representations in M1 might have a greater capacity for use-dependent plasticity than extensor representations. Moreover, it fits with the literature that shows functional differences between flexors and extensors of the forearm. Specifically, flexion movements typically require finer force control, and are more commonly executed, than force-driven extension movements (Shim et al. 2007; Yu et al. 2010). Additionally, forearm flexors are involved in precision grip and whole-hand grasping movements whilst forearm extensors are involved in releasing a precision grip and expanding the hand from a grasping movement (Yu et al. 2010).

Although there is preliminary evidence for a greater capacity for use-dependent plasticity of the flexor M1 representation than the extensor M1 representation of the forearm, it is important to investigate use-dependent plasticity following other types of motor learning – such as visuomotor adaptation. Visuomotor adaptation tasks with a gradually implemented distortion target implicit learning mechanisms more so than explicit learning mechanisms: with a gradual distortion, the learning of motor movements is thought to occur largely automatically, and outside of the participant's awareness (Green and Shanks 1993; Hinder et al. 2008; Mazzoni and Krakauer 2006). M1 is thought to be critical to the early stages of implicit motor learning (Nitsche et al. 2006). Furthermore, use-dependent plasticity induced by visuomotor adaptation tasks has been empirically linked to the learning process itself, rather than repeated muscle contractions or other performance variables (Bagce et al. 2013; Riek et al. 2012). Thus, visuomotor adaptation tasks are ideal for investigating implicit motor learning and associated M1 plasticity.

In addition to understanding the differential use-dependent plasticity responses in different muscle representations, it is important to understand the mechanisms that underlie use-dependent plasticity. Research suggests that GABAergic inhibition acting within M1

plays a role in use-dependent plasticity (Celnik and Cohen 2004; Sanes and Donoghue 2000). Paired-pulse TMS can be used to measure GABAergic inhibition (Hallett 2000; Kujirai et al. 1993). When a subthreshold conditioning stimulus (CS), which alone is not sufficient to evoke a MEP, precedes a suprathreshold test stimulus (TS) by 1-5 ms, the MEP amplitude is smaller than when a TS is delivered alone (Hallett 2000; Kujirai et al. 1993). This process is known as short interval intracortical inhibition (SICI) (Kujirai et al. 1993). SICI can be quantified by expressing the MEP amplitude from paired-pulse TMS as a ratio of the amplitude of a TS-alone MEP (Kujirai et al. 1993; Rothwell et al. 2009). Pharmacological studies strongly suggest that SICI is mediated by GABA-A receptor activity (Butefisch et al. 2000; Ziemann et al. 2001).

Paired-pulse TMS has been used to investigate the role of SICI in use-dependent plasticity. Many studies have measured changes in SICI following motor training, showing a decrease in SICI following motor training (Coxon et al. 2014; Liepert et al. 1998; Perez et al. 2004; Smyth et al. 2010; Ziemann et al. 2001). These findings suggest that the increase in MEP amplitude following motor training is mediated, at least in part, by a reduction in SICI. However, other studies have reported no change in SICI following motor learning despite an increase in MEP amplitude (Rogasch et al. 2009; Rosenkranz and Rothwell 2006), therefore, the role of SICI in motor learning requires further investigation.

The present study investigated use-dependent plasticity in flexor and extensor representations in M1 using a visuomotor adaptation task comprising a flexor-learning task and an extensor-learning task. The flexor-learning task aimed to increase the engagement of the flexor carpi radialis (FCR), thus, the FCR was the prime mover. The extensor-learning task aimed to increase the engagement of the extensor carpi radialis (ECR) muscle, thus, the ECR was the prime mover. Single-pulse and paired-pulse TMS was used to measure changes in MEP amplitude and SICI in both the prime mover and non-prime mover representations

before and after the adaptation task. The current study aimed to investigate potential differences in motor learning of flexor and extensor muscles and use-dependent plasticity in flexor and extensor representations with the visuomotor adaptation task, and to investigate whether there were any changes in SICI associated with the visuomotor adaptation task.

Methods

Participants

Complete data sets were collected from 19 participants with normal or corrected vision, and with age ranging from 18 to 28 yr (median age 21 yr). Participants were right-hand dominant according to the Edinburgh Handedness Inventory (Oldfield 1971) with a median Laterality Quotient of 0.82 (range 0.53-1.00). Participants had no history of neurological disorder, were not taking any medications acting on the central nervous system and had no contraindications to TMS (Rossi et al. 2009). All participants gave written informed consent prior to testing. The study was approved by Murdoch University Ethics Committee (approval number: 2015/247).

Twenty-nine participants were recruited and screened for experimental testing, however 7 of the recruited participants had to be excluded due to technical issues arising with electromyography (EMG) recording that prevented clean EMG signals, and 3 of the recruited participants had high (>80% maximum stimulator output) resting motor threshold (RMT), and therefore the experiment was aborted and no data were collected from these participants.

Visuomotor Adaptation Task

During the learning task, the participant's right forearm was affixed in a neutral wrist position (midway between pronation and supination). This was achieved by placing the participant's forearm in a purpose-built manipulandum (see Figure 1*a*), like those used

previously (Marinovic et al. 2017). The participant's forearm rested on foam-covered metal plates at the bottom of the manipulandum, and their wrist and forearm were secured by twelve foam-covered adjustable metal braces; the participant was able to see their wrist in the foreground (though the movements were isometric). The six degree-of-freedom force transducers (JR3 45E15A-163-A400N60S, Woodland, CA), fitted at the end of the manipulandum, allowed the recording of wrist forces produced in radial/ulnar deviations and flexion-extension deviations. The force data were sampled at a rate of 2 kHz using two 16-bit National Instruments A/D boards (NI BNC2090A, NI USB6221, National Instruments Corporation, USA) and displayed on a computer screen using a custom made Matlab script.

<Figure 1 here>

Participants were seated 90 cm in front of a computer screen. Each trial began with the green visual word cue "Relax" presented on the otherwise black computer screen. Next, a circle with a red outline was presented in the middle of the computer screen, representing the start position. In addition, a small red cursor was displayed on the screen, which displayed the resting wrist position in the manipulandum: the participant's arm was adjusted such that the cursor displaying the resting wrist position appeared in the start position circle. On each trial, one green target circle and four audio tones were presented; the target circle appeared 300 ms prior to the fourth audio tone, 10 cm above the start position circle. Participants were instructed to move the cursor from the start position to the green target circle as quickly as possible on the fourth tone. Real-time visual feedback of the cursor movement allowed the participant to see how accurate their directional movement was in relation to the target. Participants were instructed to use this visual feedback to adjust their movement in the next

trial. 20 N was set as the force required to reach the green circle target (the cursor was not controlled by scaling force: only direction of the movement influenced the direction of the cursor, and if excess force was generated during the ballistic wrist movement the cursor would overshoot the target but not alter in direction).

In total, there were three baseline blocks (no adaptation), an adaptation and de-adaptation block with the flexor as the prime mover, and an adaptation and de-adaptation block with the extensor as the prime mover (see Figure 1*d*). In the baseline blocks, participants were required to make ballistic radial deviation movements of the wrist (90°); each baseline block consisted of 30 trials. In the adaptation block, the target was rotated one-degree in either the flexion or extension direction (depending on the prime mover condition) with each consecutive trial; there was a total of 30 trials with a one-degree rotation, such that on the 30th trial participants were required to make a wrist movement 30° away from the green target circle to successfully reach the target. Participants then performed 30 trials where they were required to make this wrist movement 30° away from the green target circle to successfully reach the target. Adaptation blocks in the flexor prime mover condition required a combined flexion/radial deviation movement 30° to the left (120°), while adaptation blocks in the extensor prime mover condition required a combined extension/radial deviation movement30° to the right (60°) (see Figure 1*b*). These directional movements engage the FCR and ECR muscles, respectively. In the de-adaptation block, the rotation of the target was reversed one-degree with each consecutive trial, until it returned to the 90° radial deviation movement; there was a total of 30 trials in the de-adaptation blocks. A gradual visuomotor rotation was imposed in both the adaptation and de-adaptation blocks, which targets a greater implicit component to the learning process than abrupt rotations. A gradual visuomotor rotation can avoid large differences in the time course of adaptation across participants; when using an abrupt rotation participant's that become aware of the rotation might use cognitive

strategies such as aiming 30° to the left or right of the target which can substantially reduce the time course of adaptation (Taylor et al. 2014).

Transcranial Magnetic Stimulation

EMG activity was recorded from the relaxed flexor carpi radialis (FCR) and extensor carpi radialis (ECR) on the right forearm using Ag-AgCl surface electrodes in a belly-tendon arrangement (Zipp 1982). During the experiment, a netting sock was fitted over the electrodes to keep them in place while the participant had their arm in the manipulandum. The raw EMG signal was amplified by a CED 1902 at a gain of 1000x prior to sending it to a CED 1401 analogue to digital converter. This in turn allowed the bandpass filtered (10-1000Hz) and digitised (14-bit resolution sampling rate of 4kHz) EMG signal to be displayed and recorded for offline analysis on the computer 'Signal' software program (Cambridge Electronic Design, UK).

Single-pulse TMS was delivered through a figure of eight coil connected to a Magstim BiStim 200^2 (Magstim Co., Whitland, Dyfed, UK). For all stimulation, the coil was held perpendicular to the scalp at a 45° angle between the anterior-posterior and medial-lateral lines of the participants left hemisphere. Single-pulse TMS was delivered to determine the: (a) optimal site for stimulation; (b) RMT; and (c) stimulation intensity required to elicit a MEP of ~0.5 mV in amplitude. To identify the optimal site for stimulation, suprathreshold pulses were delivered over the left M1; the optimal site was defined as the site that elicited the largest and most reliable MEPs in FCR and ECR. A single site was used for both the FCR and ECR muscle because there is significant overlap in the motor representation for the two muscles (Godfrey et al. 2013; Zartl et al. 2014; Z'Graggen et al. 2009). To identify RMT, single-pulse TMS was delivered to determine the lowest stimulus intensity required to elicit a MEP with a peak-to-peak amplitude greater than 0.05 mV in at least five out of ten

consecutive trials, while the target muscle was at rest (Rossini et al. 2015). RMT was identified separately for FCR and ECR. The test-alone intensity was determined by delivering single-pulse TMS at increasing intensities until MEP amplitude was close to 0.5 mV in both FCR and ECR. In our sample, test-alone MEP amplitude was generally larger in ECR than FCR; this fits with literature showing lower RMT in ECR than FCR (Alaerts et al. 2009; Godfrey et al. 2013; Mirdamadi et al. 2015; Tamburin et al. 2005).

Blocks of single-pulse and paired-pulse TMS trials were delivered between baseline, adaptation, and de-adaptation blocks of the motor learning task. For paired-pulse TMS, the intensity of the conditioning stimulus was set at 80% RMT (FCR and ECR RMT values were averaged to calculate a single RMT), the intensity of the test stimulus was set at the same intensity used for the single-pulse TMS trials, and the inter-stimulus interval was 2 ms. This paired-pulse protocol is consistent with the well-established guidelines for exciting inhibitory cortical networks (Kujirai et al. 1993; Rossini et al. 2015).

Procedure

Throughout the two-hour experiment session, participants were seated comfortably in an adjustable computer chair, with their right forearm affixed in the manipulandum. The order of the prime mover condition was counterbalanced across participants.

Participants first completed a thirty-trial familiarisation task to ensure they understood what the task required; the familiarisation task was identical to the baseline task and therefore consisted of ulnar deviation movements only (average completion time was ~4 minutes). The remainder of the experiment involved alternating between blocks of TMS and blocks of the motor learning task (see Figure 1*d*); TMS blocks were delivered at eight timepoints. Each TMS block consisted of 18 single-pulse and 18 paired-pulse trials, with trials presented in a

pseudo-randomised order. As such, each participant underwent eight blocks of 36 TMS trials, each block took 4 minutes to complete. The motor learning task consisted of a baseline, adaptation, and de-adaptation block for each prime mover muscle. A final baseline block (ulnar deviation movements only)was also performed after the second de-adaptation task. Thus, each participant performed seven learning task blocks (see Figure 1*d*). Baseline and de-adaptation blocks took 4 minutes to complete on average, and adaptation blocks took 8 minutes to complete on average.

Data Analysis

Data reduction was performed using custom Matlab software (Mathworks). Wrist forces were transformed to screen coordinates and filtered with a low-pass 2nd order Butterworth filter with a cut-off frequency of 10 Hz. Movement onsets were estimated from the tangential speed time series derived from the force output and based on a sensitive algorithm proposed in Teasdale et al. (1993). The angle between the position of the cursor at movement onset and the cursors position 100 ms later, was computed as the movement direction (see Figure 1*c*). This early phase of movement direction was used to prevent participants using online visual feedback to correct the path of the cursor which could result in variable movement directions (Desmurget and Grafton 2000).

MEP data were analysed offline. EMG activity from each trial was inspected for voluntary muscle activity. On average, the RMS of pre-stimulus EMG activity was .008 mV. Trials in which there was excessive muscle activity during the 50 ms prior to TMS pulse were excluded from analysis; excessive muscle activity was determined by visually inspecting pre-TMS EMG activity for each trial and removing trials where there was visible high frequency EMG activity that exceeded the average pre-TMS EMG activity by ~120% (i.e. pre-stimulus

EMG activity ≥.018 mV). Overall, 5% of trials were excluded from analysis due to EMG noise. For all trials without voluntary muscle activity, MEPs were quantified in terms of peak-to-peak amplitude (mV), calculated from the EMG recording 10-50 ms following the TMS pulse.

SICI was quantified as the ratio of the average peak-to-peak amplitude (mV) of the paired pulse MEPs to the average peak-to-peak amplitude of the single pulse MEPs (Paired Pulse MEP / Single Pulse MEP; Kujirai et al. 1993). Thus, a value <1 indicated inhibition of the MEP, while a value >1 indicated facilitation of the MEP.

To analyse the data, we wrote custom code in R (R Core Team, 2016) using the functions lmer (lme4 package), t-test (Stats package), and cohensD (lsr package). To determine whether there was a statistically significant difference in the degree of adaptation achieved at the end of the adaptation blocks, behavioural performance (directional error) on the last six flexor and extensor adaptation trials was analysed using a two-tailed paired *t*-test. Fourlinear mixed model analyses were performed; two investigated the effect of FCR and ECR muscle usage (as induced by adaptation) on change in MEP of the prime mover and non-prime mover representations as a function of time (pre-adaptation, adaptation, de-adaptation, post de-adaptation), and the other two investigated the effect of FCR and ECR muscle usage on change in SICI of the prime mover and non-prime mover representations as a function of time. These analyses allowed us to include in the analysis two participants who had missing data for one of their muscles due to excessive background noise. We used the Satterthwaite approximation (Luke 2017; Satterthwaite 1941) to calculate *F*-tests and estimate *p*-values for the main effects and their interaction in the mixed model. Type of adaptation (flexion vs. extension) and time of measurement were treated as fixed factors, while participants were treated as a random factor into the model. To determine whether MEP amplitude and SICI for the prime mover and non-prime mover muscles differed at the

three time points compared to baseline, we employed one sample permutation tests using the *onetPermutation* function from the DAAG package (5000 iterations). An alpha level of .05 was used to determine significance for all statistical analyses. Cohen's *d* was used to estimate effect sizes for the paired *t*-tests (benchmark values to define small, medium, and large effects are .2, .5, and .8, respectively; Cohen 1992). The goodness of fit of the linear mixed models (r^2) was estimated using the r.*squaredLR* function from the MuMIN package (Bartoń 2013), and represents the proportion of the variance that is explained by the terms in the model (Bartoń 2013).

Results

Visuomotor Adaptation Task: Mean Directional Error

As can be seen in Figure 2a, despite mean directional error at the end of the flexor and extensor adaptation blocks being close to full adaptation in both conditions, the mean directional error was marginally more accurate (i.e. closer to 0) for the extensor adaptation compared to the flexor adaptation. A paired *t*-test comparing the de-trended mean directional error (mean directional error at baseline – mean directional error at the last 6 trials) for the flexor and extensor adaptation blocks revealed no significant difference between the two means, t_{18} = -1.26, p = .22, 95% CI [-10.5, 2.6]; this suggests that the level of adaptation was comparable at the end of the flexor and extensor adaptation blocks.

<Figure 2 here>

MEP Amplitude

Figure 2b shows the normalised MEP amplitude (raw MEP at adaptation time point / raw MEP at pre-adaptation) of the prime mover muscles (FCR and ECR) across the three

time points of the adaptation task (adaptation, de-adaptation, post de-adaptation). The linear mixed model analysis revealed a main effect of MUSCLE ($F_{1, 89.8} = 7.78$, $p = .006$, $r^2 = .068$), but no main effect of TIME ($F_{2, 85.3} = 1.26$, $p = .288$, $r^2 = .022$), and no MUSCLE * TIME interaction ($F_{2, 85.3} = 0.47$, $p = .626$, $r^2 = .099$). Although the mixed model found no main effect of time, the one sample permutation test comparing the three adaptation task time points to baseline for the ECR prime mover muscle found statistically reliable effects during adaptation ($p = 0.0008$) and de-adaptation ($p = 0.0062$), but not post de-adaptation ($p = 0.312$). Specifically, MEP amplitude of the ECR prime mover muscle decreased significantly at adaptation and de-adaptation compared to baseline, before returning to baseline levels at post de-adaptation. For the FCR prime mover muscle, the permutation test failed to find any reliable differences (adaptation: $p = 0.53$; de-adaptation: $p = 0.74$; post de-adaptation: $p = 0.96$), suggesting that MEP amplitude of the FCR prime mover muscle was not significantly different at adaptation, de-adaptation and post de-adaptation compared to baseline.

Figure 2d shows the normalised MEP of the non-prime mover muscles across the three time points of the adaptation task. The linear mixed model analysis failed to reveal a main effect of MUSCLE ($F_{1, 89.2} = 0.45$, $p = .50$, $r^2 = 0.004$) but revealed an effect of TIME ($F_{2, 84.9} = 4.59$, $p = .012$, $r^2 = 0.08$). The MUSCLE * TIME interaction, however, was not statistically significant ($F_{2, 84.9} = 0.048$, $p = .95$, $r^2 = .13$). As can be seen in Figure 2d, the main effect of time is driven by MEP amplitude in both muscles increasing from adaptation to post-adaptation, with MEP amplitude at adaptation less than baseline and MEP amplitude at post-adaptation above baseline. However, the one sample permutation test comparing the three adaptation task time points to baseline for the ECR non-prime mover muscle found no effects during adaptation ($p = 0.28$), de-adaptation ($p = 0.41$) or post de-adaptation ($p = 0.16$), suggesting that there was no statistically reliable difference between MEP amplitudes of the ECR non-prime mover muscle at adaptation, de-adaptation, and post de-adaptation compared

to baseline. For the FCR non-prime mover muscle, the permutation test found a statistically reliable difference in MEP amplitude at adaptation (p = 0.042), but no differences during de-adaptation (p = 0.57) or post de-adaptation (p = 0.28). This suggests that MEP amplitude of the FCR non-prime mover muscle decreased significantly at adaptation compared to baseline, while non-prime mover FCR MEP amplitudes at de-adaptation and post de-adaptation were not reliably different from baseline.

Short Interval Intracortical Inhibition

To allow the direct comparison between muscles, we normalised SICI ratios in relation to the values obtained at pre-adaptation (SICI ratio at adaptation time point / SICI ratio at pre-adaptation). As shown in Figure 2c, SICI ratios were consistent across all time points of the adaptation task for the FCR prime mover muscle but a reduction of inhibition from baseline was evident for the ECR prime mover muscle (indicated by a ratio >1.0). Similar to single pulse MEPs, the linear mixed model analysis of SICI indicated a statistically significant main effect for MUSCLE ($F_{1, 88.3}$ = 6.95, p = .009, r^2 = .063), but no main effect for TIME ($F_{1, 84.4}$ = 0.11, p = .889, r^2 = .002), and no MUSCLE * TIME interaction ($F_{1, 88.3}$ = 0.26, p = .760, r^2 = .07). The one sample permutation test comparing the three adaptation task time points to baseline for the ECR prime mover muscle found statistically reliable effects during adaptation (p = 0.034), but not during de-adaptation (p = 0.107) or post de-adaptation (p = 0.060). For the FCR prime mover muscle, the permutation test failed to find any reliable differences (adaptation: p = 0.85; de-adaptation: p = 0.96; post de-adaptation: p = 0.98). This suggests that there was a significant reduction in SICI (less inhibition) of the ECR prime mover muscle at adaptation compared to baseline, while SICI at de-adaptation and post de-adaptation was not reliably different from baseline; SICI of the FCR prime mover muscle remained similar to baseline across all three time points.

Figure 2e shows the normalised SICI ratios of the non-prime mover muscles across the three time points of the adaptation task. The linear mixed model analysis of SICI failed to indicate a statistically significant main effect for MUSCLE ($F_{1, 89.0} = 0.68$, $p = .41$, $r^2 = .006$) or TIME ($F_{1, 84.9} = 0.05$, $p = .947$, $r^2 = .001$), and no MUSCLE * TIME interaction ($F_{1, 84.9} = 1.32$, $p = .270$, $r^2 = .03$). The one sample permutation test for the ECR non-prime mover muscle found no statistically reliable effects during adaptation ($p = 0.31$), de-adaptation ($p = 0.50$) or post de-adaptation ($p = 0.63$). For the FCR non-prime mover muscle, the permutation test failed to find any reliable differences (adaptation: $p = 0.44$; de-adaptation: $p = 0.33$; post de-adaptation: $p = 0.08$).

Discussion

The primary aim of the current study was to investigate changes in MEP amplitude and SICI of the flexor and extensor prime mover and non-prime mover muscles following adaptive motor learning. There was no change in MEP amplitude of the flexor prime mover or extensor non-prime mover at any time point of the flexor adaptation task. There was a significant decrease in MEP amplitude of the extensor prime mover following adaptation and de-adaptation of the extensor adaptation task, compared to baseline. MEP amplitude in both non-prime mover muscles was increased from adaptation to post-de-adaptation, however, the only difference compared to baseline was a decrease in MEP amplitude of the flexor non-prime mover following adaptation to the extensor task. There was a decrease in SICI for the extensor prime mover following adaptation, compared to baseline but there was no change in SICI for the flexor prime mover or either of the non-prime mover muscles. . This provides evidence that the extensor M1 representation exhibits plastic change following adaptive motor learning.

Performance accuracy

While the mean directional error at the end of the extensor adaptation block was marginally more accurate than the mean directional error at the end of the flexor adaptation block, our statistical analysis did not reveal any significant difference between the two. This suggests that participants' level of adaptation, and by extension the degree of their adaptive motor learning, was comparable at the end of the extensor and flexor adaptation blocks. Moreover, the mean directional error at the end of the flexor and extensor adaptation blocks was close to 0, which indicates participants were making movements close to full adaptation; this can be contrasted to a mean directional error of -30 which represents the movement participants would make if they had not learned the adaptation. Because the visuomotor adaptation task used in the present study required implicit motor learning, the evidence that participants performed close to full adaptation in both conditions suggests that the task effectively induced implicit motor learning of the extensor and flexor adaptation tasks. However, it is worth noting that we did not ask participants whether they were aware of any rotation, so we cannot be entirely certain that the task was implicit for all participants. Nevertheless, the similar level of accuracy at the flexor adaptation block and the extensor adaptation block in the present study is consistent with the findings of Godfrey et al. (2013); they used an explicit motor learning task consisting of a flexion-resisted finger-tracking task, and an extension-resisted finger-tracking task, and observed a similar level of accuracy between the two conditions.

Use-dependent plasticity in extensor but not flexor following adaptation

Results showed a significant difference between the normalised MEP amplitudes of the extensor prime mover muscle and the normalised MEP amplitudes of the flexor prime mover muscle. Interestingly, there was a significant decrease in MEP amplitude in the extensor and flexor muscles following extensor adaptation compared to baseline, but no change in MEP amplitude in the flexor or extensor muscles following flexor adaptation compared to baseline. That is to say, there was a decrease in CSE in the flexor and extensor representations following learned movements which involved more activation of the wrist extensors, but there was no change in CSE following learned movements which involved more activation of the wrist flexors. This decrease in CSE of the extensor and flexor representations following extensor adaptation is striking when contrasted with the unchanging CSE of the two representations following flexor adaptation, despite the similar level of learning performance for the two adaptation tasks. The change in CSE may indicate that extensor-specific adaptive motor learning involves both extensor and flexor M1 representations, which is consistent with the notion that motor output from overlapping cortical sites converge onto individual muscles with different "gains" depending on the final movement to be performed (Melgari et al. 2008; Schieber 2001; Suzuki et al. 2012). It is worth noting, however, that the change in CSE following extensor adaptation was more pronounced and longer-lasting in the extensor representation than the change in CSE that was observed in the flexor representation following extensor adaptation; the change in CSE in the extensor prime mover was evident following both adaptation and de-adaptation, whereas the change in CSE in the flexor non-prime mover was only evident following adaptation (not de-adaptation). As a change in CSE reflects plasticity induction, this provides some evidence for adaptive motor learning-induced plasticity acting on the ECR and FCR M1 representations following an extensor-targeted task. Additionally, the finding of an increase in CSE for both

non-prime mover muscles from adaptation to post-de-adaptation (albeit not different from baseline) is consistent with the idea that antagonists are initially more inhibited and become less inhibited as the agonist muscles are functionally more engaged (Day et al. 1984).

A reduction in CSE of the prime mover and non-prime mover muscles of the extensor task and no change in CSE of the prime mover and non-prime mover muscles of the flexor task contrasts results obtained by Godfrey et al. (2013). Godfrey and colleagues reported a lack of significant change in CSE of the extensor muscle, and a significant increase in CSE of the flexor muscle, regardless of whether the flexor acted as the prime mover or non-prime mover in a finger tracking task. Godfrey et al. (2013) measured MEPs at a range of TMS intensities to obtain an input/output (I/O) function and showed a change in the slope of I/O function for the flexor irrespective of whether it acted as the prime mover or non-prime mover. In the present study, we measured MEPs at a single TMS intensity that elicited MEPs of ~0.5 mV in the flexor and extensor. It would be valuable to obtain an I/O function following the visuomotor task used in the current experiment. Nonetheless, we expect the stimulus intensity used in the current study elicited MEPs ~ 50% of the maximal MEP for flexors and extensors (i.e. halfway up the I/O function; Devanne et al. 1997). The intensity that elicits MEPs ~50% of the maximal MEP is considered an ideal test stimulation intensity for assessing changes in CSE because the MEP has similar capacity to increase and decrease in response to the experimental manipulation (Kukke et al. 2014). Furthermore, a change in the slope of the I/O function will likely be reflected by a change in the MEP amplitude to a test stimulus intensity that elicits MEPs of ~50% maximal at baseline (Kukke et al. 2014). Therefore, it is reasonable to compare the current results with those of Godfrey and colleagues. Godfrey et al. (2013) showed a change in flexor excitability irrespective of whether the flexor or extensor was the prime mover; in the current study we showed a change in extensor and flexor excitability following extensor adaptation but not flexor adaptation.

This contrast may have arisen due to the design of the respective motor learning tasks used in each study. The task used in the present study required participants to perform a movement of the wrist joint in the flexor or extensor plane as quickly as possible towards the target. As such, participants produced power-driven wrist movements – movements that align more closely with extensor motor function than flexor motor function in daily activity. Flexion-based movements, like a precision grip, require finer force control than extension-based movements, like releasing a precision grip (Oliveira et al. 2008; Schieber 1991; Yu et al. 2010), and during finger extension movements, significant force is produced in surrounding joints, including the wrist (Li et al. 1998; Oliveira et al. 2008; Reilly and Hammond 2000; Schieber 1991). It is therefore possible that the motor learning task, requiring power-driven wrist movements, engaged the extensor muscle to a greater extent than the flexor muscle; in this situation, the extensor M1 representation would have been functionally more engaged which could have resulted in the change in CSE that we observed for the extensor prime mover. Conversely, the learning task used in Godfrey may have engaged the extensor muscle to a lesser extent, and in turn, the extensor M1 representation may not have been as functionally engaged. This is because the task involved low-force, precise finger contractions, which requires the finer force control inherent in flexion motor function (Godfrey et al. 2013; Shim et al. 2007; Yu et al. 2010). However, it is important to remember that there was a similar level of accuracy at the flexor and extensor learning tasks in both studies; therefore, the assertion that each task differentially engaged the flexor and extensor muscles must be considered with caution. Future studies should test whether the task used in the current study engaged extensors to a greater extent than flexors by measuring EMG from the extensors and flexors during task performance.

Previous research has consistently shown an increase in MEP amplitude in the target muscle involved in synchronised motor learning tasks (Liepert et al. 1999), ballistic motor

learning tasks (Hammond and Vallence 2006; Muellbacher 2001; Ziemann et al. 2001), and motor sequence learning tasks (Coxon et al. 2014; Godfrey et al. 2013; Smyth et al. 2010). Therefore, it might seem surprising that extensor motor learning was associated with a decrease, and not an increase, in CSE in the corresponding M1 representation. . The reduced M1 excitability of the extensor prime mover muscle following adaptation and de-adaptation may indicate that another brain region interacted with M1 to play a role in learning. A likely candidate is the cerebellum. Participants with cerebellum degeneration have consistently failed to exhibit learning on visuomotor adaptation tasks (Criscimagna-Hemminger et al. 2010; Smith and Shadmehr 2005). Furthermore, a non-invasive brain stimulation protocol that increases excitability of the cerebellum has been shown to improve participants' performance on a visuomotor adaptation task compared to sham stimulation (Galea et al. 2011; Leow et al. 2017) and when the same protocol is used to increase excitability of M1 (Galea et al. 2011). Thus, it is possible that the cerebellum may have been more involved, and thus more excitable, during the adaptive motor learning task, while M1 was inhibited.

It is known that the cerebellum has an inhibitory influence on M1 excitability, known as 'cerebellar brain inhibition' (CBI) (Daskalakis et al. 2004; Pinto and Chen 2001; Tremblay et al. 2016; Ugawa et al. 1991). Therefore, CBI might explain the significant decrease in M1 excitability that was observed following the extensor visuomotor adaptation task. Existing research that has measured CBI during visuomotor adaptation tasks has found an increase in M1 excitability following learning, and a decrease in the inhibitory influence of the cerebellum on M1 (Jayaram et al. 2011; Schlerf et al. 2012; Schlerf et al. 2015). However, these studies have used abrupt distortions (Jayaram et al. 2011; Schlerf et al. 2012; Schlerf et al. 2015), no time restrictions and therefore no motor planning restriction (Jayaram et al. 2011), and multiple targets rather than a single target (Schlerf et al. 2012; Schlerf et al. 2015); these explicit motor learning designs contrast the gradually implemented visuomotor

distortion with a short reaction time used in the current study - that is known to induce implicit learning (Leow et al. 2017). Future research should measure CBI following adaptation using an implicit learning visuomotor task.

Change in SICI of the extensor but not flexor following adaptation

Results showed a significant difference between the normalised SICI ratios of the extensor prime mover and the normalised SICI ratios of the flexor prime mover. There was a significant decrease in SICI following adaptation for the extensor prime mover, but no change in SICI of the flexor prime mover across all time points. There were no statistically reliable differences in SICI between the two non-prime mover muscles or across all time points of the adaptation task for either non-prime mover muscle. Absence of a change in FCR SICI suggests that the task did not affect the excitability of intracortical inhibitory circuits acting on the flexor representation.

Curiously, our results showed a decrease in SICI of the extensor prime mover following adaptation. If SICI was the mechanism driving the observed decrease in ECR CSE, we would expect an associated increase in SICI. However, in the current study there was a decrease in SICI, suggesting that the decrease in ECR CSE was not mediated by ECR SICI. Interestingly, the decrease in ECR SICI is consistent with the decrease in SICI of the extensor prime mover that was observed by Godfrey et al. (2013) following a finger tracking task. A lack of change in ECR CSE but a significant decrease in ECR SICI has been observed following a waveform tracking task requiring extension movements (Smyth et al. 2010). It has previously been suggested that adaptation to the type of repetitive precision tracking task used in the two studies mentioned above might be mediated by a change in intracortical inhibition rather than a change in CSE (Godfrey et al. 2013). It is also possible that the type

of implicit adaptive motor learning involved in the present study is also mediated by a change in SICI, rather than change in CSE. Given that the change in SICI was specific only to the extensor representation following extensor adaptation in the present study, despite the changes in CSE in both the extensor and flexor muscles following extensor adaptation, this could certainly be the case. It has long been suggested in the motor learning literature that inhibitory and excitatory networks may act independently, even within the same M1 representation (Liepert et al. 1998; Ziemann et al. 1996).

Conclusions

The present study provides some evidence to suggest that the extensor and flexor M1 representations exhibit plastic change following extensor-targeted adaptive motor learning, in the form of a decrease in M1 excitability. This finding contributes to literature endeavouring to piece together a systems-level view of the brain networks involved in adaptive motor learning (Caligiore et al. 2017). More broadly, due to the significant change in extensor prime mover CSE, but no change in flexor prime mover CSE, following a task that required a power-driven wrist movement, the present study provides further support for the distinct neural control of flexor and extensor muscles of the upper limb. Additionally. the change in SICI of the extensor muscle but not the flexor muscle following extensor adaptation, despite the change in CSE in both muscles, reveals a unique neurophysiological response of the two muscles following adaptive motor learning – further pointing to the distinct neural control of the two muscles; plastic changes might depend on task requirements that relate to the functional role played by different muscles. Future research and clinical protocols need to recognise the distinct neural control and motor function of these muscles.

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Figure captions

Fig. 1 ***Experimental set-up.*** Experimental set up with the participant's right forearm secured in the manipulandum (a). Directional movements required for baseline trials (90°), peak flexor adaptation trials (120°), and peak extensor adaptation trials (60°) from starting position (b). Directional error calculation (c). Schematic of flexor learning task and extensor learning task (d). Double arrows represent blocks of TMS. Panels (a), (b), and (c) adapted from "Unexpected acoustic stimulation during action preparation reveals gradual re-specification of movement direction" by W. Marinovic, J. Tresilian, J. L. Chapple, S. Riek and T. Carroll, 2017, *Neuroscience, 348*, p. 27. Copyright 2017 by Elsevier Ltd

Fig. 2 ***Behavioural and neurophysiological results.*** Mean directional error (º) at the last 6 trials of the flexor adaptation block and the last 6 trials of the extensor adaptation block (a). Normalised MEP amplitudes (ratios of baseline values) for the ECR and FCR prime mover muscles across the different time points of the adaptation task (b). Normalised SICI ratios (ratios of baseline values) for the ECR and FCR prime mover muscles across the different time points of the adaptation task (c). Normalised MEP amplitudes for the ECR and FCR non-prime mover muscles across the different time points of the adaptation task (d). Normalised SICI ratios for the ECR and FCR non-prime mover muscles across the different time points of the adaptation task (e). Error bars represent the within participants 95% CI. Dotted horizontal lines represent optimum accuracy (0º mean directional error) at the adaptation task (a), relative pre-adaptation MEP values for the two muscles (b and d), and relative pre-adaptation SICI values for the two muscles (c and e)