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RESEARCH ARTICLE

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Afferent stimulation facilitates performance on a novel motor task

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Abstract Training on a motor task results in performance improvements that are accompanied by increases in motor cortex excitability. Moreover, periods of afferent stimulation result in increased motor cortex excitability. There is increasing evidence to suggest that raised motor cortical excitability may facilitate movement and learning. Here we examined whether a period of electrical stimulation of hand afferents (''associative stimulation''), known to increase motor cortex excitability, facilitated the performance of a complex sensorimotor task. Three groups of nine normal subjects participated in these studies. All subjects were trained on the grooved pegboard test (GPT). Training consisted of three blocks, each of five trials, of placing pegs as quickly as possible. The time to complete each block was recorded. One group of subjects had a 1-h period of associative stimulation prior to training on the GPT. A second group received non-associative stimulation (which does not change cortical excitability) of the same hand afferents while a third group received no stimulation prior to training. Motor evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) and abductor digiti minimus (ADM) muscles both prior to and following stimulation and performance of the GPT. In contrast to non-associative stimulation, associative stimulation increased motor cortical excitability, as evidenced by an increase in the amplitude of MEPs evoked in the FDI, one of the stimulated muscles, but not the ADM. Training on the GPT resulted in significant improvements in the time taken to complete the task for all three groups. However, in subjects who had preconditioning associative stimulation, performance on the GPT improved more rapidly. Additionally, there was a strong trend for the improvement in the performance of the stimulated group to be greater than that of the control group. The results of the present study suggest that increased motor cortical excitability, induced by associative stimulation, may facilitate the performance of a novel complex sensorimotor task.

Keywords Afferent stimulation · Motor cortex · Motor performance · Human

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Introduction

The organisation of the human motor cortex may be modified by changes in afferent input. For example, increases in motor cortical excitability are seen following electrical stimulation of peripheral nerves (Hamdy et al. 1998; Ridding et al. 2000) or paired peripheral and cortical stimulation (Stefan et al. 2000; Ridding and Uy 2003). The practice of simple motor tasks also results in reorganisation of the primary motor cortex (Classen et al. 1998; Karni et al. 1998; Butefisch et al. 2004). This is evidenced by an increase in the amplitude of motor evoked potentials (MEPs) that follows transcranial magnetic stimulation (TMS) in muscles involved in the training task. Further, increases in performance have been positively correlated with MEP facilitation (Muellbacher et al. 2001; Garry et al. 2004).

There is increasing evidence that experimentally induced increases in motor cortical excitability may facilitate motor learning. Firstly, Butefisch et al. (2004) have recently shown that applying focal TMS to the motor representation of a muscle involved in a simple motor task enhanced the encoding of the motor memory of that task. Secondly, increases in motor cortical excitability induced by transcranial direct current stimulation facilitate movement in a reaction-time task (Nitsche et al. 2003). Finally, a recent study has shown that transcranial direct current stimulation can also facilitate functional improvement in a small group of chronic stroke patients (Hummel et al. 2005).

Here we investigated whether preconditioning the motor cortex of normal subjects with a period of afferent stimulation, known to increase motor cortical excitability, facilitates the performance of a novel and complex sensorimotor task, in this instance the grooved pegboard test (GPT). The GPT is a task routinely used to assess manual dexterity (Tremblay et al. 2003) and requires the fine manipulation of grooved pegs between the thumb and the index finger.

Methods

Subjects

A total of 27 subjects participated in the study (age range: 20–58 years, 15 males and 12 females). The subjects had no relevant medical history and all investigations were performed on the dominant hand, which was the right hand, as assessed by the Edinburgh Handedness Inventory. All subjects gave their written, informed consent to the studies, which were conducted in accordance with the Declaration of Helsinki and were approved by The University of Adelaide Human Research Ethics Committee.

Recording

Surface electromyographic activity (EMG) was recorded from the right first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles, using disposable silver–silver chloride surface electrodes. The EMG activity was amplified (1,000×), filtered (20 Hz to 1 kHz), and then sampled at 5 kHz (Cambridge Electrical Design 1401, Cambridge, UK). Data was stored on a computer for off-line analysis.

Stimulation

Focal TMS was performed using a flat figure-of-eight shaped coil (external wing diameter 9 cm) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was held over the scalp, with the handle pointing posteriorly and oriented at approximately 45° to the sagittal midline, so that the induced current flowed perpendicular to the estimated alignment of the central sulcus. The optimal position for evoking responses in FDI and ADM was established and marked on the scalp with a soft-tip pen to ensure reliable coil placement between trials.

Experimental procedures

The subjects were randomly assigned to one of three groups, associative stimulation (AS), non-associative stimulation (NS) or the control, and were naïve to both the hypothesis and the training task. The groups were matched with respect to age and sex (AS group 5 males, age 30 ± 12 (mean ± SD) years; NS group 5 males, 32 ± 11 years; control group 5 males, 32 ± 9 years). The resting motor threshold was determined and defined as the minimum stimulator intensity needed to produce an MEP of at least 50 μV in the relaxed FDI muscle, in at least five out of ten successive trials (Rossini et al. 1994). Following threshold determination, the intensity of the TMS was adjusted to evoke an MEP of approximately 0.5–1 mV in both the relaxed FDI and ADM, prior to afferent stimulation. This procedure was also followed for all subjects prior to motor training (MT); this required a reduction of stimulator output intensity after associative stimulation for the AS group subjects, due to an increase in the MEP amplitude following associative stimulation. MEPs were recorded with all muscles relaxed and trials in which background EMG activity was present were excluded from analysis. Muscle relaxation was monitored by giving subjects visual feedback of their EMG with a high gain oscilloscope and auditory feedback.

Pre training MEPs were recorded in FDI and ADM for all groups (Pre Train). Following the MT task, MEPs were recorded immediately following (Post Train) and 10 min following (Post Train_{10}) the task. Additionally, only for the AS and NS groups, MEPs were recorded before associative or non-associative stimulation (Pre Stim), immediately following (Post Stim) and 10 min following associative/non-associative stimulation (Post Stim_{10}). This resulted in a total of three time points at which MEPs were recorded for the control group, and six time points for the two stimulation groups.

Afferent stimulation paradigm

Subjects in the AS group received a period of associative stimulation prior to the MT task. The associative stimulation paradigm previously reported by Ridding and Uy (2003) was used to increase the excitability of the corticospinal projection to the stimulated muscles. Short-duration electrical stimuli were delivered to the FDI and abductor pollicis brevis (APB) simultaneously (Digitimer DS7A stimulators, Digitimer Ltd., Welwyn Garden City, UK). The timing between successive pairs of stimuli was randomised in the range 0.15–2.85 s. The stimulus intensity (range 10–30 mA) was adjusted for each muscle and set at a level just sufficient to evoke a visible motor response. This stimulation paradigm was applied for 1 h and was non-painful for all subjects. Subjects in the NS group received similar stimulation to the two muscles at the same rate. However, in contrast to the associative stimulation paradigm, in this condition the two (FDI and APB) muscles never received synchronous stimulation. This afferent stimulation paradigm does not produce any significant change in motor cortical excitability (Ridding and Uy 2003). The same number of stimuli are applied to each muscle as in the

AS protocol. This paradigm was used to control for general attentional effects. Subjects in the control group were permitted to move freely in the hour prior to performing the MT task.

Motor training task

All subjects participated in the MT task, which consisted of repeated trials using the GPT (Lafayette, IN, USA). The pegs are key shaped and must be appropriately rotated to match the groove in the corresponding hole. Subjects were encouraged to place the 25 pegs as quickly as possible and the time taken to complete the test was recorded. The instructions were standardised and subjects repeated the test in blocks of five trials, with 2 min rest between blocks. A total of three blocks were completed. On average, this gave a total training time of approximately 15 min.

Data analysis

Data from the associative/non-associative stimulation paradigms and the MT task were assessed separately. Two repeated measures analysis of variance (ANOVA) were performed with within-subject factors of TIME (three levels: Pre Stim, Post Stim and Post $Stim_{10}$) and MUSCLE (two levels: FDI and ADM) to determine the effect of AS or NS on MEP amplitude. A separate ANOVA assessed the effect of MT on MEP amplitudes for all three groups with within-subject factors TIME (three levels: Pre Train, Post Train and Post $Train_{10}$) and MUSCLE (two levels), and between-subject factor GROUP (three levels). An additional ANOVA was conducted on the GPT performance data, with factors GROUP (three levels) and BLOCK (three levels). Post hoc testing was performed where appropriate. The significance level was set at $P < 0.05$ and, if not stated otherwise, all group data are given as mean ± SD.

Results

MEP changes following associative stimulation

Analysis of variance revealed a significant effect of MUSCLE ($F_{1,8} = 23.1$, $P = 0.001$) on MEP amplitude, therefore the analysis was repeated for each muscle separately. This revealed a significant main effect of TIME ($F_{2,16} = 3.9$, $P < 0.05$) for FDI, but not ADM ($F_{2,16} = 0.5$, $P < 0.05$). Further analysis of FDI MEP amplitudes revealed that this was due to a significant difference between Pre Stim MEP amplitude and Post $Stim_{10}$ values (Pre Stim FDI MEP amplitude 1.1 ± 0.1 mV, Post $Stim_{10}$ FDI amplitude 1.7 ± 0.3 mV; paired *t*-test, $P < 0.05$; see Fig. 1).

MEP changes following non-associative stimulation

Motor evoked potential amplitudes were unchanged following the period of NS for both FDI (Pre Stim FDI MEP amplitude 0.8 ± 0.4 mV, Post $Stim_{10}$ FDI amplitude 1.2 ± 0.9 mV) and ADM (Pre Stim ADM MEP amplitude 0.7 ± 0.6 mV, Post $Stim_{10}$ ADM amplitude 0.6 ± 0.5 mV). There was no difference between the muscles and no main effect of time (ANOVA, $P > 0.05$).

MEP amplitude changes following MT

In order to obtain test MEPs prior to training of 0.5–1 mV the intensity of stimulation was adjusted for subjects in the AS group. This resulted in a test intensity of $43.9 \pm 18.3\%$ being used (reduced from $51.8 \pm 12.7\%$ prior to associative stimulation). In two of the subjects in the NS group, the stimulation intensity was adjusted. This resulted in a stimulation intensity of $53.5 \pm 10.3\%$ being used (reduced from $55.5. \pm 11.5\%$ prior to non-associative stimulation). In the control subjects, a stimulus intensity of $54.4 \pm 11.4\%$ was employed. Subjects in both stimulation groups performed the MT task 10 min following the stimulation, while the control subjects were permitted to move freely in the period prior to training. There were no significant differences in the pre training MEP amplitudes between the three groups, for either muscle (AS group FDI = 0.9 ± 0.2 mV, ADM = 0.6 ± 0.1 mV; NS group FDI = 1.2 ± 0.8 mV, ADM = 0.6 ± 0.5, control group FDI = 0.9 ± 0.1 mV, ADM = 0.6 ± 0.1 mV; ANOVA, $F_{2,24} = 0.71$, $P = 0.5$).

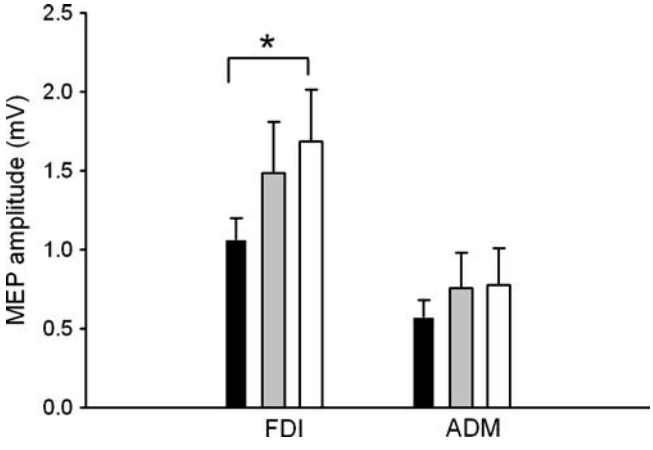

Fig. 1 MEP amplitudes in FDI and ADM, following 1 h of associative stimulation. Data represents the group mean ($n = 9$) and *error bars* illustrate the standard error of the mean (SEM). Columns represent Pre Stim values (*black bar*), immediately following the stimulation (Post Stim, *grey bar*) and 10 min following the stimulation (Post $Stim_{10}$, *white bar*). At Pre Stim, the stimulation intensity was adjusted to elicit a MEP of approximately 1 mV. There was a significant increase in FDI MEPs 10 min following the end of the associative stimulation (*$P < 0.05$)

Following the pegboard training task, analysis of the MEP amplitude data revealed a significant main effect of MUSCLE ($F_{2,24} = 28.8$, $P < 0.001$). The analysis was then repeated for each muscle separately. FDI MEP amplitude increased in the AS group only following MT (Post $Train_{10}$ FDI MEP amplitude 1.3 ± 0.2 mV, paired t-test $P < 0.05$, see Fig. 2), but there was no main effect for time or a time × group interaction for either muscle ($P > 0.05$). There were no significant changes in the amplitude of MEPs in the ADM following the training for any of the three groups.

Changes in GPT performance

There was no difference between GPT completion times for the three groups at block 1 (control group 57.4 ± 7.9 s, AS group 59.1 ± 8.7 s, NS group 59.0 ± 8.6 s; ANOVA, $P > 0.05$). When the data for the three training blocks were examined, however, there was a significant reduction in the time taken to complete the task across the three blocks (effect of BLOCK, $F_{2,48} = 100.2$, $P < 0.001$; Fig. 3). There was no significant difference between the three groups when data from all the three training blocks was examined (GROUP, $P > 0.05$). However, there was a very strong trend towards a difference between the groups in the rate of performance improvement, as indicated by the interaction between the factors of BLOCK and GROUP ($F_{2,48} = 2.5$, $P = 0.052$). Inspection of the raw data suggested that the difference between the groups was greatest between blocks 1 and 2. Therefore, given this strong trend in the data, an additional repeated measures ANOVA was used to compare block 1 and block 2 across the three groups. This analysis revealed a significant BLOCK × GROUP interaction ($F_{2,24} = 5.8$, $P = 0.009$), as shown in Fig. 3. This was due to a greater increase in the performance of the AS group when compared with the control group ($P < 0.001$, unpaired t-test), between blocks 1 and 2, while there was no difference when comparing the performance of the control and NS groups ($P > 0.05$).

Additionally, when comparing percentage improvement between blocks 1 and 3, there was a strong trend for subjects in the stimulation group to improve their performance more than the control group (independent samples t-test, $P = 0.056$). Across the three training blocks, the control subjects improved GPT completion times by $11.3 \pm 3.3\%$, the NS group by $12.9 \pm 7.4\%$, while the AS group improved by $15.6 \pm 5.4\%$.

Discussion

The main, and novel, finding of this study was that increasing the excitability of the motor cortex, by the application of peripheral associative stimulation, facilitated the performance of a complex sensorimotor training task involving the hand. Non-associative stimulation did not result in performance facilitation. This suggests that the effects of associative peripheral stimulation on performance are related to the increased motor cortical excitability and not general attentional effects. Therefore, these findings suggest that enhanced motor cortical excitability may facilitate processes important for motor performance and movement.

The associative stimulation paradigm employed in the present study has been shown to increase the excitability of the corticospinal projection to the stimulated muscles (FDI and APB) for more than 1 h, with the change in excitability increasing over this period (Ridding and Uy 2003). The results from the present study support this previous finding, since MEPs in the FDI muscle were larger in amplitude immediately following the associative stimulation, but not significantly so until

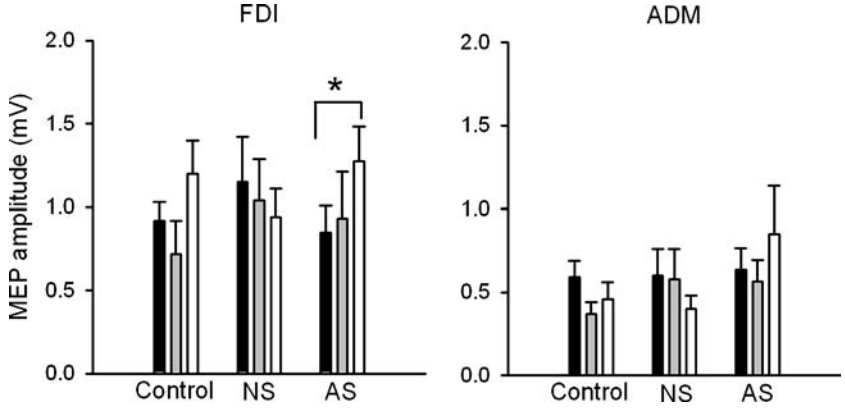

Fig. 2 MEP amplitudes (mean + 1 SEM) following the motor training (MT) task for FDI and ADM. The data of the control group, who performed the task without any intervention, are shown on the *left* of each panel, the data of the non-associative stimulation group in the *middle* of the panel and the data of the associative stimulation group are shown on the *right* of each panel. Columns represent Pre Train values (*black bar*), immediately following the training (Post Train, *grey bar*) and 10 min following the training (Post $Train_{10}$, *white bar*). Following the MT task, MEP amplitudes increased for the FDI in the associative stimulation group (*$P < 0.05$)

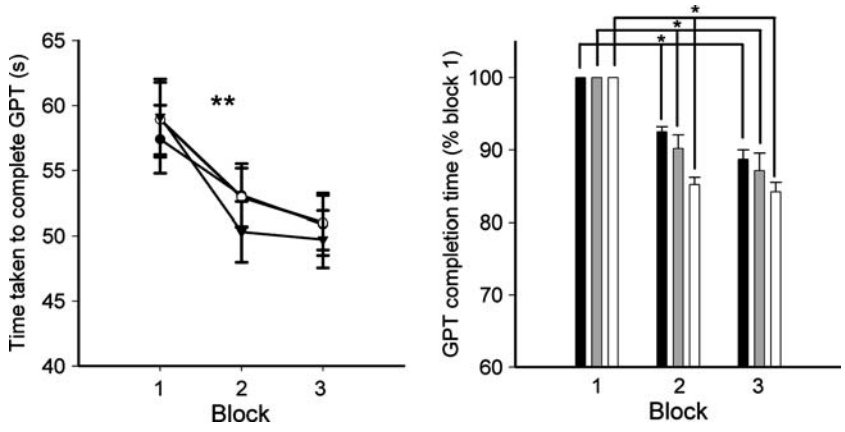

Fig. 3 **a** Time taken to complete the GPT for the control (*filled circles*), NS (*open circles*) and AS groups (*filled triangle*). The mean of five trials in each block is shown and *error bars* indicate ±1 SEM. There was a significant GROUP × BLOCK interaction (**$P = 0.009$) due to a greater reduction in the GPT completion times for the AS group than for the control and NS groups when comparing block 1 and block 2. **b** Normalised (to block 1) GPT times for control subjects (*black bar*), NS subjects (*grey bar*) and AS subjects (*white bar*). The GPT completion times are significantly different between blocks 1 and 2, and blocks 2 and 3 for all groups (*$P < 0.05$)

10 min after the end of the stimulation period. Additionally, the intensity of the test stimulus needed to evoke an FDI MEP of 0.5–1 mV at the Pre Train timing was less than that needed at the Pre Stim time. This is further evidence that there was a lasting increase in the excitability of the corticospinal projection to the stimulated muscles. Therefore, it seems very likely that the excitability of the corticospinal projection to FDI and APB was increased during performance of the GPT in the stimulation group.

The NS paradigm, in contrast to the AS intervention, did not produce a significant change in MEP amplitudes. This finding, again, confirms the results of a previous study (Ridding and Uy 2003). Non-associative stimulation involves the application of the same number of stimuli, at the same average frequency and the same stimulus intensity over the 1 h stimulation period as given during the associative stimulation. However, in the NS paradigm, the two muscles never receive synchronous stimulation. Therefore, subjects in the NS group served as an important control for the general effects of peripheral stimulation, which may have resulted from the subjects attending more to the stimulated hand.

Peripheral associative stimulation, as used in the present study, induces an increase in motor cortex excitability that is associated with an enhancement of intracortical facilitation (Pyndt and Ridding 2004). Similar changes in motor cortex excitability and intracortical facilitation have been reported following a paradigm using paired peripheral and central stimulation, known as paired associative stimulation or PAS (Stefan et al. 2000; Ridding and Taylor 2001). Based upon the time course of the induced excitability change, its specificity and its dependence on *N*-methyl-D-aspartate (NMDA) receptor activation, PAS is likely due to a long-term potentiation (LTP)-like mechanism (Stefan et al. 2002). The mechanism responsible for the excitability change induced by the associative stimulation paradigm employed in the present study is not known. However, given the similarity of the excitability changes induced by associative stimulation (Pyndt and Ridding 2004) and those seen following PAS, it may also involve LTP-like mechanisms.

Several other lines of evidence suggest that increased motor cortex excitability may facilitate movement or motor learning. For example, Butefisch et al. (2004) demonstrated that by combining a simple movement with TMS it was possible to enhance the motor memory of kinematic details of the trained movement. Also, it has recently been shown that hand function improved in a small group of stroke patients following a single session of anodal transcranial direct current stimulation (Hummel et al. 2005), which is known to increase motor cortical excitability (Nitsche and Paulus 2000). This form of stimulation can also improve visuo-motor learning (Antal et al. 2004) and implicit motor learning (Nitsche et al. 2003). The findings of the present study extend these observations in that we have demonstrated that preconditioning with peripheral associative stimulation, which increases motor cortical excitability, can facilitate performance improvements of a complex sensorimotor task. Specifically, associative stimulation increased the rate at which naïve subjects improved their performance on the GPT. Additionally, there was a strong trend for the amount of performance improvement to be increased.

The time taken to complete the first five trials of the GPT task (block 1) did not differ between the three groups, despite the demonstrated increase in cortical excitability in the AS group prior to commencing the task. This suggests that increased motor cortical excitability, per se, would not be sufficient to explain GPT performance. Rather, an ability to become proficient in the task more rapidly than the other two groups cha-

racterises the performance of the AS group, as evidenced by the significant improvement in the block 2 completion times for the AS group only.

Motor training on simple ballistic tasks increases motor cortical excitability and this increase in excitability correlates positively with measures of performance change (Muellbacher et al. 2001). This suggests that the MEP facilitation seen during training might be related to the induced functional change. Additionally, both training induced functional change and the associated MEP facilitation can be blocked by NMDA receptor antagonists (Butefisch et al. 2000), suggesting that both mechanisms are dependent on LTP-like processes. Therefore, it is likely that both MT and associative stimulation result in increases in motor cortical excitability that are dependent on an LTP-like mechanism.

Recently, it has been shown that training on a ballistic thumb task prevented the subsequent induction of LTP-like plasticity by PAS (Ziemann et al. 2004). The results of these studies closely parallel those of cortical slice studies conducted on rats (Rioult-Pedotti et al. 1998, 2000) and together they provide evidence that the excitability changes induced by PAS and motor learning in human subjects share, at least in part, similar cortical networks that may rely on LTP-like processes. However, this finding by Ziemann et al. (2004) might also suggest that an increase in cortical excitability, induced by PAS, may block subsequent training induced changes in performance. Here we have demonstrated that motor performance is facilitated at a time at which motor cortical excitability is increased. The reason for this apparent anomaly is most likely due to the difference between the MT tasks. The GPT task was chosen because it is a complex sensorimotor task that reflects functional abilities. The practise of this task resulted in performance improvements. However, in contrast to the ballistic training task used by Ziemann et al. (2004), it did not result in any MEP change. This suggests that the performance improvement, seen with the GPT task in the present study, may not have been associated with LTP-like changes (see below). Therefore, the lack of MEP change following training on the GPT may at least partly explain why associative stimulation did not block performance changes following training.

In the present study, although subjects in the control and NS groups improved their performance on the training task, it was not accompanied by a significant increase in the MEP amplitude in a muscle involved in the task (FDI). This finding may appear to be contradictory to previous studies that reported significant MEP facilitation in the muscles employed in MT tasks (Muellbacher et al. 2001). However, the training period employed in the present study was only approximately 15 min in duration. This duration is shorter that that used in many other studies (Muellbacher et al. 2001; Ziemann et al. 2004) and may not induce similar LTP-like changes. However, in the AS group, MT of the same duration was accompanied by a larger performance improvement and a significant increase in MEP amplitude. It may be that the increased MEP amplitude is due to a progressive increase in motor cortical excitability, which is known to persist for up to 1 h following peripheral associative stimulation (Ridding and Uy 2003).

In conclusion, the results of the present study demonstrate that increased motor cortical excitability, induced by peripheral associative stimulation, can facilitate the performance of a complex motor task. Whether this reflects facilitated movement or an increase in the rate of learning is not clear, although the present data suggest the latter. The mechanism by which performance is facilitated is not known, but may involve LTP-like mechanisms. Given the obvious therapeutic potential of this result, further studies are warranted.

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