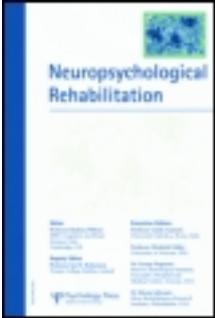


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Visual feedback-related changes in ipsilateral cortical excitability during unimanual movement: Implications for mirror therapy

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Provision of a mirror image of a hand undertaking a motor task (i.e., mirror therapy) elicits behavioural improvements in the inactive hand. A greater understanding of the neural mechanisms underpinning this phenomenon is required to maximise its potential for rehabilitation across the lifespan, e.g., following hemiparesis or unilateral weakness. Young and older participants performed unilateral finger abductions with no visual feedback, with feedback of the active or passive hands, or with a mirror image of the active hand. Transcranial magnetic stimulation was used to assess feedback-related changes in two neurophysiological measures thought to be involved in inter-manual transfer of skill, namely corticospinal excitability (CSE) and intracortical inhibition (SICI) in the passive hemisphere. Task performance led to CSE increases, accompanied by decreases of SICI, in all visual feedback conditions relative to rest. However, the changes due to mirror feedback were not significantly different to those observed in the other (more standard) visual conditions. Accordingly, the unimanual motor action itself, rather than modifications in visual feedback, appears more instrumental in driving changes in CSE and SICI. Therefore, changes in CSE and SICI are unlikely to underpin the behavioural benefits of mirror therapy. We discuss implications for rehabilitation and directions of future research.

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Keywords: Mirror therapy; Ipsilateral cortical excitability; Transcranial magnetic stimulation; Rehabilitation; Ageing.

INTRODUCTION

Mirror therapy (MT) is a psychophysiological technique, first established by Ramachandran and Rogers-Ramachandran (1996), as a visual illusion to alleviate phantom limb pain, a condition in which a person experiences the painful sensation of an amputated or missing limb. MT involves placement of a mirror in a person's midsagittal plane, thus superimposing a mirror image of one limb over the (obscured) contralateral limb. Since its conception, research focusing on improving (behavioural and/or subjective) outcome measures such as motor performance or pain reduction (Thieme, Mehrholz, Pohl, Behrens, & Dohle, 2012) has provided substantial support for the use of MT in stroke rehabilitation (Altschuler et al., 1999; for an overview, see Thieme et al., 2012; Yavuzer et al., 2008) and in the treatment of chronic regional pain syndrome (CRPS) (McCabe et al., 2003; for an overview, see Ramachandran & Altschuler, 2009). Considerably less research, however, has focused on investigating the neural mechanisms which underlie the manifested behavioural changes elicited via MT.

Contrary to behavioural MT studies which, despite their relatively small sample sizes, appear to show consistent beneficial effects of mirror training with regard to improved outcome measures (Altschuler et al., 1999; Chan et al., 2007; McCabe et al., 2003; Ramachandran, Rogers-Ramachandran, & Cobb, 1995) the consensus regarding the neural underpinnings of mirror training is much less certain. A possible reason for this might be the wide array of imaging and brain stimulation techniques employed by the relatively few studies that have attempted to elucidate the neural mechanisms underlying MT, such as functional magnetic resonance imaging (fMRI) (Shinoura et al., 2008), transcranial magnetic stimulation (TMS) (Carson & Ruddy, 2012; Fukumura, Sugawara, Tanabe, Ushiba, & Tomita, 2007; Funase, Tabira, Higashi, Liang, & Kasai, 2007; Garry, Loftus, & Summers, 2005; Laepchen et al., 2012; Nojima et al., 2012), and electroencephalography (EEG) (Touzalin-Chretien & Dufour, 2008). Methodological differences in regard to task complexity (i.e., simple versus complex motor tasks), outcome measures used (i.e., tests of motor behavioural improvement in both the limb undertaking the task and the contralateral quiescent limb), and the nature of the visual feedback (e.g., vision of both limbs versus solely vision of the mirror feedback) provided during the experiments may also contribute to the absence of a consensus regarding the neural mechanisms that mediate the improved behavioural outcomes. A more precise

understanding of the neural basis of the mirror feedback phenomena (e.g., changes in corticospinal excitability as well as specific changes in intra- and inter-cortical circuits) is, however, crucial if MT is to be adopted more widely as a rehabilitation and clinical tool for a number of distinct clinical populations (e.g., stroke sufferers, as well as those suffering from chronic pain or unilateral muscle weakness to name just a few). As such, more neurophysiological studies on MT are required.

To investigate the potential neurophysiological mechanisms underpinning MT, previous studies have predominantly examined changes within the hemisphere ipsilateral to a moving limb during a unilateral motor task (Fukumura et al., 2007; Funase et al., 2007; Garry et al., 2005; Nojima et al., 2012) on the assumption that excitability increases in this hemisphere are related to performance gains in the untrained limb (e.g., Carroll, Lee, Hsu, & Sayde, 2008; also see Garry et al., 2005; Hinder, Schmidt, Garry, & Summers, 2010a, 2010b; Lee, Hinder, Gandevia, & Carroll, 2010). In 2005 Garry and colleagues asked participants to perform a continuous (rhythmic) unimanual finger abduction-adduction task, while provided with different types of visual feedback (Garry et al., 2005). TMS was applied over the M1 ipsilateral to the moving hand. Results demonstrated a generalised excitability increase in the ipsilateral (inactive) hemisphere during unilateral movements relative to a resting condition (where both limbs were quiescent) regardless of the nature of the visual feedback provided. More importantly, however, a Mirror Vision condition (in which participants watched a mirror image of the moving hand) led to larger excitability increases in ipsilateral primary motor areas than the other visual feedback conditions (such as viewing the active hand, the passive hand or fixating on a centrally aligned mark). The authors suggested that this additional excitability increase in the mirror feedback condition may underlie the behavioural benefits of mirror feedback reported in previous studies, such as performance gains in the untrained limb following viewing a mirror image of the trained limb during a motor task (Altschuler et al., 1999). Several subsequent studies (Laepchen et al., 2012; Nojima et al., 2012; Shinoura et al., 2008; Touzalin-Chretien & Dufour, 2008) have formed conclusions that are consistent with Garry and colleagues' (2005) original findings; however other studies (Fukumura et al., 2007) have only partially supported Garry et al. or have provided quite differing conclusions (Carson & Ruddy, 2012). For instance, in 2007 Fukumura and colleagues conducted a study in which participants performed a left hand wrist movement under different task conditions in which they were provided with mirror feedback of their active hand and/or imagined movement of the passive hand. Only when the motor task was undertaken in combination with motor imagery did mirror feedback lead to larger excitability increases (as measured by TMS-induced motor evoked potentials during task execution) in the ipsilateral hemisphere compared to those observed in

the non-mirror conditions. Using a similar motor task, Carson and Ruddy (2012) asked participants to perform a unimanual left hand wrist movement under different experimental conditions (No Vision, Mirror Vision, Passive Vision). Although Mirror Vision induced ipsilateral excitability increases, these changes were not significantly greater than in the condition in which participants did not see either hand. Moreover, it was found that vision of the passive hand lead to a significantly *lower* excitability increase in the hemisphere ipsilateral to the working hand when compared to Mirror Vision or No Vision conditions. Taken together, the Fukumura et al. (2007) and Carson and Ruddy (2012) results show that modifications in visual feedback during a motor task affect the magnitude of the increase in corticospinal excitability in the hemisphere ipsilateral to a unimanual movement. However, contrary to the earlier findings by Garry et al. (2005), their results do not support the notion that MT confers a greater increase in ipsilateral corticospinal excitability than other feedback conditions. As such, these studies would argue against the supposition that the behavioural benefits of MT are a result of a greater increase in ipsilateral corticospinal excitability (Garry et al., 2005).

The apparently disparate conclusions with regard to the efficacy of mirror feedback in promoting increases in excitability of the ipsilateral hemisphere may, at least in part, stem from a lack of formal definition as to what should be concluded to represent a beneficial neurophysiological effect. In this regard, based on the assumption that mirror feedback results in improved performance in an untrained limb due to its effect on corticospinal excitability in the ipsilateral hemisphere, we propose that for mirror feedback to represent a valuable therapeutic intervention it *must* promote changes in corticospinal excitability that significantly *outweigh* changes that are elicited when the motor task is undertaken in the usual manner. Specifically, because one generally focuses on the hand undertaking a motor task (e.g., reaching and grasping a cup of tea, turning a key in a lock), we propose that mirror vision must elicit excitability changes (in the ipsilateral cortex) *above and beyond* those which occur when directly viewing the active hand. It is apparent that the vast majority of the aforementioned studies failed to apply this criterion when forming their conclusions with regard to the efficacy of mirror feedback; indeed a number of studies (Carson & Ruddy, 2012; Fukumura et al., 2007; Nojima et al., 2012) did not investigate the effects of vision of the active hand to permit the suggested comparison to be made retrospectively.

If we re-appraise the results of the aforementioned studies in regard to the definition of beneficial neurophysiological changes following MT, it is apparent that of those which did employ a condition that focused on the active hand (Funase et al., 2007; Garry et al., 2005; Tominaga et al., 2011), all failed to demonstrate mirror vision-elicited changes in corticospinal excitability that were significantly larger than those manifested in the standard visual condition (i.e., vision of the active hand). In only one study (Garry et al.,

2005) did this comparison approach significance ($p = .069$), and, supported through a large effect size value ($d = 0.91$), may have failed to reach statistical significance as a result of the small sample size employed in that study. Therefore, while there appears to be some evidence to suggest mirror vision may promote ipsilateral cortex excitability, when assessed under our formalised definition, more research is required to further investigate this hypothesis.

Even though the (behavioural) effects of mirror feedback have been investigated in different clinical populations (Altschuler et al., 1999; McCabe et al., 2003; Yavuzer et al., 2008), to our knowledge no studies have specifically addressed MT in the context of ageing. This is surprising given that ageing incontrovertibly leads to functional and structural changes in the brain that not only affect behavioural aspects of motor performance (Seidler et al., 2010), but also neural control mechanisms underpinning movement performance (Fujiyama, Garry, Levin, Swinnen, & Summers, 2009; Hinder, Fujiyama, & Summers, 2012; Hinder, Schmidt, Garry, Carroll, & Summers, 2011; Talelli, Waddingham, Ewas, Rothwell, & Ward, 2008; Ward, 2006). Furthermore, older adults are more reliant on visual control and feedback to permit accurate motor performance (Swinnen et al., 1998; Voelcker-Rehage, 2008), and use more visual strategies while learning and performing motor tasks (Swinnen et al., 2010). Thus, a pertinent question is whether older adults exhibit greater responses (in terms of ipsilateral corticospinal excitability) to mirror vision when provided with it during the performance of a motor task. If this was found to be the case then MT would have the potential to be applied in rehabilitation programmes that are specifically tailored to aiding recovery in older people after injury. It could assist in regaining the loss of independence due to unilateral impaired motor functions not only after stroke (Thieme et al., 2012), but also after fall-related injuries; two of the major concerns which can adversely affect motor control in older people.

The current experiment had two main aims: Firstly, we wished to pursue the question of whether (as suggested by Garry et al.'s 2005 finding), mirror feedback promotes ipsilateral M1 facilitation compared to the more standard feedback conditions; secondly, we aimed to determine the effects of MT in older populations where visual effects could be expected to be more profound. Because of the purported role of SICI in motor learning and transfer (Laepchen et al., 2012; Perez & Cohen, 2008), and because of age-related changes in SICI (Hinder et al., 2012; Peinemann, Lehner, Conrad, & Siebner 2001) we also investigated intracortical inhibition in the active, and the inactive, hemisphere. The current experiment was undertaken following the study design of Garry and colleagues (2005), and an a priori power analysis revealed that a total 12 subjects would be required to detect an effect comparable to that reported in Garry and colleagues ($d = 0.91$).

Considering we were also interested in whether older adults exhibit greater responses to mirror vision (i.e., the addition of an extra variable) our study was conducted with two groups of 12.

METHODS

Participants

Twelve younger (mean age = 24.6 years, $SD = 4.7$, 8 men and 4 women) and 12 older (mean age = 70.3 years, $SD = 5.5$, 3 men and 9 women) adults participated in the experiment. All declared themselves as right-handed, and had normal or corrected-to-normal vision and were screened for contraindications to transcranial magnetic stimulation (TMS). Additionally, a medical history questionnaire revealed that they were free from any known neuromuscular disorders and did not have a history of neurological illnesses that might affect neurophysiological measures (as assessed by TMS). The experimental procedures were approved by, and carried out in accordance with, local ethical guidelines laid down by the Tasmanian Human Research Ethics Committee Network, and conformed to the declaration of Helsinki. Prior to beginning the experiment participants asked any questions regarding techniques and procedures and, when they were happy, signed an informed consent form. Subjects either received course credit, or \$20 reimbursement for their research participation.

Movement task

Participants were seated in a height adjustable chair with their forearms resting on the table and their palms facing down. Subjects were asked to perform discrete unilateral index finger abduction movements, carried out with either the left or right hand (instructed by the experimenter) and consisting of both a dynamic movement phase and a tonic (isometric) contraction phase. The hand undertaking the task is referred to as the “active” hand, while the contralateral hand, which remained quiescent throughout the movement trials, is referred to as the “inactive” hand. The initial part of the movement (index finger abduction) was performed against the resistance of a rubber band, which was put around the index finger and the middle finger of both hands (i.e., one rubber band on each side). Participants then maintained an isometric force against this resistance (i.e., the stretched elastic band) before relaxing such that their index finger returned back to the start position without resistance or effort (index finger adduction). The tension in the band was adjusted individually for each participant such that they could undertake the task “without excessive finger force and without finding repetitive movements fatiguing”. An auditory

metronome (0.5 Hz, 500 ms tone duration) was used to pace participants' movements. One complete abduction-adduction cycle was performed on each beat of the metronome (duration of one complete cycle = 2000 ms). Participants were asked to synchronise their finger abduction with the onset of the metronome beat and to (tonically) maintain the index finger abducted for the duration of the tone. The start and end points of the movement were indicated by dots on the table, individually adjusted to ensure reasonably large movement amplitudes for each participant (i.e., participants were asked to move to the end of their biomechanical range of motion during the abduction phase, while the rest of the hand was kept still and relaxed).

During the period in which participants undertook the movements they were provided with different types of visual feedback. In accordance with Garry et al. (2005) there were five different visual experimental conditions: Active Vision, Passive Vision, Central Vision, Mirror Vision and Baseline. In the Active and Passive Vision conditions, participants visually fixated on the active or inactive hand, respectively, while vision of the opposite (unattended) hand was occluded with a wooden box. In the Central Vision condition, participants looked straight ahead fixating a centrally aligned marker in the wall and vision of both hands was prevented by covering them with two boxes. In the Mirror Vision condition, a mirror was placed vertically in the midsagittal plane and participants viewed a mirror reflection of their active hand. Direct vision of the inactive hand was not possible due to the positioning of the mirror; however, the mirror image of the active hand appeared superimposed on top of the obscured position of the inactive hand. A custom-built screen, situated in the coronal plane between participants' upper body and their active hand, further prevented a direct view of the active hand (see Figure 1). In all four of these (active task) conditions, participants undertook the unilateral motor task. In the fifth condition (Baseline condition) *both* hands remained quiescent, participants looked straight ahead and vision of both hands was prevented by covering each of them with a box.

In each active task, participants performed two blocks of 30 trials (1 trial = 1 movement) with each hand (for a total of 20 blocks, each of 1 minute duration). The order of hands and visual conditions was counterbalanced between subjects, with the exception of the Baseline condition, which was always performed prior to (Baseline 1) and following (Baseline 2) the four active conditions for each hand. Participants received one familiarisation trial with the Active Vision condition prior to the main experiment, and were allowed rest breaks between blocks to minimise possible fatigue effects. The experiment lasted approximately 2 hours, which included set-up time and familiarisation with the experimental task.



Figure 1. Experimental set up for the Mirror Vision condition. A mirror was placed vertically in the midsagittal plane and participants viewed a mirror reflection of their active hand, with the mirror image of the active hand appearing superimposed on top of the obscured position of the inactive hand. A custom-built screen, situated in the coronal plane between participants' upper body and their active hand, further prevented a direct view of the active hand.

Electromyographic recordings

Bilateral electromyographic (EMG) recordings were obtained from the left and right first dorsal interosseus (FDI) muscles, the primary agonists for the finger abduction task. Participants' skin was prepared with a lightly abrasive gel and cleaned with an alcohol wipe before attaching Ag/AgCl electrodes (Meditrace 130, Tyco Healthcare, Mansfield, MA) in a belly-tendon montage. EMG signals were amplified ($\times 1000$) and a notch filter (50 Hz) was applied prior to sampling using a 16-bit AD system (Power 1401, CED Limited, Cambridge, UK) and collected data were stored on a computer for subsequent offline analysis. EMG recordings enabled us to monitor task accuracy (i.e., movement synchrony with the tone of the metronome beat in the active hand) as well as quiescence in the inactive hand during task execution.

Transcranial magnetic stimulation

TMS was used to investigate corticospinal excitability and short interval intracortical inhibition (SICI) of the motor pathways from the inactive left and right motor cortices (lM1 and rM1) during right and left hand movements, respectively (i.e., we measured excitability of projections from M1 ipsilateral to the movement). TMS was delivered by two Magstim 200 magnetic stimulators (Magstim Company, UK) connected by a Bistim unit and a figure of eight coil (70 mm diameter).

The position over the M1 that consistently induced the largest motor evoked potentials (MEPs) in the contralateral muscle of interest was defined as the motor hotspot. It was determined by placing the coil over the approximate location of the representation of the left and right FDI within M1 (~ 5 cm lateral and 2 cm anterior to Cz) and subsequently moving the coil around in small steps to different scalp positions to identify the location in which suprathreshold stimulation consistently produced the largest MEPs in the target muscle. The exact location orientation of the coil (with posterior-to-anterior-induced current in the cortex, i.e., coils at $\sim 45^\circ$ to the midline and in a plane tangential to the scalp surface) was then marked on the scalp and TMS intensity was reduced in 2% increments until the lowest TMS intensity was identified that elicited at least three out of five MEPs $\geq 50 \mu\text{V}$ (Garry et al., 2005; Hinder et al., 2011). This intensity was deemed to be resting motor threshold (RMT). During the experiment, alternating single-pulse and paired-pulse stimulation were delivered to the motor cortex of the inactive hemisphere. Single-pulse magnetic stimulation at suprathreshold (130% RMT) was applied to assess corticospinal excitability of the projections from the inactive hemisphere. Paired-pulse magnetic stimulation was applied to assess intracortical inhibitory processes (SICI). SICI was measured according to a paired-pulse paradigm by applying a subthreshold conditioning stimulus before a suprathreshold test stimulus (130% RMT) with an interstimulus interval (ISI) of 3 ms (Kujirai et al., 1993). The conditioning pulse was initially set to 70% of RMT, but subsequently adjusted to ensure that the elicited MEPs were suppressed by approximately 50%. TMS was delivered within every fifth movement cycle, 250 ms after the onset of the metronome beat during the isometric phase of the finger abduction. We recorded 12 MEPs per block (six single-pulse and six paired-pulse MEPs) and conducted two blocks per hand and visual condition, thereby collecting 24 MEPs for each condition (12 single-pulse and 12 paired-pulse MEPs).

Data and statistical analysis

We firstly visually inspected all trials to ensure that EMG activity in the FDI of the active hand was present prior to and at the time point of TMS delivery (i.e.,

synchrony of muscle activation with the onset of the metronome beat), indicating that a tonic contraction was present during the delivery of each TMS pulse. Trials with poorly timed, or absent, FDI activation, i.e., asynchrony of movement (AOM), were discarded from further analysis. Following removal of these trials we calculated root-mean-squared (rms) EMG in the *inactive* hand ($\text{rmsEMG}_{\text{inactive}}$) in the period 115–15 ms prior to each TMS pulse. Additional trials were excluded from further analysis if $\text{rmsEMG}_{\text{inactive}}$ exceeded 0.025 mV. In the remaining trials, rms EMG of the *active* hand ($\text{rmsEMG}_{\text{active}}$) was calculated in the same time window, while peak-to-peak MEP amplitudes elicited in the FDI of the inactive hand by TMS were calculated in the 50 ms period commencing 15 ms after TMS delivery. Single-pulse MEP amplitudes were averaged and normalised to the MEPs obtained during the Baseline conditions in each hand on a participant-by-participant basis. Normalised (n) MEPs were subsequently log transformed (referred to as $\text{Ln } n\text{MEP}$) to reduce skewness that is otherwise associated with normalised (i.e., ratio) data (Hinder et al., 2010a; Sinclair & Hammond, 2008). Paired-pulse MEP amplitudes were averaged for each vision condition and divided by the corresponding single-pulse MEP amplitudes to calculate a SICI ratio for all five vision conditions (referred to as SICI). Accordingly, $\text{SICI} < 1$ indicates inhibition is present, with lower SICI indicating greater inhibition. SICI was log transformed and normalised to SICI obtained during the Baseline conditions (referred to as $\text{Ln } n\text{SICI}$) in each hand on a participant-by-participant basis. Positive $\text{Ln } n\text{SICI}$ represents a decrease in inhibition while negative values indicate an increase in inhibition, relative to Baseline.

The number of rejected trials (due to voluntary activity in the inactive hand or asynchrony of movements in the active hand) was compared using independent sample t -tests to compare rejection rates across participant groups. Additional independent t -tests were performed to further compare differences in raw single-pulse MEP values as well as raw SICI at Baseline across participant groups. To compare $\text{rmsEMG}_{\text{active}}$, $\text{Ln } n\text{MEP}$ and $\text{Ln } n\text{SICI}$ we used repeated measures analysis of variance (RM ANOVAs) with hand (left, right) and vision condition (Active Vision, Mirror Vision, Central Vision, Passive Vision, Baseline) as within-subject factors and age (younger, older) as a between-subjects factor. Analysis of $\text{rmsEMG}_{\text{active}}$ investigated whether there were statistically significant differences in the strength of the voluntary contraction in the four visual conditions in which an active contraction was required. Analysis of $\text{Ln } n\text{MEP}$ and $\text{Ln } n\text{SICI}$ was aimed at investigating variations in corticospinal excitability and intracortical inhibitory processes in the inactive hemisphere as a function of visual feedback and age. The alpha level was set to .05 (with a Greenhouse-Geisser's degree of adjustment for violated assumed sphericity) and post-hoc pairwise comparisons examined all significant interactions using the Sidak adjustment. To aid the interpretation of the tests of significance partial eta-squared and Cohen's d are also presented and

interpreted as a measure of effect size with cut-offs ≥ 0.2 small, ≥ 0.5 medium, ≥ 0.8 large for Cohen's d and ≥ 0.01 small, ≥ 0.06 medium, and ≥ 0.14 large for partial eta-squared (Cohen, 1988).

RESULTS

All results are presented as means (M) \pm standard deviations (SD), and 95% confidence intervals (CI).

Analysis did not reveal statistically significant differences between 100% RMT for participants of the younger group, 46.3 ± 8.8 , $CI = 42.4, 50.2$, and the older group, 46.3 ± 8.5 , $CI = 42.8, 49.9$ ($p = 1.0$).

Rejection rates

The average rate of discarded trials (over all participants in both groups) was 5.95% (5.74% due to increased EMG activity, 0.21% due to AOM). Independent t -tests compared the rejection rates due to high rms EMG in the inactive hand and asynchrony of movement (AOM) in the active hand between participant groups. Participants of both groups did not differ significantly in their ability to synchronise their movements with the onset of the metronome beat during the four active conditions, AOM in % for younger group: $M = 0.15 \pm 0.16$, $CI = 0.05, 0.24$, AOM in % for older group: $M = 0.28 \pm 0.28$, $CI = 0.12, 0.44$, $t(24) = 1.44$, $p = .167$, $d = 0.57$. Older subjects, however, showed a significantly higher rejection rate due to high rmsEMG in the inactive hand prior to the TMS pulse, $M = 8.6 \pm 8.2$, $CI = 3.0, 13.4$, when compared to participants of the younger group, $M = 2.9 \pm 4.0$, $CI = 1.5, 6.6$, $t(24) = 2.17$, $p = .045$, $d = 0.89$.

Since the strength of contraction in the active hand is able to influence the size of MEP amplitudes in the inactive hand (Liepert, Dettmers, Terborg, & Weiller, 2001; Muellbacher, Facchini, Boroojerdi, & Hallett, 2000), we also analysed rmsEMG_{active}. This analysis showed significantly larger rmsEMG_{active} in the left hand (0.476 mV) in comparison to rmsEMG_{active} in the right hand (0.371 mV), $F(1, 22) = 9.83$, $p = .005$, $\eta_p^2 = .309$. However, more importantly, rmsEMG_{active} did not differ significantly across the four active viewing conditions, $F(3, 66) = 1.01$, $p = .396$, $\eta_p^2 = .044$. Except for a trend towards significance for the interaction between hand and age ($p = .057$, younger: left hand versus right hand, $d = 0.78$, older: left hand versus right hand, $d = 0.15$), no other significant differences were found ($ps > .2$).

MEP amplitudes

Raw MEP amplitudes for both groups did not differ significantly at Baseline, younger group: $M = 1.93 \pm 1.22$ mV, $CI = 1.24, 2.62$, older group: $M =$

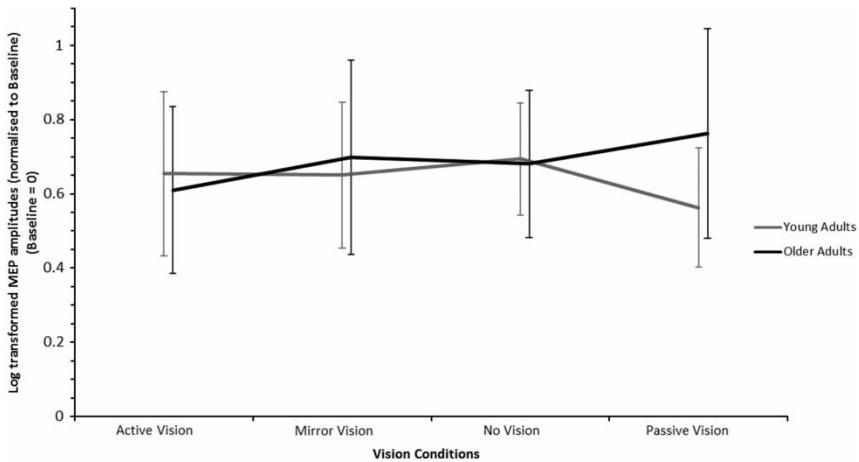


Figure 2. Mean and 95% CI of log transformed and normalised MEP amplitudes (Ln nMEP) reported relative to Baseline MEP amplitudes (i.e., Baseline = 0 on the y-axis) for the four active vision conditions for younger and older groups.

1.45 ± 0.93 mV, CI = 0.91, 1.97, $p = .471$, $d = 0.45$. Accordingly, normalised and log transformed MEP values (Ln nMEP) were subsequently analysed in two steps. An initial analysis revealed an absence of main effects and interactions in which age was a factor, age: $F(1, 22) = 0.12$, $p = .733$, $\eta_p^2 = .005$; hand x age: $F(1, 22) = 0.36$, $p = .552$, $\eta_p^2 = .016$; vision x age: $F(4, 88) = 1.01$, $p = .409$, $\eta_p^2 = .044$; hand x vision x age: $F(4, 88) = 1.83$, $p = .130$, $\eta_p^2 = .077$ (see Figure 2 for an overview of Ln nMEP for the four active vision conditions).

Since that initial analysis did not reveal substantive effects involving the factor age, we collapsed the data across age and conducted a subsequent 2×5 RM ANOVA ($N = 24$). Analysis revealed a significant main effect of vision condition, $F(4, 92) = 38.64$, $p < .001$, $\eta_p^2 = .627$. Post-hoc comparisons (Sidak) revealed that the MEP amplitudes in all four vision conditions were significantly enhanced compared to Baseline (all $ps < .001$, all $ds > 2.0$), indicating that unilateral activation increased ipsilateral corticospinal excitability. No other differences were found between the visual conditions (all $ps > .992$, all $ds < 0.16$, 95% CI). Furthermore, neither the main effect of hand, $F(1, 23) = 0.74$, $p = .398$, $\eta_p^2 = .031$, nor the interaction of hand x vision, $F(4, 92) = 1.17$, $p = .331$, $\eta_p^2 = .048$, was significant.

The analysis of Ln nSICI was conducted in the same manner as the Ln nMEP values. An initial t -test revealed that SICI at Baseline did not differ between participants of both groups, younger group: $M = 0.52 \pm 0.17$, CI = 0.49, 0.56, older group: $M = 0.48 \pm 0.17$, CI = 0.45, 0.52 ($p = .557$, $d = 0.24$). As with Ln nMEP, the omnibus ANOVA for Ln nSICI failed to

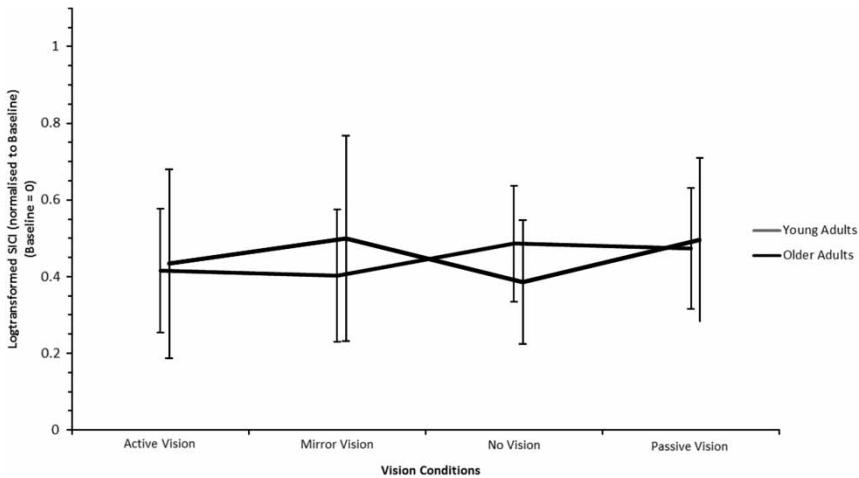


Figure 3. Mean and 95% CI of log transformed and normalised SICI (Ln nSICI) reported relative to Baseline SICI (i.e., Baseline = 0 on the y-axis) for the four active vision conditions for younger and older groups.

reveal any significant effects with age as a factor, age: $F(1, 22) = 0.004$, $p = .941$, $\eta_p^2 < .001$; hand x age: $F(1, 22) = 0.47$, $p = .499$, $\eta_p^2 = .021$; vision x age: $F(3, 66) = 1.52$, $p = .217$, $\eta_p^2 = .064$; hand x vision x age: $F(3, 66) = 1.53$, $p = .214$, $\eta_p^2 = .065$ (see Figure 3 for an overview of LN nSICI for all four active conditions).

A subsequent 2×5 RM ANOVA ($N = 24$) conducted after collapsing across both age groups revealed a significant main effect of vision condition, $F(4, 92) = 24.94$, $p < .001$, $\eta_p^2 = .520$. Post-hoc comparisons (Sidak) revealed that SICI in all four vision conditions was significantly enhanced compared to Baseline (all $ps < .001$, all $ds > 1.6$), indicating that unilateral activation resulted in a decreased intracortical inhibition in the ipsilateral hemisphere. No other differences were found between the visual conditions (all $ps > .911$, all $ds < 0.18$). Furthermore, neither the main effect of hand, $F(1, 23) = 0.41$, $p = .527$, $\eta_p^2 = .018$, nor the interaction of hand x vision, $F(4, 92) = 0.45$, $p = .773$, $\eta_p^2 = .019$, was significant.

DISCUSSION

The current study investigated the extent to which different forms of visual feedback mediate the (well-described) increases in excitability of corticospinal projections to a passive limb during movements undertaken with the contralateral limb. In an attempt to provide insights into the neural mechanisms

underlying the behavioural improvements resulting from MT (see Ramachandran & Altschuler, 2009; Thieme et al., 2012), a specific focus of this study was to assess whether mirror feedback of the moving limb led to more pronounced increases in ipsilateral corticospinal excitability compared to direct vision of the active limb. Furthermore, we were interested in investigating to what degree changes in ipsilateral intracortical inhibition (SICI) might be affected by provided visual feedback and how such modifications relate to induced changes in corticospinal excitability. Because MT is likely to be most beneficial in older populations (e.g., following stroke or immobilisation of a limb due to traumatic injuries or falls) we also aimed to determine whether ageing was associated with a change in the role of vision in mediating changes in corticospinal excitability and SICI ipsilateral to the moving limb.

Overall, we demonstrated that (relative to a condition when both hands were at rest) unimanual movements increase corticospinal excitability in the ipsilateral (e.g., passive) hemisphere when either no visual feedback of either hand, or feedback of the active hand, passive hand, or a mirror image of the active hand was provided. However, we failed to show any significant differences in the extent of these increases in corticospinal excitability *between* the different feedback conditions. Most notably, and in regard to our hypothesis that mirror visual feedback would provide additional excitability gains relative to the “ecological” or “natural” condition whereby participants watched the active hand, the Mirror Vision condition conferred no additional excitability gains relative to the Active Vision condition. Accordingly, for the present task the unimanual motor action itself appears to be instrumental in modifying ipsilateral corticospinal excitability with the nature of the feedback provided while undertaking that task of little/less consequence.

The present results are not consistent with earlier studies that have noted the importance of specific types of visual feedback for facilitating the most potent changes in ipsilateral corticospinal excitability during motor tasks (Carson, Welsh, & Pamblanco-Valero, 2005; Garry et al., 2005; Laepchen et al., 2012; Nojima et al., 2012), and for influencing the extent of performance gains in the untrained hand as a result of cross-limb transfer following a (unilateral) motor learning task (Laepchen et al., 2012; Nojima et al., 2012). It is apparent, however, that these studies did not specifically contrast neurophysiological or behavioural measures following provision of mirror visual feedback with those derived following direct visual feedback of the active hand. As alluded to previously, we propose that for mirror feedback to be concluded as being instrumental in driving performance gains in the untrained limb (e.g., with respect to cross-limb transfer) or in driving neural adaptation in the untrained/inactive cortex, the behavioural or neural adaptation following mirror visual feedback must be more pronounced than

that observed following visual feedback of the active hand. Accordingly, while offering some insight into the mechanisms underlying MT, current research has not been able to offer definitive answers as to why MT subjectively appears to have such profound effects (see Ramachandran & Altschuler, 2009; Thieme et al., 2012).

Facilitation of corticospinal excitability in the passive hemisphere due to voluntary contraction of the ipsilateral limb has been shown in many previous studies (Aziz-Zadeh, Maeda, Zaidel, Mazziotta, & Iacoboni, 2002; Muellbacher et al., 2000; Perez & Cohen, 2008; Strafella & Paus, 2000) and has been proposed to occur due to crossed facilitation of neural pathways (Ruddy & Carson, 2013). There is evidence to suggest that the increases in ipsilateral corticospinal excitability are driven by decreases of intracortical mechanisms within the ipsilateral hemisphere (Muellbacher et al., 2000), as well as by an interaction between intracortical and transcallosal circuits (i.e., decrease of SICI and increase in interhemispheric inhibition) (Perez & Cohen, 2008). The current results, which showed a decrease in SICI in the ipsilateral hemisphere in all four active conditions when compared to baseline, do support the notion that increases in corticospinal excitability were driven, at least in part, by a decrease in SICI in the ipsilateral hemisphere.

It is apparent that, in the absence of volitional movement of either limb, profound effects on brain circuits and motor behaviour can also be evoked by movement/action observation (Aziz-Zadeh et al., 2002; Strafella & Paus, 2000). Specifically, action observation (AO) effects have been demonstrated to cause short-term changes in corticospinal excitability (i.e., during movement observation; see Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995), as well as long-term changes in motor cortical functions (i.e., formation of a motor memory as assessed by changes in motor representation; see Stefan et al., 2005), and have often been associated with the existence of an action observation/action execution matching system in the human brain (Touzalin-Chretien & Dufour, 2008). Even though originally associated with observation of another individual performing a task (Aziz-Zadeh et al., 2002; Strafella & Paus, 2000), AO-like effects have also been proposed to be responsible for the beneficial behavioural effects of mirror feedback during *self-execution* of a motor task (Garry et al., 2005; Laeppchen et al., 2012; Nojima et al., 2012). Garry and colleagues (2005) previously argued that putative therapeutic effects, such as an improved motor performance measured as range of motion, speed and accuracy in hemiparetic patients, which have been reported in recent behavioural-focused MT research (Altschuler et al., 1999; Yavuzer et al., 2008), may be caused by an *interaction* of voluntary unimanual movements and AO effects. The current study allowed us to go some way in determining which of these factors is most instrumental in driving the observed excitability change in the ipsilateral hemisphere that has previously been reported in MT-based research (Garry

et al., 2005; Laeppchen et al., 2012; Nojima et al., 2012). Based on our results, which showed a significant facilitation in MEP amplitudes in *all* active conditions (all $ps < .001$, all $ds > 2.0$) compared to the baseline condition, but no significant difference in the extent of the facilitation observed in the Mirror Vision and Active Vision conditions ($p = 1.0$, $d = 0.16$), the unimanual movement appears to play a more important role in modifying corticospinal excitability in the passive hemisphere than observing the unimanual action through provided (mirror) visual feedback (i.e., AO). Moreover, although our results showed the ipsilateral corticospinal excitability increase was accompanied by a decrease in SICI, we did not find significant differences in the extent of this decrease in inhibition as a consequence of the various feedback conditions between the Mirror/Active Vision condition and the Central Vision condition (excitability: all $ps > .992$, $ds < 0.16$; SICI: all $ps > .911$, all $ds < 0.18$). The absence of differences in ipsilateral corticospinal excitability increase and in the decrease in SICI between the Active Vision and the Mirror Vision condition indicates that the variation in visual feedback provided during task performance, asking participants to either focus on their contralateral limb (Mirror Vision) or their ipsilateral limb (Active Vision), does not appear to be the underlying/driving factor with regards to previously reported MT-related behavioural improvements (see Ramachandran & Altschuler, 2009; Thieme et al, 2012). Our finding is in agreement with Cowles and colleagues (2013), who showed that AO effects provided little additional benefit on top of conventional practice effects in the recovery early after stroke. However, caution must be applied when relating results of an acute stroke population to the present study conducted in healthy young and older adults.

In summary, our results suggest mirror feedback – when considered to represent AO-like effects - cannot be regarded as the *most influential* factor with regard to enhancing ipsilateral corticospinal excitability or decreasing ipsilateral SICI during MT, at least with respect to the particular finger abduction movement task employed in our study.

Considering the large 95% CI around the small effect size ($d = 0.16$) obtained when considering differences in ipsilateral excitability between the Mirror Vision and the Active Vision conditions, 95% CI = $-0.46, 0.67$, the nature of the provided feedback may *potentially* still play a role in inducing corticospinal excitability changes than can be assumed solely on the basis of the current non-significant findings. That is MT and mirror feedback, when used within a therapeutic setting, may therefore still be capable of underpinning increases in ipsilateral corticospinal excitability that have previously been associated with MT-based behavioural improvements. However, given the apparently small effect size observed herein, in order to confidently conclude whether the nature of the visual feedback plays an important role in mediating changes in ipsilateral corticospinal

excitability, studies with large sample sizes appear necessary. For example, a sample size of approximately 90 participants would be required if the true Cohen's d effect size was 0.3.

The current study also aimed to determine whether healthy ageing is associated with a change in the efficacy of visual feedback in mediating changes in corticospinal excitability ipsilateral to the moving limb. As indicated previously, healthy ageing results in numerous changes in the brain that have been shown to influence behavioural aspects of motor performance, such as coordination, speed, gait and balance (for an overview, see Seidler et al., 2010). Furthermore, ageing is associated with changes in the neural control mechanisms that underpin movement performance (Fujiyama et al., 2009; Hinder et al., 2011, 2012), and more specifically can result in changes in the efficient ability to modulate intrahemispheric (Hortobágyi & DeVita, 2006; Peinemann et al., 2001) and interhemispheric inhibitory mechanisms (Talelli et al., 2008), with the latter mechanism being related to the reduced integrity of the corpus callosum in later life (Hoy, Fitzgerald, Bradshaw, Armatas, & Georgiou-Karistianis, 2004). Reduced callosal inhibition is linked to changes that affect the behavioural aspects of motor performance in older populations, and is (amongst other indicators) expressed as an increase in bilateral activation during the execution of unilateral motor tasks (when compared with younger adults). Evidence for this stronger ipsilateral corticomotor output during unimanual movement tasks (i.e., less lateralised task-related activation in primary and non-primary motor areas) in the elderly has been provided within imaging studies (Ward & Frackowiak, 2003), as well as within behavioural studies measuring output at the level of the muscles, i.e., mirror activity (Hinder et al., 2011). Considering the greater propensity for mirror activity in older people, together with their greater reliance on visual feedback and control to permit accurate motor performance (Swinnen et al., 1998; Voelcker-Rehage, 2008), we hypothesised that older people would be predisposed (compared to younger adults) to manifest changes in ipsilateral excitability on the basis of changes in visual feedback. However, this hypothesis was not supported by the current experiment; that is, older adults did not show any greater degree of excitability change in response to mirror vision than did younger adults. Furthermore, our results did not show significant feedback-related differences in the modulation of intracortical inhibitory processes (examined by way of SICI) between younger and older participants. Both age groups exhibited SICI that was similar at rest, together with a commensurate decrease in SICI in the inactive hemisphere (consistent with Hinder et al., 2011) due to the ipsilateral unimanual movement (regardless of the provided visual feedback). Because previous studies have failed to address the neural mechanisms of MT in aged populations, this result adds new, albeit unexpected, knowledge to the application of mirror feedback-based approaches in the older population.

It is possible that the present motor task was not complex enough to elicit or reveal age-related variations in neural responses to the provided visual feedback, at least with respect to overall changes in corticospinal excitability or SICL. Indeed, age-related performance differences are more visible in complex than in simple tasks (Dykiert, Der, Starr, & Deary, 2012; Fujiyama, Hinder, Garry, & Summers, 2013; Voelcker-Rehage, 2008), whereas performance is comparable for younger and older adults in more simple tasks (Breitenstein, Daum, & Schugens, 1996). It is therefore possible that the current task was not demanding enough to force older adults to engage in strategies to utilise visual feedback to ensure task accuracy. Alternatively, vision may not have had an effect on age-related variation in excitability in the current motor task due to the fact that provision of visual feedback was not required for an accurate, successful task execution. It is possible that a more goal-directed task, representative of an fundamental everyday action (e.g., a reaching movement to a specific point in which feedback would have helped with the performance), would have caused the effects of the different vision conditions to be more obvious, especially within the older participants, when considering their demonstrated greater reliance on visual feedback and control to permit accurate motor performance (Swinnen et al., 1998; Voelcker-Rehage, 2008).

Previous research has shown that older adults exhibit additional activation in other motor-related regions (e.g., premotor and prefrontal cortex) during movement tasks in comparison with younger adults (Heuninckx, Wenderoth, Debaere, Peeters, & Swinnen, 2005; Hutchinson et al., 2002; Mattay et al., 2002; for an overview, see Seidler et al., 2010). Accordingly, it is possible that changes may have occurred upstream of M1 and thus remained undetected in the current experiments. Indeed, recent work from our lab has demonstrated age-related changes in PMd and M1 interhemispheric connectivity during a simple reaction time (RT) task to be associated with different levels of motor performance in older adults (Fujiyama, Hinder, & Summers, 2013; Hinder et al., 2012). In a simple RT task (i.e., left index finger abduction) Hinder and colleagues (2012) showed that modulation of LPMd-rM1 interaction early in the preparation period was associated with faster responses in a group of older, but not in younger, participants. In a subsequent study Fujiyama et al. (2013), used the same simple RT task and a disruptive (virtual lesion) TMS approach to demonstrate a causal role of the left PMd in preparing right hand movements. Considering this greater connectivity between IPMd-rM1 to be important in the planning and execution of ipsilateral movements in older adults, future studies examining changes within this network could be beneficial to further investigate the potential for mirror feedback-induced neurophysiological effects in younger and older populations (see Ruddy & Carson, 2013). It is conceivable that changes upstream of M1 (between secondary or preparatory motor regions and primary motor

cortex), or within several regions of the parietal or occipital cortex (Filimon, Nelson, Ruey-Song, & Sereno, 2009; Rossit, McAdam, Mclean, Goodale, & Culham, 2013) may relate to the seemingly robust positive effects of MT at the behavioural level. An investigation of the corresponding networks may therefore be helpful to further uncover the neural mechanisms underlying the behavioural benefits of MT (see Ramachandran & Altschuler, 2009; Thieme et al., 2012).

Further evidence to suggest areas upstream of M1 may play a role in MT is the finding that AO activates PMv (Iacoboni, 1999) and enhances connections between PMv and M1 (Lago et al., 2010). That is interhemispheric and intra-hemispheric connectivity in areas upstream of M1 may play an important role in MT. Furthermore, AO facilitation, even though mainly found in M1 (Aziz-Zadeh et al., 2002), has also been detected in premotor areas (Iacoboni, 1999; Rizzolatti, Fogassi, & Gallese, 2001). Therefore, assuming that cortico-cortical projections from the premotor cortex to M1 play a major role in mediating the influence of visual input on M1 excitability (Strafella & Paus, 2000), future TMS studies targeting those may be worthwhile.

A complementary approach to that discussed above may also involve combining TMS measurements with non-invasive brain stimulation techniques to up- or down-regulate specific motor regions of interest and investigating the impact upon the neural mechanisms (e.g., PMd-M1 connectivity) and how these are subsequently affected by alterations in visual feedback. Indeed, if net excitability (as investigated by traditional TMS measurements) is not the driving factor underlying the beneficial effect of mirror feedback (see Ramachandran & Altschuler, 2009; Thieme et al., 2012), this approach could give further insight into the underlying neurological mechanisms of MT.

In summary, we have shown that, regardless of age, mirror feedback during a unilateral task does not promote greater changes in excitability and inhibition of ipsilateral corticospinal excitability than those elicited when provided with more standard forms of visual feedback. As such, the unimanual motor action itself appears more instrumental than the type of visual feedback in driving those manifested behavioural changes reported within MT. Future work is warranted to further determine the neural underpinnings of MT such that its clinical benefit can be maximised in younger and older populations.

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