Induction of plasticity in the human motor system by motor imagery and transcranial magnetic stimulation

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Key points

- Delivering transcranial magnetic brain stimulation over the motor cortex during motor imagination leads to enhanced motor output, which is selective for the muscles primarily involved in the imagined movement.
- This novel protocol may be useful to enhance function after damage to the motor system, such as after stroke.

Abstract

Several paired stimulation paradigms are known to induce plasticity in the motor cortex, reflected by changes in the motor evoked potential (MEP) following the paired stimulation. Motor imagery (MI) is capable of activating the motor system and affecting cortical excitability. We hypothesized that it might be possible to use MI in conjunction with transcranial magnetic stimulation (TMS) to induce plasticity in the human motor system. TMS was delivered to the motor cortex of healthy human subjects, and baseline MEPs recorded from forearm flexor, forearm extensor and intrinsic hand muscles. Subjects were then asked to imagine either wrist flexion or extension movements during TMS delivery (n = 90 trials). Immediately after this intervention, MEP measurement was repeated. Control protocols tested the impact of imagination or TMS alone. Flexion imagination with TMS increased MEPs in flexors and an intrinsic hand muscle. Extensor imagination with TMS increased MEPs in extensor muscles only. The control paradigms did not produce significant changes. We conclude that delivering TMS during MI is capable of inducing plastic changes in the motor system. This new protocol may find utility to enhance functional rehabilitation after brain injury.

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Introduction

Performing a mentally simulated movement (motor imagery, MI) initiates complex neuronal mechanisms involving multiple interconnected areas in the central nervous system. The subtle activation of cortical and subcortical areas during MI mirrors the pattern of activity during overt movement (Ingvar & Philipson, 1977; Roland et al. 1980; Rao et al. 1993), and presumably represents

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motor preparation and rehearsal (Yue & Cole, 1992; Decety et al. 1994). As well as the spatial similarity of the activated regions, the timing of a simulated movement seems to follow the constraints of an actual movement (Jeannerod, 1995). Cortical activation during MI even includes the primary motor cortex and corticospinal neurons (Beisteiner et al. 1995; Lotze et al. 1999; Rossini et al. 1999; Romero et al. 2000; Dechent et al. 2004), so that motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) are enhanced during MI (Pascual-Leone et al. 1995; Abbruzzese et al. 1996; Kasai et al. 1997; Facchini et al. 2002).

It is known that plastic changes in motor output can be induced by pairing two stimuli which activate the same circuit, for example a peripheral nerve stimulus with TMS (paired associative stimulation; Stefan et al. 2000; Di Lazzaro et al. 2009). An alternative approach is to pair a single input with endogenous activity. This has been shown to generate long-term changes in animals when the firing of a single cell activates intracortical (Jackson et al. 2006) or intraspinal (Nishimura et al. 2013) microstimulation, and in humans when TMS is triggered from an electromyogram (EMG) produced by a voluntary movement (Edwardson et al. 2014). This approach can also enhance the gains made during motor learning (Buetefisch et al. 2015). However, difficulties with generating appropriate stimulus timing to induce plasticity given known conduction delays can limit the utility of this approach (Brown et al. 2016). Alternatively, subjects can be asked to respond to a visual cue, and the stimulus timed to be before the movement given an estimate of the subject’s reaction time (Thabit et al. 2010).

Given this background, we wondered whether MI could be exploited as an alternative way to activate the cortico-motoneuronal system in a plasticity protocol. This could be especially helpful following injury to the motor system (e.g. after a stroke), when overt movements may no longer be possible. Several prior studies have investigated whether MI could augment rehabilitation (Jackson et al. 2001; Crosbie et al. 2004; Dijkerman et al. 2004; Liu et al. 2004; Page et al. 2005; Sharma et al. 2006; Grangeon et al. 2010), enhance the impact of physical therapy (Warner & McNeill, 1988) or improve motor learning (Yáñuez et al. 1998). However, these studies did not investigate the potential of combining MI with specific stimulation of a central or peripheral pathway.

One previous report succeeded in inducing plastic changes in motor output to the leg by pairing afferent input from peripheral nerve stimulation with MI (Mrachacz-Kersting et al. 2012). A similar protocol also succeeded in increasing corticospinal output in stroke patients (Mrachacz-Kersting et al. 2019). These are promising results, but we recently showed that, in the upper limb, protocols which use sensory input to generate plasticity may have an intrinsic bias towards certain muscle groups. We showed that it was possible to generate robust changes generated in flexor and intrinsic hand muscles, but minimal effects in extensors (Foysal & Baker, 2019). Interestingly, this bias was not seen in a protocol which used only TMS, without paired sensory input.

MI produces an event-related desynchronization (ERD) in the electroencephalogram (EEG) (Pfurtscheller & Neuper, 1997). Several studies have attempted to induce plastic changes by delivering stimulation triggered by this ERD. When subjects repeatedly imagined opening their hand and this was paired with passive hand opening produced by a robot orthosis, the cortex appeared to become more excitable to TMS, but the maximum output generated by high stimulus intensities was reduced (Kraus et al. 2016b). Similar results were seen after pairing TMS with the MI-induced ERD (Kraus et al. 2016a). A combined protocol, in which both TMS and passive hand movement were paired with MI, was capable of increasing maximal corticospinal output as assessed by TMS (Guggenberger et al. 2018; Kraus et al. 2018). These results were especially notable because changes were generated in a finger extensor muscle, in which (as noted above) it can be difficult to generate plasticity.

The use of ERD as a trigger provides an objective way of checking whether MI is being performed successfully, but the additional requirement for an EEG recording and associated specialist trigger hardware may limit the clinical application of this approach. We therefore developed a new paradigm to deliver TMS with MI, and assessed whether this was capable of generating changes in a wide range of upper limb muscles. Our results showed powerful effects on motor output, which even included the extensor muscles, which are often a target for rehabilitative therapy (Kamper et al. 2003). We suggest that this simple approach, which does not require the ability to generate an overt movement, may find future application as an intervention to enhance rehabilitation.

Methods

Ethical approval

All procedures were approved by the local ethics committee of Newcastle University Medical School (ethical approval number 000023/2008) and were in accordance with the Declaration of Helsinki except for registration in a database. Prior to each experiment, full written informed consent was obtained from each participant.

Subjects

Results were obtained from 10 healthy volunteers (2 male; age range 19–45 years), with no history of neurological conditions. Each subject was tested in six different
experimental sessions, in which the protocols described below were delivered in random order and with an intervening interval of at least 7 days. During the study, subjects were seated in a comfortable height-adjustable chair with the right forearm resting on an adjacent table. Participants were instructed to stay relaxed during the entire experiment unless performing a task or MI. Complete muscle relaxation was ensured by real-time monitoring of the EMG signal on a video screen placed in front of the subject and experimenter.

Recordings

Electromyogram (EMG) was recorded from the right forearm flexors (Flex), forearm extensors (Ext), abductor pollicis brevis (APB) and first dorsal interosseous (1DI). A pair of adhesive surface electrodes (Kendall model H59P, MedCat, Klazienaveen, The Netherlands) were placed on the appropriate compartment of the forearm with an inter-electrode spacing of 2–3 cm for Flex/Ext, and over the muscle belly with spacing around 1 cm for APB/1DI. We verified that overt wrist flexion/extension movements produced selective activation of the Flex and Ext recordings as expected. Electrodes were connected to an amplifier (D360, Digitimer, Welwyn Garden City, UK; gain, 1000; bandpass filter, 30 Hz to 2 kHz). EMG signals were digitized (micro1401, Cambridge Electronic Design, Cambridge, UK) and stored on a personal computer (Spike2 software, Cambridge Electronic Design) for later off-line analysis.

Transcranial magnetic stimulation

A figure-of-eight coil (model D70²) connected to a Magstim 200² stimulator (Magstim Ltd, Whitland, UK) was used to deliver focal TMS to the left hemisphere. The coil was positioned tangentially over the head with the handle pointing posterolateral at a 45° angle to the sagittal plane. The coil was fitted with optical markers; further markers attached to a headband on the subject’s forehead allowed maintenance of a fixed coil location relative to the head (Brainsight, Rogue Resolutions Ltd, Cardiff, UK).

For each subject, MEPs from the Flex and Ext recordings were assessed with suprathreshold TMS to locate the optimal site to produce responses in both channels. This site was then marked as the ‘hotspot’ TMS to locate the optimal site to produce responses in both channels. This site was then marked as the ‘hotspot’ in the Brainsight system, and used for delivering TMS throughout the experiment. Following previous studies (Rossini et al. 1994; Stefan et al. 2000), resting motor threshold (RMT) was determined as the minimum stimulator intensity required to evoke at least 50 µV peak-to-peak response in both relaxed muscles in at least 5 out of 10 repeated trials. MEPs were assessed at 1.2 × RMT throughout the subsequent experiment.

Experimental procedures

Prior to each study which used MI, participants were given some practice in MI, during which they were instructed to imagine the desired movement (flexion or extension). During this training session, a few cortical stimuli were applied while the subject practiced MI. Peak to peak increase in the MEP amplitude during MI without any noticeable background EMG activity was regarded as indicating that the subject performed MI successfully (Fadiga et al. 1998). Most subjects reported that it was difficult to stay focused and imagine the movement repeatedly for the prolonged period which we needed. However, we found that if participants were asked to perform an overt movement just before they imagined the same action, it improved the concentration, efficacy and timing of imagination. Therefore, we adopted an approach in which subjects were first asked to perform overt movements, followed by MI which coincided with TMS delivery. Each cycle started with the performance of three overt movements. These were phasic flexion or extension movements around the wrist, performed a little faster than once per second. After the third movement, subjects imagined performing further repeated similar movements. This MI continued until TMS delivery; after a brief rest (> 1 s), subjects then started the next cycle of overt movements. Subjects were not given specific instructions on how many imagined movements to make, merely that they should continue with MI until the TMS pulse. The last overt movement ended several seconds before TMS delivery, as confirmed from monitoring the EMG. The cycle of overt movement, MI and TMS was repeated every 8 s. The first cycle was initiated by the verbal instruction ‘start now’; subsequent cycles were triggered by the TMS pulse which ended the previous cycle.

At the start of all experiments, baseline MEPs were recorded from all four muscles (TMS rate 0.1 Hz; intensity 1.2 × RMT; subject at rest; n = 20 stimuli; Fig. 1A). One of six intervention protocols was then performed, in some of which 90 TMS pulses (rate 0.1 Hz; intensity 1.1 × RMT) were paired with various task conditions; this lasted 15 min. Immediately after the intervention, MEPs were again assessed as in the baseline period (n = 80 stimuli).

The six intervention protocols tested are illustrated in Fig. 1B. In the first two, TMS was paired with MI of either flexion or extension movements (Fig. 1Ba and b). The remaining protocols served as controls, and tested either the effect of MI without TMS (Fig. 1Bc and d), or TMS without MI (Fig. 1Be and f). The latter two controls were especially important, since they included the overt movements used to maintain subject focus, but without the instruction to imagine the movement afterwards. Occasionally, subjects requested a brief break (1–2 min) during an intervention protocol if they felt that they were losing concentration on the MI.
Figure 2 illustrates example EMG recordings during two of the intervention protocols. The period of overt movements produced clear modulation of the EMG (white bars; wrist flexion, Fig. 2A, wrist extension, Fig. 2B). This was followed by MI, where EMGs showed no modulation (black bars). TMS was delivered during the MI (arrows). This example makes clear that there was coactivation of all recorded muscles during the wrist movements.

Data analysis

We initially intended to analyse the time course of any plastic changes after the intervention, by recording responses to four blocks of 20 stimuli (each block followed immediately after the previous one). However, we found that there was high variability between subjects in time course. Some showed the maximum plastic change immediately after the intervention, whereas for others the increase was delayed. Averaging the time course across subjects did not appropriately represent this, and the high inter-subject variability reduced statistical power. Accordingly, we decided to combine all 80 responses after the intervention into one average, to yield a robust estimate of MEP magnitude which effectively showed whether plasticity had occurred or not.
Evoked EMGs for all four muscles were first processed by blanking the stimulus artefact for the period 0–6 ms after the TMS pulse, and high pass filtering at 1 Hz to remove a small DC offset often introduced by the amplifier. Traces were then rectified and averaged separately for each muscle. The artefact blanking procedure led to an apparent small double artefact visible on some of the illustrated averages. The area under the curve for each sweep was measured in a window which started from a point at or before the MEP onset latency as assessed by the experimenter (range 11.8–15.2 ms post-stimulus) and ended 50 ms after the stimulus. Significant differences between MEPs before and after a given intervention at the single subject level were assessed using Student’s t test. These were used only for illustration, and to count how many subjects showed significant changes as a measure of consistency between individuals. Accordingly, the significance threshold was set to $P < 0.05$, uncorrected for multiple comparisons. Average MEP areas after an intervention were expressed as a percentage of the baseline measurement, and significant changes at the population level were assessed by a two factor repeated measures ANOVA, with factors recorded muscle and intervention type. Mauchly’s test of sphericity revealed that the data were not spherically distributed; the Greenhouse–Geisser correction was therefore used. Subsequent post hoc paired t tests were performed to identify significant changes, with $P$ values corrected for multiple comparisons using the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995) and a corrected threshold of $P < 0.05$. Analysis was performed using custom scripts in the MATLAB environment (The Mathworks Inc., Natick, MA, USA); repeated measures ANOVA was performed in SPSS Statistics (IBM Corp., Armonk, NY, USA), after confirming that residuals were not significantly different from a normal distribution (Shapiro–Wilk test, $P > 0.05$).

**Results**

Across all experiments, the resting motor threshold was $36.0 \pm 5.8\%$ of the maximum stimulator output (mean ± SD). MEP amplitudes before the intervention, assessed as area under the curve of rectified EMG, were $0.57 \pm 0.30$, $1.01 \pm 0.43$, $0.84 \pm 0.76$ and $1.31 \pm 0.81$ mV ms for the Flex, Ext, APB and 1DI muscles, respectively. There was no significant effect of muscle on baseline MEP amplitude (repeated measures ANOVA, $F(1.97,17.7) = 3.19; P = 0.066$).

Figure 3 illustrates example results from a single subject. Each column presents the changes seen after a different intervention, with baseline MEPs shown in black, and MEPs after the intervention in red. When TMS was paired with flexion MI, the MEP in all four recorded muscles increased significantly (marked by asterisks, $P < 0.05$). When extension MI was paired with TMS there was a more focal increase only in the Ext muscle; the Flex muscle MEP was significantly reduced. In the remaining (control) interventions, some significant changes were observed in this subject, although these largely appeared inconsistent and were all decreases in MEP amplitude.

Figure 4 presents results for all subjects. For each muscle, the size of the MEP after the intervention is expressed as a percentage of the baseline (Fig. 4A–D, upper panels). Measurements from each subject are shown as circles; the mean ± SD is presented as a square. These
data were used for statistical analysis to demonstrate consistent changes following the intervention (indicated by asterisks next to the mean data points). However, it is increasingly recognized that there is considerable inter-subject variability in the response to plasticity protocols (e.g. Wiethoff et al. 2014); an average across all subjects does not appropriately represent this variation. To provide such information, beneath each plot is a bar display (Fig. 4A–D, lower panels) which indicates the number of subjects which showed a significant increase (black), decrease (grey) or no significant change (white). This provides an indication of how consistent the

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**Figure 3. Example results from a subject after testing two intervention and four control protocols**

The vertical dotted line indicates TMS onset. Black trace, MEP before; red trace, MEP after the intervention. *Significant difference in MEP amplitude between before and after intervention (P < 0.05, t test). Rows show responses recorded from forearm flexors (Flex), extensors (Ext) and intrinsic hand muscles (APB, 1DI). Columns show results following the six different intervention protocols illustrated in Fig. 1B. [Colour figure can be viewed at wileyonlinelibrary.com]
findings were across subjects. We have used uncorrected significance levels in these calculations at the single subject level; accordingly, we would expect up to two subjects to show significant changes by chance under the null hypothesis.

Repeated measures ANOVA with Greenhouse–Geisser correction revealed a significant main effect of intervention type ($F(2.44,22.0) = 11.1; P < 0.0005$, partial $\eta^2 = 0.551$) but not EMG ($F(1.39,12.5) = 0.013; P = 0.958$, partial $\eta^2 = 0.0015$). There was a significant intervention–EMG interaction ($F(5.03,45.2) = 3.1; P = 0.017$, partial $\eta^2 = 0.256$). Post hoc $t$ tests revealed three significant changes (asterisks in Fig. 4; $P < 0.05$ corrected for multiple comparisons). For flexion MI paired with TMS, there was a significant increase in MEP for the Flex and APB muscles. There were also increases in MEPs for the 1DI and Ext in some subjects. For 1DI, the average increase was 44%, which just failed to reach significance when averaged across subjects after correction for multiple comparisons using the Benjamini–Hochberg procedure ($P = 0.0094$, criterion $P < 0.0083$ for false discovery rate of 5%). Extension MI paired with TMS produced a significant increase in MEP only for the Ext muscle; however, this was a highly consistent finding, with all subjects showing this effect. The control interventions had no significant effect on the MEP size.

Subjects were required not to produce EMG modulation during MI, and this was checked continually during the experiment by the experimenter. To confirm that small changes in background activation could not have explained our results, we analysed the change in background EMG before and after the intervention. Repeated measures ANOVA with Greenhouse–Geisser correction revealed no significant effect of either intervention type ($F(1.19,10.7) = 1.22; p = 0.306$), EMG ($F(1.09,9.84) = 0.95; p = 0.362$) or their interaction ($F(1.15,10.3) = 0.82; p = 0.404$).

**Discussion**

In this study, we have demonstrated for the first time that stimulation of the motor cortex delivered at the same

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**Figure 4.** Group results for all muscles after delivery of two intervention and four control protocols

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time as MI can generate plastic changes in motor output. Importantly, changes were seen in all hand and forearm muscles which we studied, even in extensor muscles which we have previously shown may be resistant to induction of plasticity using other protocols (Foysal & Baker, 2019).

**Motor imagery with TMS induced plasticity**

It is well known that plasticity can be produced by pairing pre- and postsynaptic activation (Hebb, 1949). In Hebb’s original description, this pairing could be relatively loose in time; subsequent work has led to the concept of spike timing-dependent plasticity (STDP), in which millisecond-level precision is needed in the relative timing of pre- and postsynaptic activity (Bi & Poo, 2001). When plasticity is induced by pairing afferent nerve stimuli with TMS at short intervals (paired associative stimulation), it appears to follow the rules of STDP (Stefan et al. 2000), generating long term potentiation or depression depending on the relative timing of the arrival of the activity evoked by the two stimuli at the cortex. It is unlikely that our protocol involving MI and TMS accessed these mechanisms. Any changes in cortical activity with MI should have a broad time course, comparable to the time frame of the imagined movement. In addition, in our study subjects imagined repeated movements, which would further blur the timing of changes in cortical activity relative to the stimulus. The TMS pulse could not therefore occur in a millisecond-precise period relative to a postsynaptic spike.

However, there is evidence that coactivation of pre- and postsynaptic activity on a less accurate timescale can also generate plastic change. Paired associative stimulation can lead to long term depression, if the peripheral nerve stimulation follows TMS by 250–450 ms (Schabrun et al. 2013). Pairing afferent inputs with motor imagination generated long term potentiation, which was lost by shifting input timing by around 200 ms (Mrachacz-Kersting et al. 2012). This is outside the typical window for STDP, and may indicate the action of a different process. Additionally, a general increase in excitability may raise the probability that a postsynaptic cell responds to a presynaptic input (see Fig. 5E and associated text in Brown et al. 2016). This monosynaptic response would occur at short and fixed latency, possibly leading to the generation of STDP without precisely paired stimuli. Even using invasive cortical microstimulation through implanted electrodes, Seeman et al. (2017) found that only a minority of tested sites exhibited plasticity dependent on timing as expected by STDP. It is known that delivering cortical stimulation to coincide with overt movement can lead to plastic changes (Thabit et al. 2010; Lucas & Fetz, 2013; Edwardson et al. 2014; Buetefisch et al. 2015). It is likely that similar mechanisms are at work in the plasticity which we observed when pairing TMS with MI.

One potential confounding factor in our study was that MI was always preceded by overt movement. We found this helpful to improve the consistency of MI, which is known to affect the associated cortical activation (Lebon et al. 2012). It seems unlikely that the plasticity which we observed was generated by the consequences of the preceding overt movement. Most importantly, control interventions which retained the same practice movements, but without the requirement for MI, did not generate plastic changes. Additionally, the movements were completed around 4 s prior to the delivery of the TMS pulse; this is a very long interval, and we would expect all cortical effects of the movements to be over well within this time. Two previous studies showed plastic changes induced merely by practicing a movement, although there were important differences from our protocol. In the work of Rosenkranz & Rothwell (2006), subjects actively tried to increase the speed of movement; here, the only requirement was to make the flexion or extension movements as requested. In the study of Classen et al. (1998), subjects performed movements every 1 s for 30 min, a total of around 1800 movements. This is considerable more intense practice than the 270 movements performed over 15 min in our experiment.

One limitation of our study is that we were not able to provide information on the time course of plastic changes, which we found highly variable between subjects. This caused us to analyse our results simply by combining responses to all stimuli given after the intervention. It is possible that longer periods of stimulation with MI could enhance plastic changes and lead to a more consistent and long-lasting increase in MEPs, as has been reported with other paradigms (Fitzpatrick et al. 2016). This would allow a more detailed examination of the time scale of the changes in future.

**Specificity of plastic changes**

In animal preparations, plasticity shows the property of specificity: only the stimulated pathway is enhanced, whilst other circuits are left unchanged (Barrionuevo & Brown, 1983). Plasticity induced in the human motor system can also show specificity in some circumstances (Stefan et al. 2000). Our new paradigm involving MI did show some degree of specificity. After flexion or extension imagination, there was enhancement of MEPs in the muscle group congruent to the imagined movement, but not in the antagonist. However, during flexion MI, plastic changes also spread to an intrinsic hand muscle; this was not seen during extension MI. In this context, it should be noted that the overt practice movements often resulted in some co-contraction across all recorded
muscles (see Fig. 2); it is therefore likely that the imagined movements also involved limited activation of the cortical representation of many muscles. In addition, we delivered TMS at a scalp location chosen to optimize responses in the forearm flexor and extensor muscles. This was unlikely to be the optimal site to generate responses in intrinsic hand muscles, and it is possible that spread of plastic changes would not have occurred if the hot-spot had been instead selected based on these muscles.

Using focal juxta-threshold intracortical microstimulation, Zaaimi et al. (2018) found that the majority of sites within primary motor cortex do not coactivate forearm flexors with extensors, or forearm with intrinsic hand muscles; this implies a high level of specificity within the corticospinal output. When subjects imagine activating a single hand muscle, MEP enhancement is limited to that muscle, suggesting that MI can focally access the relevant cortical sites (Facchini et al. 2002). It is likely, therefore, that the additional ‘spillover’ plasticity in hand muscles following MI of wrist flexion arises not from any non-specificity in the cortical representation, nor in its activation by MI, but in the processes generating plasticity. In this regard, we have recently demonstrated considerable non-specificity using a different plasticity protocol (Foyals & Baker, 2019). When we paired stimulation of the motor point of either forearm flexor or extensor muscles with TMS, we found plastic changes in intrinsic hand and forearm flexor muscles, but not in the extensors. This has some similarities to the present findings, although it is of note that here we were able to generate plastic changes in the extensors by extensor MI. Furthermore, these changes were confined to the extensor muscles, with no changes in either flexors or intrinsic hand muscles. It remains unclear why flexor MI should generate a less focal plastic change than extensor MI.

The site of plasticity

MI is known to activate the motor cortex (Lotze et al. 1999; Kraus et al. 2018), and it is therefore tempting to assume a cortical locus for the plastic changes which we observed. However, changes in MEP amplitude could reflect an increase in cortical and/or subcortical excitability. Short-latency spinal reflexes are enhanced during MI (Bonnet et al. 1997; Li et al. 2004), in a similar way to during voluntary movement (Pierrot-Deseilligny & Lacert, 1973). It appears that this phenomenon is not related to changes in fusimotor drive, but to an increased excitability of the motoneuron pool (Gandevia et al. 1997), which would also increase MEP amplitude. However, others have reported a reduction in spinal excitability during MI (Oishi et al. 1994; Yahagi et al. 1996), which may represent the deployment of an inhibitory system intended to prevent the overt manifestation of the imagined movement. Spinal, as well as cortical, circuits are capable of undergoing plastic changes (Lamy et al. 2010; Dixon et al. 2016; Foyals et al. 2016); such spinal plasticity is under cortical control (Chen et al. 2006a,b). It is therefore most likely that pairing MI with TMS induces changes at multiple levels of the neuraxis.

Motor imagery and rehabilitation

Our results were obtained in healthy subjects, but they raise the interesting possibility that MI paired with TMS could be used to enhance rehabilitation in patients with motor impairments. Some forms of damage to the motor system can lead to difficulties with MI: for example, after damage to the parietal cortex, patients are inaccurate at using MI to estimate the time that an action will take (Sirigu et al. 1996). However, patients with acute or chronic hemiplegia can activate partially damaged motor networks during MI (Johnson, 2000; Johnson et al. 2002). Such covert activation can be extracted using implantable electrode arrays (e.g. Ajiboye et al. 2017), forming the basis for the clinical promise of brain–machine interfaces. This suggests that MI remains intact in many patients.

Several studies have reported positive outcomes after incorporating MI into a rehabilitative regime (Jackson et al. 2001; Page et al. 2001; Crobbie et al. 2004; Dijkerman et al. 2004; Liu et al. 2004; Page et al. 2005; Sharma et al. 2006; Mulder, 2007; Grangeon et al. 2010; Mateo et al. 2015). One crucial aim of rehabilitation is to reorganize the motor system network (Jones, 2000) by inducing activity–dependent plasticity in the motor cortex (Jones, 1993; Florence et al. 1998), brainstem (Foyals et al. 2016) or spinal cord (Wolpaw & Tennissen, 2001; Dunlop, 2008). MI has often been used alone to activate motor connections in the absence of an actual movement, or in conjunction with physical training, physiotherapy or behavioural therapy. Our results suggest that robust plastic changes in cortical outputs can be induced when MI is paired with single pulse TMS, and extend previous work (Kraus et al. 2016a, 2018; Guggenberger et al. 2018) which triggered TMS from ERD generated by MI. Exploiting MI might be more feasible than protocols which attempt to pair TMS with overt movement, as in some patient groups increased variability in reaction time might hinder accurate timing of TMS relative to movement onset. Our paradigm has the advantage that it does not require an EEG recording and associated hardware to trigger TMS at a precise time during the ERD. Importantly, both our paradigm and that of previous work seem able to access plasticity in forearm extensor muscles (Kraus et al. 2016a, 2018; Guggenberger et al. 2018). These are often left weak in stroke survivors, and form an important target for rehabilitation to improve motor function (Kamper et al. 2003). Spontaneous plasticity during recovery appears

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biased against extensor muscles (Zaaimi et al. 2012), and some stimulation-based paradigms share this bias (Foyasa & Baker, 2019). The addition of a new protocol capable of enhancing extensor output, even in the absence of voluntary movement, may provide a useful addition to the toolkit of functional rehabilitation.

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