Primary motor cortex involvement in initial learning during visuomotor adaptation

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ABSTRACT

Human motor behaviour is continually modified on the basis of errors between desired and actual movement outcomes. It is emerging that the role played by the primary motor cortex (M1) in this process is contingent upon a variety of factors, including the nature of the task being performed, and the stage of learning. Here we used repetitive TMS to test the hypothesis that M1 is intimately involved in the initial phase of sensorimotor adaptation. Inhibitory theta burst stimulation was applied to M1 prior to a task requiring modification of torques generated about the elbow/forearm complex in response to rotations of a visual feedback display. Participants were first exposed to a 30° clockwise (CW) rotation (Block A), then a 60° counterclockwise rotation (Block B), followed immediately by a second block of 30° CW rotation (A2). In the STIM condition, participants received 20 s of continuous theta burst stimulation (cTBS) prior to the initial A Block. In the conventional (CON) condition, no stimulation was applied. The overt characteristics of performance in the two conditions were essentially equivalent with respect to the errors exhibited upon exposure to a new variant of the task. There were however, profound differences between the conditions in the latency of response preparation, and the excitability of corticospinal projections from M1, which accompanied phases of de-adaptation and re-adaptation (during Blocks B and A2). Upon subsequent exposure to the A rotation 24 h later, the rate of re-adaptation was lower in the stimulation condition than that present in the conventional condition. These results support the assertion that primary motor cortex assumes a key role in a network that mediates adaptation to visuomotor perturbation, and emphasise that it is engaged functionally during the early phase of learning.

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1. Introduction

Humans exhibit a characteristic capacity to adapt their behaviour rapidly upon exposure to novel task contexts, such as those created by the imposition of external force fields (Shadmehr & Mussa-Ivaldi, 1994) or the distortion of sensory feedback (Krakauer, Ghilardi & Pine, 1999). Initially induced errors between desired and actual movement outcomes are typically followed by incremental improvements in task performance. The latter phase has generally been conceived of in terms of the recalibration of an internal model that encapsulates the input-output properties of the motor system (Kawato, 1999). In circumstances in which the relationship between the current state of an effector (joint torques or position) and sensory feedback of that state has been modified, for example by rotation of the visual environment, the mechanisms of adaptation are frequently inferred on the basis of aftereffects (Krakauer et al., 1999; Wigmore, Tong & Flanagan, 2002). These are expressed upon removal of the distortion, whereby trajectory errors in the opposite direction to those exhibited upon initial exposure to the altered environment are observed.

There is a body of evidence that implicates the primary motor cortex (M1) as part of a network of brain regions involved in the learning and retention of motor skills. The extent of its contribution varies in a task and time-dependent fashion. In the initial stages of acquiring skills for which (at least initially) a significant degree of cognitive involvement is required, there are relatively high levels of activity in cortical regions including prefrontal, bilateral sensorimotor, and parietal cortices. With practice, a decrease in the activity of these cortical areas is accompanied by a progressive increase in the engagement of sub-cortical zones including the cerebellar dentate, and the thalamus and putamen (Floyer-Lea & Mathews, 2004). It has therefore been proposed that for tasks of this nature, the initial phases of skill acquisition

are mediated via regions of a cortical network specialised for executive function, motor planning/execution and the processing of somatosensory feedback, and that sub-cortical circuits in the cerebellum and basal ganglia assume a commensurately greater role as automaticity of performance is achieved (e.g., Floyer-Lea & Mathews, 2004). For the present purposes, we conceive of early motor learning as that which occurs within a practice session, as opposed to that which accrues over the course of multiple practice sessions (e.g., Rozenkranz, Kacar & Rothwell, 2007). Consistent with the above scheme, early learning of a "fast-as-possible" ballistic motor task is associated with elevated excitability of corticomotor pathways, as indicated by an increase in the amplitude of the motor evoked potential (MEP) in response to transcranial magnetic stimulation (TMS) of M1 (Rozenkranz et al., 2007).

These indications of M1 contributions notwithstanding, it is clear that the cerebellum and other subcortical structures also play an important role in early motor learning, particularly in the context of adaptation to visuomotor rotations and force-field perturbations. Individuals with cerebellar damage fail to exhibit learning in these contexts (Criscimagna-Hemminger, Bastian & Shadmehr, 2010; Smith & Shadmehr, 2005). Indeed it has been argued that in these tasks, disruption of M1 function, for example by means of single pulse TMS administered during movement, impairs primarily those components of (early) motor learning in which the same motor commands are repeated—following the most rapid phase of performance adaptation. The corresponding contention has been that primary motor cortex mediates a slow, repetition-dependent, component of motor memory, dissociable from error detection, which plays a significant role in the retention of motor memories (Orban de Xivry, Criscimagna-Hemminger & Shadmehr, 2011). Indeed, the impact of stimulation delivered to M1 immediately following the termination of movement (in a visuomotor adaptation paradigm) suggests that it has a specific role in this regard (Hadipour-Niktarash, Lee, Desmond & Shadmehr, 2007). Similarly, if repetitive TMS (rTMS) is applied to M1 prior to force field adaptation, the initial rate of learning is unaffected, whereas when tested on the following day, retention is impaired (Richardson et al., 2006). Proactive interference is similarly reduced (Cothros, Kohler, Dickie, Mirsattari & Gribble, 2006).

On the basis of measures of performance alone, the conclusion might therefore be drawn that the cerebellum plays a critical role in the rapid phase of early motor learning, and that the primary motor cortex is not engaged to a significant degree during error-based adaptation. It seems unlikely however that this demarcation is absolute. If during adaptation there is awareness that a perturbation has been imposed, cognitive resources will necessarily be committed. The involvement of cortical regions specialised for executive function, motor planning/execution and the integration of somatosensory feedback would therefore be anticipated. Given that qualitatively similar improvements in performance may be obtained when quite distinct modes of learning are operative (Hinder, Tresilian, Riek & Carson, 2008; Hinder, Riek, Tresilian, de Rugy & Carson, 2010), we reasoned that the contributions of cortical regions, including M1, to the rapid early phase of adaptation may be obscured when only overt measures of behaviour are evaluated. This reservation extends to circumstances in which M1 function is disrupted directly, for example by means of TMS. In this regard, it has been proposed previously that the motor system accommodates this challenge by altering the activity in other brain areas involved in movement planning and execution in a manner that preserves motor output (e.g., Ortu, Ruge, Deriu & Rothwell, 2009; Shemmell, Riek, Tresilian & Carson, 2007; Touge, Gerschlager, Brown & Rothwell, 2001).

We sought to make palpable the contribution of M1 to the initial phases of adaptation by focusing on a measure of movement planning. We therefore placed specific emphasis on reaction time (RT). Although RT has been used historically in this manner (Henry & Rogers, 1960; Klapp, 1995), it is considered infrequently in contemporary studies of motor learning. In order to ensure that the initial stages of learning were accentuated, we employed a task that required adaptation (A1), counter-adaptation (B) and subsequent re-adaptation (A2) to a visuomotor rotation. The magnitude of the transition between the A1 and B variants, and the B and A2 variants of the task, made highly probable the awareness that a perturbation had been imposed. We observed that when participants were required to make a transition between adaptation (or re-adaptation) and counter-adaptation, RT was elevated profoundly. The prior administration of inhibitory rTMS to M1 reduced markedly the magnitude of this effect. The overt characteristics of performance (aftereffects) were initially unaffected by disruption of M1, however the rate of subsequent re-adaptation was diminished.

2. Materials & methods

2.1. Participants

Eight self-reported right-handed participants volunteered for the study and participated in up to three experiments (five testing sessions per person in total). All participants were free of neurological disorders, were not taking any medication, and gave informed consent to the procedures, which were approved by the Medical Ethics Committee of the University of Queensland, and conformed to the Declaration of Helsinki.

2.2. Electromyographic recording

Electromyographic (EMG) activity in the right flexor carpi radialis (FCR) muscle was recorded using bipolar (Ag/AgCl) surface electrodes (1 cm diameter) placed approximately 2 cm apart on the muscle belly, parallel to the muscle fibres. The EMG signals were amplified (P511 amplifier, Grass Instruments USA), band-pass filtered (30 Hz – 1 kHz), sampled at 2 kHz and stored on a computer for later off-line analysis.

2.3. Experiment 1

In an initial experiment we sought to determine the effect of continuous theta burst stimulation (cTBS), which consists of 3 pulses of 50 Hz stimulation repeated every 200 ms for a total of 300 pulses (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005), on the excitability of the corticomotor pathway innervating the right FCR. For the intrinsic muscles of the hand, this type of cTBS results in LTD-like plasticity lasting approximately 30 min (Huang et al., 2005).

In two sessions, separated by at least one week, participants either received (cTBS session) or did not receive (NO-cTBS session) theta burst stimulation delivered by a Magstim Rapid via a 55 mm butterfly coil (Magstim Company, UK). The order of sessions was counterbalanced across participants. The optimal coil position over left M1 was first determined by marking a spot on the scalp 5 cm lateral and 2 cm anterior to the vertex. The coil was then moved around this spot until the largest response was obtained. In the cTBS session, the stimulus intensity was set at 80% of active motor threshold (AMT) defined as the minimum intensity required to elicit a 200 μV motor evoked potential (MEP) in at least 50% of 10 stimuli while the participant held an isometric contraction of 5% of maximum voluntary contraction of the FCR muscle. The level of background contraction was determined prior to the experiment whereby each participant performed a brief maximum voluntary isometric contraction that generated forearm pronation torque only. Participants were given feedback of the applied torque during the determination of AMT. This consisted of a bar and target displayed on a computer monitor positioned in front of them. In the NO-cTBS session, the participants sat quietly for a period (approx. 30 s) equivalent to that required to deliver the stimulation in the cTBS condition.

Prior to and following the intervention, test MEPs were elicited in the right FCR. Test stimulus intensity was set at 150% of resting motor threshold (RMT), which was defined as the minimum intensity required to elicit a 50 μV response in at least 50% of 10 stimuli. Eight test responses were obtained over a 1 min period with random inter-stimulus intervals of between 4 and 8 s. Immediately following the intervention, the participants sat quietly for 4 min after which further sets of test MEPs were elicited every 3 min for 30 min.

2.4. Experiment 2

In each of two sessions, separated by approximately two weeks (mean 13.5 day, minimum 11 day), the same 8 participants performed a centre out isometric aiming task under the influence of a visuomotor rotation (Hinder, Walk, Woolley, Riek & Carson, 2007; Hinder et al., 2008). As it has been reported previously (Krakauer, Ghez & Ghilardi, 2005) that the retention of visuomotor adaptation may persist for longer than one week, we adopted a number of measures (reported below) to verify that at the commencement of each session there was no effect due to previous exposure to the task. The visuomotor rotations were presented in an 'ABA' block format. In each block of trials there was a specific relationship between the direction of torque production and the direction of the ensuing cursor movement displayed on a computer monitor: 'A' blocks consisted of a cursor rotation of 30° clockwise (CW), while in the 'B' block a 60° counter-clockwise (CCW) was imposed. In requiring adaptation, de-adaptation and subsequent re-adaptation, this task design accentuates the initial stages of learning. We also assessed adaptation to the re-imposition of the A rotation 24 h after the initial exposure (A24).

In one session (STIM condition) cTBS was applied to the contralateral M1 prior to exposure to the initial A block. In the other "conventional" session (CON condition) cTBS was not administered. The order of the two conditions was counterbalanced across the eight participants.

2.5. Apparatus

Participants sat 65 cm from a computer screen, positioned at eye level. The right arm was placed in a padded brace with the elbow flexed at 90° and the forearm in a neutral position. Participants grasped an instrumented vertical cylindrical handle, with pads positioned above and below in order to minimise movement of the hand (Fig. 1, also see Hinder et al., 2008, for further details). Forces and torques exerted on the isometric manipulandum were recorded using a 6° of freedom force/torque transducer (Delta ATI, Industrial Automation, USA). Force (flexion/extension) and torque (pronation/supination) were sampled at 2 kHz.

2.6. Procedure

Visual feedback of pronation/supination (x-axis) and flexion/extension (y-axis) torque was provided via a cursor. When participant's relaxed their arm, the cursor coincided with the start position—a yellow dot in the centre of the screen (Fig. 1). Each trial began with a random period of 1–3 s, during which participants were instructed to stay within the start zone. One of the eight targets, equally spaced at 45° intervals around and at a constant distance of 5.4 cm from the start zone, was then presented as a yellow dot, accompanied by an auditory tone. Participants were instructed to initiate their response as soon as the target appeared, and move the cursor to the target as quickly as possible by producing isometric torque in one or both of the 2° of freedom of the elbow-forearm complex. Elbow flexion/extension torque resulted in an upward/downward cursor movement while pronation/supination torque resulted in cursor movement to the left, and right, respectively. Once the participant had held their torque within the target zone (defined as a region of $\pm 5\%$ tolerance around the specified torque requirement)
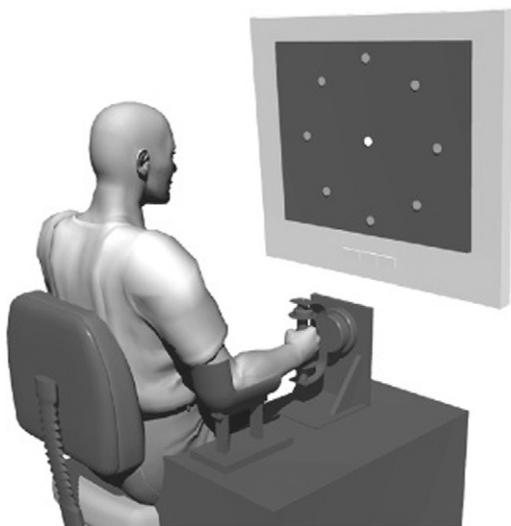

Fig. 1. Setup for Experiment 2 showing participant position, force measuring device and computer screen with targets.

for a period of 100 ms a second tone was generated, at which point participants relaxed, and the cursor returned to the start zone. Each trial lasted 10 s. During trials in which the participant failed to acquire the target (< 1% of total trials) there was no second tone and the target disappeared. The trial was not repeated, and the next trial began as normal.

All participants first undertook a short familiarisation (NULL) block (5 trials per target, 40 trials total), during which the cursor moved in the intuitive direction, i.e., flexion torque moved the cursor up. They were subsequently exposed to a block of trials (18 trials per target, 144 trials total; block A1) in which the visual feedback of the cursor was rotated by 30° clockwise (CW, assigned negative by convention). Following A1, participants were exposed to another visuomotor environment (18 trials per target, 144 trials total; block B) which consisted of a 60° counter-clockwise (CCW) rotation of the visual feedback. Following the B block, participants performed a second A block (30° CW rotation (18 trials per target, 144 trials total; block A2). After a 24 h period, the participants returned to the laboratory to perform a short block in rotation A (A24: 6 trials per target, 48 trials total). Within all blocks (A1, B, A2, A24), the trial order was pseudo-randomised such that there were 8 (3 for A24), 16-trial cycles, each consisting of two trials to each target. Participants received no visual or verbal cues as to the nature of the visuomotor environments within each trial block. Each trial lasted 8 s and proceeded without interruption within each block. There was a 1 min interval between successive blocks that enabled resting MEPs to be recorded (see below). At the commencement of each block, participants were simply reminded to acquire each target as quickly as possible.

The resultant torque magnitude required to attain each target was identical across all participants and targets (10–20% of participants' maximum torque capacity). For targets representing combinations of torques in 2° of freedom, the vertical (flexion/extension) and horizontal (pronation/supination) torque components were determined as the cosine of the subtended angle between the target direction and the single degree of freedom target, multiplied by the single degree of freedom torque. For all trials, the angular mapping between force/torque production and cursor displacement was unitary, i.e., $x°$ error in the direction of torque production relative to the required torque direction (which, due to the rotation of the visual feedback, may not be in the same direction as the visual target) resulted in an angular error of $x°$ in visual co-ordinates.

2.7. Transcranial magnetic stimulation

In each condition single pulse TMS was used to elicit MEPs from the right FCR muscle after each set of 48 trials (6 trials to each of the 8 targets; Fig. 2). The stimulation parameters were derived in the manner described for Experiment 1. At each time of observation, eight stimuli were delivered over a 1 min period. The resulting MEPs were subsequently averaged to give an indication of the excitability of the corticospinal pathway.

In the STIM condition, the participant received cTBS prior to block A1. The stimulation parameters were those described Experiment 1. Following the cTBS, participants sat quietly for 4 min after which another set of eight MEPs were recorded. Block A1 then commenced. In the CON condition, the participant sat quietly prior to the initial A1 block for a period equivalent to that required for the cTBS to be delivered (approx. 30 s), i.e., prior to the 4 min interval.

2.8. Data reduction and analysis

Torque time series (representing cursor position), were digitally low-pass filtered at 15 Hz with a second-order, dual-pass Butterworth filter. Movement onset was determined using an algorithm based on cursor speed (Teasdale, Bard, Fleury, Young & Proteau, 1993), with an initial threshold of 15% of the maximum tangential speed. Target acquisition, or 'movement offset', was determined as the start of the first period of at least 100 ms duration in each trial in which subjects remained in the target zone. Reaction time was calculated as the time between the presentation of the target and movement onset. Angular error was calculated as the angle between the vector defined by the start and target positions, and the vector defined by the start position and actual cursor position, in a 10 ms window centred at 100 ms after movement onset. On the basis of the assumption that no response modifications based on online visual feedback could occur prior to this point, this measure assessed feedforward adaptation to the imposed rotations. For comparison purposes, angular error was also calculated at the peak rate of torque development. The patterns of results obtained using the two methods were indistinguishable. Data were averaged over the 16 trials in each cycle (two trials to each target).

To provide a context in which to interpret variations in the dependent measures (i.e., angular error, RT, MEP amplitude) across the A1, B and A2 blocks, we calculated means and corresponding 95% confidence intervals (Loftus & Masson, 1994) for the initial trials in which there was no visuomotor rotation (i.e., the NULL block). To verify that there was no carryover effect (i.e., across the two weeks interval between sessions), we calculated for each participant (and each of the three cycles of the NULL block), the difference between the mean angular error obtained in the session undertaken first, and that obtained in the session undertaken second. The difference between sessions, in terms of the mean
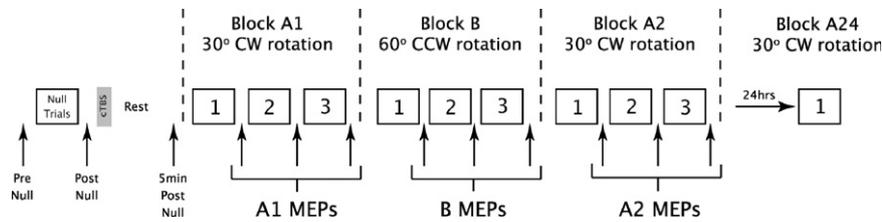
Fig. 2. Time line of Experiment 2. Each box represents 48 trials (6 trials to each of the 8 targets. Null trials indicate no rotation of visual feedback. In the STIM condition participants received 30 s of cTBS following the Null trials, and then sat quietly for 4 1/2 min before commencing block A1. In the CON condition, the participants sat quietly for 5 min before commencing block A1. In blocks A1, A2, and A24 visual feedback of cursor position was rotated by 30° in the clockwise direction, and 60° counter clockwise for block B. The upward arrow indicates the time points at which 8 MEPs in right FCR over a period of 1 min were elicited by single pulse TMS at rest. MEPs were obtained at 2 time points prior to the intervention (Pre NULL and Post NULL) and one set of measurements were obtained following the intervention (5 min Post NULL). The MEPs obtained during each adaptation block were averaged within each block as indicated by the square brackets.

angular error exhibited in the initial (NULL) blocks, was extremely small (stimulation condition first: 2.4°; control condition first: 5.1°), and did not differ between the two counterbalanced orders ($F(1, 6) = 0.05$, $p = 0.83$). There was similarly no effect of cycle, nor an interaction between the order of conditions and cycle ($p > 0.20$).

In order to restrict the main inferential analyses to those of theoretical significance, we conducted planned comparisons of means (Keppel, 1982). We note that in the context of repeated measures designs, the utilisation of an omnibus ANOVA followed by the application of post-hoc tests to decompose main effects or interactions is deemed inappropriate, as corrections for violations of the assumption of sphericity are problematic when applied to such tests. In addition, the adjustment of alpha for all possible post-hoc contrasts – most of which permit no theoretical interpretation, reduces the effective statistical power of the analysis. To aid in the interpretation of the planned comparisons, effect sizes were calculated following Cohen (1969). The effect size (f) describes the degree of departure from no effect, in other words, the degree to which the phenomenon is manifested. A small effect size is considered by convention to be indicated by an f of 0.1, a medium effect size by an f of 0.25, and a large effect size by an f of 0.4.

3. Results

3.1. Experiment 1

The mean waveform of the 8 MEPs recorded from a single participant during each epoch in the cTBS condition is shown in Fig. 3. As illustrated, the peak-to-peak amplitudes of the potentials obtained following stimulation were consistently smaller than the initial test MEPs.

In the NO-cTBS condition, the MEP amplitudes remained stable for the 30 min duration of the experiment (Fig. 4). The MEPs obtained following cTBS were smaller than in the NO-cTBS condition ($F(1,7) = 14.03$, $p < 0.01$, $f = 0.31$), an effect that was expressed immediately following cTBS, and at 9 min, 12 min, 15 min, 18 min, 21 min, 24 min and 27 min following the stimulation ($p < 0.05$ in all cases; $f = 0.17$–0.26).

3.2. Experiment 2

3.2.1. Angular error

Exposure to the 30° CW rotation in A1 resulted in angular error of approximately 20° (averaged across the first cycle of 16 trials), which was initially greater than that observed on completion of the NULL block. By the end of block A1 however, the average error had been reduced to less than 8° in both the conventional (CON) and stimulation (STIM) conditions. The two conditions did not differ reliably from one another (Fig. 5).

Initial exposure to task B resulted in an elevation of angular error to 45–49° on average (Fig. 5), which was markedly higher than that obtained at the end of the A1 block. In both conditions there was a marked subsequent reduction in error to 22–23°, suggestive of feedforward adaptation to the 60° CCW rotation. As in the A1 block however, the degree to which this aspect of

performance improved in the rotated task context was not affected by the prior administration of cTBS.

Re-exposure to task A (block A2) resulted in angular errors in the direction of the imposed rotation (CW) of 46° (Fig. 5), which were larger than those observed upon completion of task B. Over the course of the A2 block angular error was reduced in both conditions to levels that did not differ reliably from the NULL block.

At commencement of the A24 block (Fig. 6), the movements made in the STIM and CON conditions could not be distinguished with respect to angular error ($F(1, 14) < 1$, $p > 0.20$, $f = 0.17$). In the second cycle of sixteen movements however, angular error was lower in the CON than in the STIM condition ($F(1, 14) = 9.65$, $p < 0.01$, $f = 0.78$). A similar difference was expressed for the third cycle of movements ($F(1, 14) = 8.63$, $p = 0.01$, $f = 0.73$).

3.2.2. Reaction time

For both conditions, RTs (Fig. 7) in the A1 block did not differ from those observed in the NULL block. Upon initial exposure to the 60° CCW rotation in block B, the reaction times increased markedly. Most notably, in the CON condition the reaction times remained elevated over the course of the block, In marked contrast, in the STIM condition the reaction times decreased to values similar to those seen in the NULL (and A1 block) by the fifth cycle of the B block. This divergence was expressed in reaction times that were reliably longer in the CON condition than in the STIM condition during cycles 4, 5, 6, 7, 8 and 9 (all $p < 0.05$; $f = 0.48$–0.80).

Upon re-exposure to task A (block A2), there was an initial increase in the RTs exhibited in the STIM condition. Immediately thereafter (cycle 2) the RTs returned to values within the range exhibited during the NULL block. An equivalent diminution was not manifested in the CON condition. Reaction times remained elevated with respect to those present in the NULL block during cycles 1, 2, 4, 5 and 6, and were reliably longer than those obtained in the STIM condition during cycle 5 ($p < 0.05$). In the course of the A24 block, the RTs obtained for the STIM and CON conditions did not differ reliably (planned comparisons yielding p values of 0.06 to 0.14; and f values of 0.39 to 0.51).

To examine whether there was a co-variation between reaction time and adaptation rate at an individual level, we fitted a power function ($Y = aX^b$) to the angular error values obtained in the B block for each participant (Newell & Rosenbloom, 1981). These fits yielded 'a' and 'b' parameters for each participant in each condition (CON and STIM). Next, for each individual in each condition, the mean elevation in reaction time in block B was calculated using the values normalised with respect to the NULL block. We then calculated correlation coefficients to assess the strength of the linear relationship across participants between (1) the mean RT elevation in block B and the 'a' parameter obtained
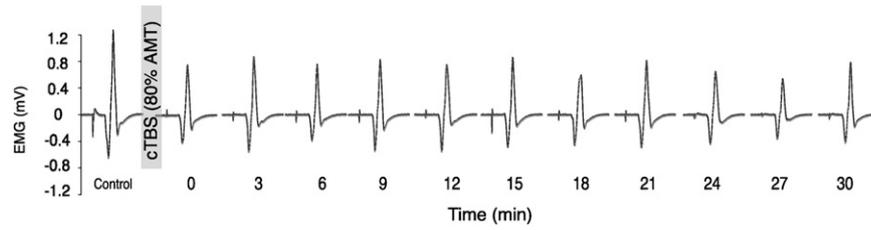
Fig. 3. MEPs from a single participant in Experiment 1. Each wave form is an average of 8 MEPs recorded in the right FCR muscle over the period of 1 min. MEPs were elicited prior to cTBS (control), following cTBS and 4 min rest (time 0), and then every 3 min for 30 min.
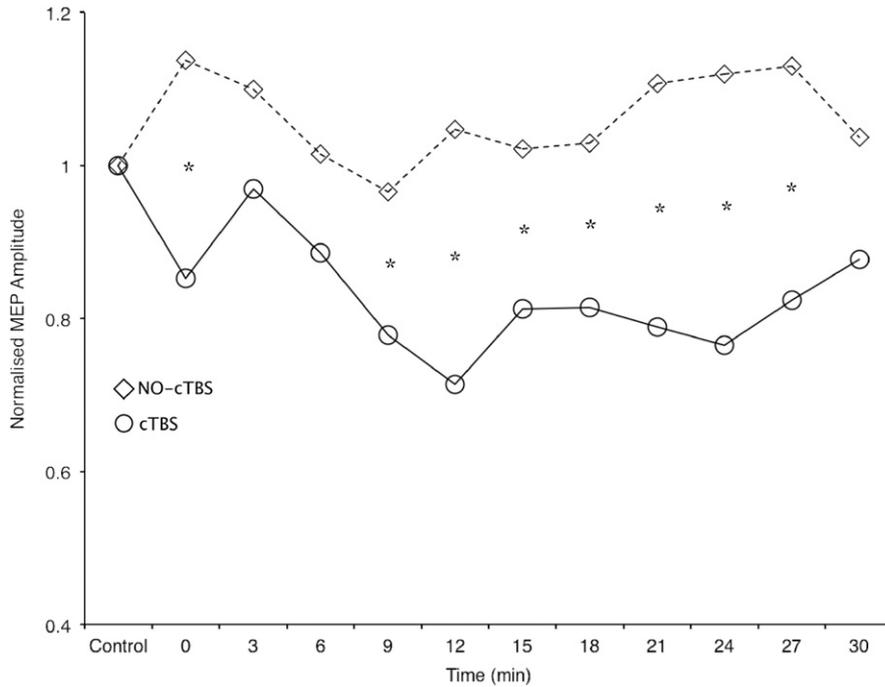

Fig. 4. Amplitudes of the motor evoked potentials (MEPs) obtained from all participants in Experiment 1. Each MEP amplitude was normalised with respect to the individual's control value prior to averaging across participants. Open diamonds represent the NO-cTBS condition; open circles represent the cTBS condition. The character * indicates instances in which the difference between conditions was statistically significant ($p < 0.05$).
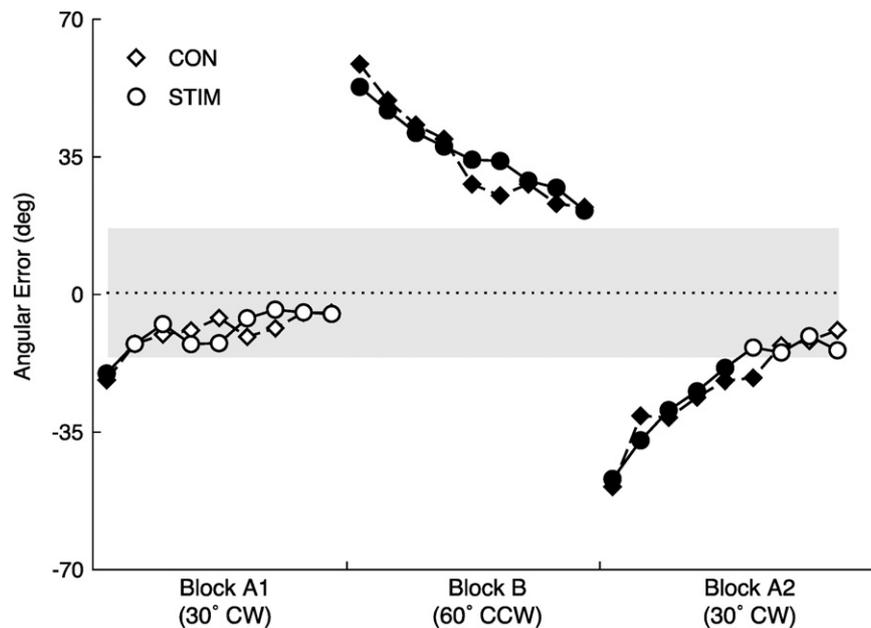

Fig. 5. The Angular Error obtained in Experiment 2 during the A1, B and A2 blocks. In each case, the averages of 16 trials are represented. Values for the Conventional (CON) condition are shown as diamonds, and for the Stimulation (STIM) conditions as circles. The confidence interval (95%) enclosing the mean (horizontal dashed line) of responses obtained during the NULL block is represented as the grey shaded area. Instances in which values deviated from the NULL response by more than the magnitude of the confidence intervals are shown as filled symbols.
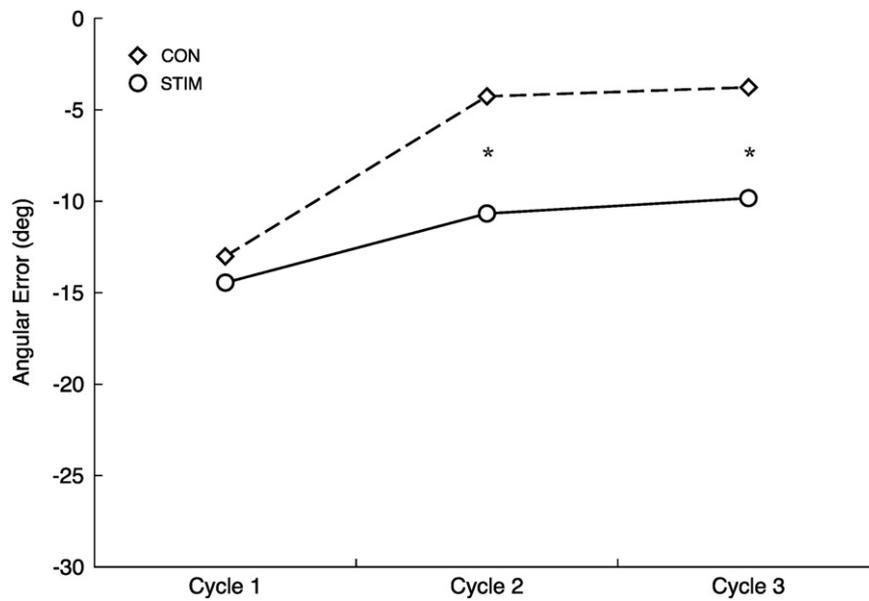
Fig. 6. The Angular Error obtained in Experiment 2 during the A24 block. In each case, the averages of 16 trials are represented. Values for the Conventional (CON) condition are shown as diamonds, and for the Stimulation (STIM) conditions as circles. The character * indicates instances in which the difference between conditions was statistically significant ($p < 0.05$).
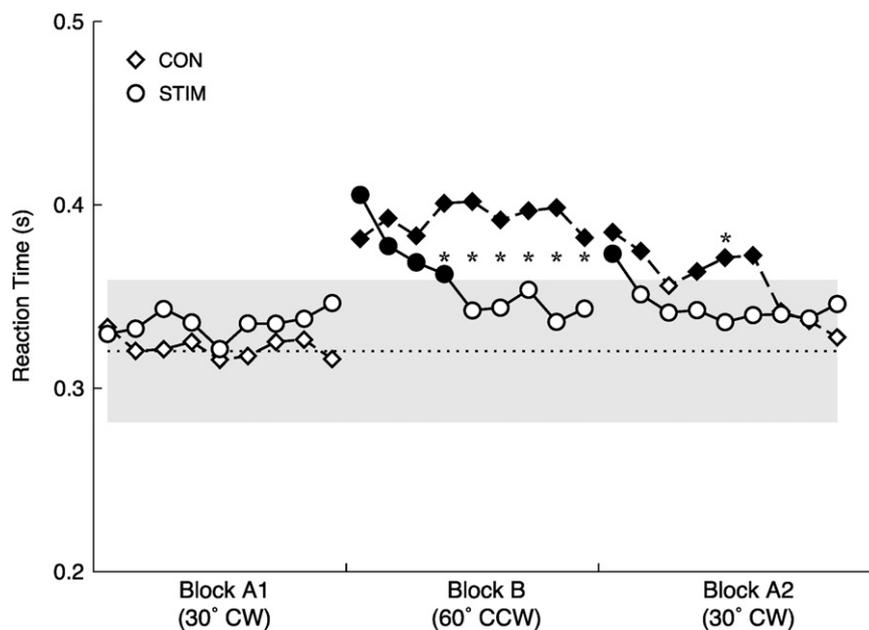

Fig. 7. The Reaction times obtained in Experiment 2 during the A1, B and A2 blocks. In each case, the averages of 16 trials are represented. Values for the Conventional (CON) condition are shown as diamonds, and for the Stimulation (STIM) conditions as circles. The confidence interval (95%) enclosing the mean (horizontal dashed line) of responses obtained during the NULL block is represented as the grey shaded area. Instances in which values deviated from the NULL response by more than the magnitude of the confidence intervals are shown as filled symbols. The character * indicates instances in which the difference between conditions was statistically significant ($p < 0.05$).

from the power function fit and (2) the mean RT elevation in block B and the 'b' parameter—which describes the rate of change obtained from the power function fit. This was undertaken separately for the CON and STIM conditions, yielding a total of four correlation coefficients. The analysis revealed a strong negative covariation ($r = -0.885$, $p = 0.005$) between the 'b' parameter derived from the power fit and the elevation in reaction time in the STIM condition. The degree of association was lower in the CON condition ($r = -.594$) and not statistically reliable ($p = 0.113$). In neither condition was there a reliable association between the 'a' parameter and the change in RT.

3.2.3. Motor evoked potentials

The normalised amplitudes of MEPs elicited by single pulse TMS at intervals during the experiments are illustrated in Fig. 8. In the conventional (CON) condition, the MEPs recorded over the course of the A block were not distinguished from those obtained following the initial trials in which there was no visuomotor rotation (i.e., the NULL block). Following exposure to the opposing visuomotor rotation (B block) however, the MEPs recorded in this condition increased markedly, and remained elevated through the course of the A2 block. No such variations in MEP amplitude were exhibited in the STIM condition. This contrariety was expressed in
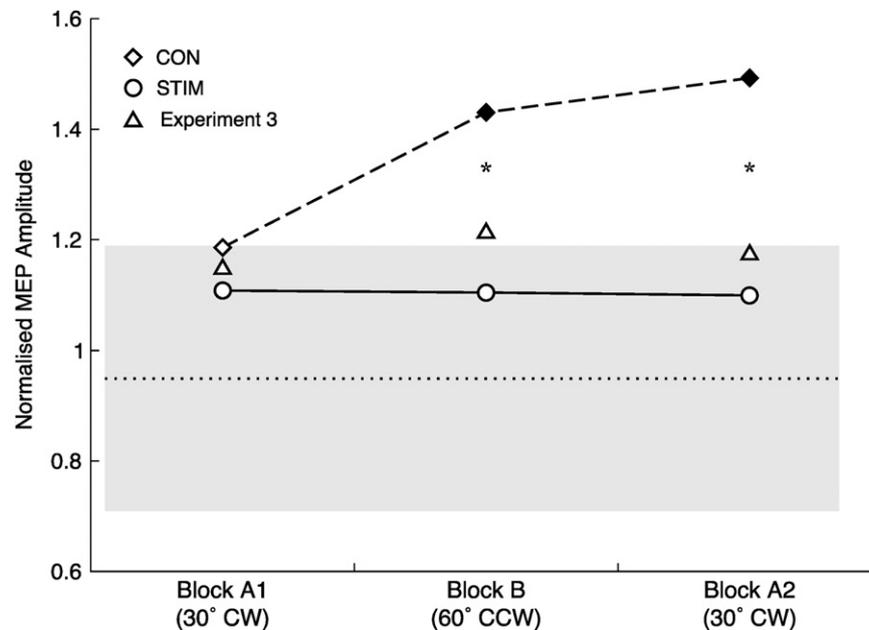
Fig. 8. Amplitudes of the motor evoked potentials (MEPs) obtained in Experiments 2 and 3. For each participant, 8 MEPs were recorded in FCR at rest following each group of 48 trials. For each individual, the values were normalised with respect to the mean of 8 MEPs recorded prior to the NULL trials (corresponding to a value of 1), and then averaged across participants for each condition in each block. Values for the Conventional (CON) condition are shown as diamonds, for the Stimulation (STIM) conditions as circles, and for Experiment 3—in which no rotations were imposed, as triangles. The confidence interval (95%) enclosing the mean (horizontal dashed line) of responses obtained during the post-NULL block is represented as the grey shaded area. Instances in which values (CON and STIM conditions) deviated from the post-NULL response by more than the magnitude of the confidence interval are shown as filled symbols. The character * indicates instances in which the difference between CON and STIM conditions was statistically significant ($p < 0.05$).

statistically reliable contrasts between the MEP amplitudes obtained in the CON condition and the STIM condition during the B ($F_{(1, 21)} = 13.87$, $p < 0.01$, $f = 0.93$) and A2 ($F_{(1, 21)} = 20.18$, $p < 0.01$, $f = 1.12$) blocks.

3.3. Experiment 3

In order to establish whether the elevations in MEP amplitude observed in the conventional (CON) condition were related to the processes of adaptation, or occurred simply as a consequence of the repeated muscular contractions required by the task, six of the eight participants each undertook an extra experimental session in which they produced the same number of contractions to the same targets. In this case, however, no visuomotor rotations were imposed (Fig. 8). Motor potentials were evoked at rest in the manner described above. There were no reliable changes in corticospinal excitability during the period of observation (planned comparisons yielding p values of 0.16 to 0.96; and f values of 0.01 to 0.20). This implies that the increase in MEP amplitude observed in the CON condition during the B and A2 blocks, was not simply attributable to the repeated muscle contractions that were performed over the course of the experiment.

4. Discussion

The purpose of the present study was to investigate the involvement of primary motor cortex during visuomotor adaptation. In contrast to previous approaches, we placed specific emphasis upon reaction time—a measure of movement planning, as a means of discerning the contribution of M1 to initial learning. To this end we used a rTMS protocol (cTBS) to disrupt the function of M1 prior to the onset of an A-B-A adaptation protocol.

The overt characteristics of performance (errors of initial bearing) during the A1 (adaptation), B (counter-adaptation), and A2 (re-adaptation) phases were consistent with earlier findings (e.g., Hinder et al., 2007). The errors (including aftereffects) exhibited in the conventional condition could not however be discriminated from those obtained following the administration of cTBS. This outcome is consistent with previous reports that repetitive TMS does not manifestly affect short-term adaptation in tasks that require the modification of finger (Baraduc, Lang, Rothwell & Wolpert, 2004) or arm (Richardson et al., 2006) movements following the application of novel external force fields.

The use in the present study of a counter-rotation (B) larger than the rotation applied in blocks A and A2 induced a change of state (90°) that is unlikely to have eluded the awareness of the participants. In the conventional condition, RT increased markedly upon transition from the 30° clockwise rotation (A1) to the 60° counter-clockwise rotation (B), an increase that was sustained throughout the period in which the counter-rotation was present. Similarly, upon progression from the counter-adaptation block (B) to the re-adaptation block (A2) reaction times remained elevated. These increases in RT support the conclusion that additional cognitive resources were committed to movement planning in order to compensate for the change in the imposed rotation.

The concurrently obtained measures of corticospinal output suggest that M1 excitability also increased in circumstances in which the participants were required to accommodate the 90° state transition. In the conventional condition, MEP amplitudes were elevated consistently during the B and A2 blocks, relative to those obtained during the NULL block. The results of a supplementary control experiment confirmed that these increases were related to the processes of adaptation, rather than simply a consequence of the repeated muscle contractions required by the task. The present observations thus indicate that during visuomotor adaptation there occur elevations of corticospinal

excitability similar to those that characterise the early learning of ballistic motor tasks (Rozenkranz et al., 2007).

A contribution of M1 to the initial phases of adaptation may be inferred on the basis of the responses to TMS elicited through the course of the A–B–A protocol. The corresponding changes in reaction time imply a covarying involvement of cortical regions specialised for motor planning and execution. The outcomes we obtained following the delivery of rTMS to the primary motor cortex corroborate these interpretations. In such circumstances, no changes in corticospinal excitability were expressed during adaptation. Indeed, in the stimulation condition, the MEPs obtained were effectively equivalent throughout the A1, B and A2 blocks. Notably, reaction times decreased markedly over the course of the counter-adaptation block (B), and during its second half they did not differ from those of the NULL block. A pattern of RT variation which was at odds with that seen in the conventional condition was also expressed for the A2 block, during which the participants re-adapted to the original (i.e., A1) 30° clockwise rotation. The quite distinct variations in reaction time that were exhibited in the two experimental conditions, and in the degree of correlation between changes in RT and angular error (observed during the B block), support the conclusion that M1 stimulation changed profoundly the nature of the adaptive response to the imposed visuomotor rotations.

As a consequence of the distributed and dynamic manner in which skill is represented, disruption or augmentation of one part of the brain, for example through the prior administration of exogenous stimulation, may alter both the weighting of elements within the motor network, and the characteristics of learning. In a recent investigation, Galea, Vazquez, Pasricha, Orban de Xivry and Celnik (2011) administered sham, cerebellar or primary motor cortex (M1) anodal transcranial direct current stimulation (tDCS) during adaptation to a 30° visuomotor rotation. Anodal tDCS generally increases the excitability of brain regions to which it is applied. Galea et al. observed that the rate of adaptation, expressed in terms of directional error, was greater in the presence of cerebellar tDCS than in the sham condition. When tDCS was delivered to M1, there was no impact upon the initial rate of adaptation. Retention of the adaptation was however superior than in conditions of sham or cerebellar stimulation.

In the present study, we used a stimulation protocol (cTBS) that is capable of *decreasing* (Experiment 1; Di Lazzaro et al., 2005; Huang et al., 2005) the excitability of circuits within M1. It was therefore striking that upon re-exposure to the 30° visuomotor rotation 24 h following the initial session, the rate of re-adaptation exhibited when stimulation had been administered was *lower* than that observed in the conventional condition. In demonstrating that a mode of stimulation that has the opposite effect on M1 excitability (i.e., decreasing) yields patterns of re-adaptation/retention that are the reverse of those obtained when anodal tDCS is applied, the present findings both complement and extend those of Galea et al. (2011). They are also consistent with a previous report that 1 Hz rTMS (inhibitory) delivered over M1 prior to adaptation to a velocity-dependent force field failed to disrupt initial learning, but was associated with an increased error rate when testing was conducted 24 h later (Richardson et al., 2006).

The outcomes of the present study demonstrate that in the initial phase of adaptive learning, perturbations of a visuomotor mapping that are sufficient to elicit awareness, lead to a greater allocation of cognitive resources (reflected in elevated RT), and an increased engagement of cortical motor networks (indicated by potentiation of corticospinal output). They also reveal that in this context, disruption of primary motor cortex alters the nature of task-related motor planning, and reduces the rate of subsequent adaptive learning.

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