



Research report

Perception of hand movement by mirror reflection evokes brain activation in the motor cortex contralateral to a non-moving hand



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ABSTRACT

We investigated whether perception of hand movement via mirror reflection evokes activation in the motor cortex (M1) contralateral to the non-moving hand (the M1 ipsilateral to the moving hand). Continuous electroencephalography (EEG) was recorded from 14 participants while they performed unimanual extension–flexion hand movements in direct view and mirror view conditions. We measured the lateralized readiness potential (LRP) as a marker of M1 activation in both conditions. Both the direct and mirror view conditions produced LRPs, with the mirror view conditions revealing clear activation in M1 contralateral to the non-moving hand (ipsilateral to the moving hand) during both flexion and extension phases. This unambiguous demonstration of M1 activation in association with a non-moving hand (which is visually-perceived as moving), suggests that perception of movement can directly lead to M1 activation.

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1. Introduction

Mirror therapy is a non-invasive treatment procedure in which visual observation of a mirror-reflected moving limb ameliorates some sensorimotor symptoms associated with an impaired (or amputated) limb. Initially proposed as a possible treatment method for persistent phantom pain in people with amputation of a limb (Ramachandran & Rogers-Ramachandran, 1996), over the years the therapy has also been applied in cases of limb paralysis or weakness due to

stroke (Altschuler et al., 1999; Thieme et al., 2012), complex regional pain syndrome (Cacchio, De Blasis, Necozone, Orio, & Santilli, 2009; McCabe et al., 2003), other neuropathic pain syndromes, and sensorimotor malfunction (Altschuler & Hu, 2008; Rosén & Lundborg, 2005; Sumitani et al., 2008). However, the precise mechanisms underlying its efficacy as a treatment are unknown, as are its neural underpinnings.

Several studies have suggested that the mirror visual feedback (MVF) from the reflected limb might activate the motor cortex (M1) contralateral to a resting (non-moving and typically hidden) hand (Altschuler et al., 1999; McCabe et al.,

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2003; Ramachandran & Altschuler, 2009; Ramachandran & Rogers-Ramachandran, 1996). Along those lines, Touzalin-Chretien and colleagues measured the lateralized readiness potential (LRP) to assess motor readiness of movement as a marker of M1 activation. Results revealed evidence of an LRP associated with the resting hand in the mirror view condition (Touzalin-Chretien & Dufour, 2008; Touzalin-Chretien, Ehrler, & Dufour, 2009, 2010). However, the findings of Touzalin-Chretien et al. were refuted by Praamstra, Torney, Rawle, and Miall (2011) with the claim that there was a methodological error in computation of the LRP in the mirror view conditions. Praamstra et al. (2011) pointed out that Touzalin-Chretien et al. computed LRP for the mirror condition by subtracting effects associated with the mirror left hand from those associated with the real right hand. This LRP calculation implies a complete reversal of contralateral and ipsilateral M1 activation, something that would require an extraordinarily large amount of neural plasticity, which is physiologically implausible according to Praamstra et al. (2011). Praamstra et al. (2011) therefore suggested a corrected method for computing LRP and conducted an experiment to apply it.

In the experiment of Praamstra et al. (2011), participants made brisk index finger extensions followed by immediate flexion in response to a visual stimulus under direct and mirror view conditions. Their results dissociated the extension and flexion phases of the movement with only the flexion portion producing an effect consistent with the motor activation contralateral to the mirror-viewed hand; thus, the extension phase did not show that effect. On the basis of their findings, the researchers suggested that the differences in findings for the two phases of the finger movements might be related to the extension phase being more intentional and the flexion phase more automatic. They also suggested that effects of the mirror were quite modest in addition to occurring only for the flexion phase of the finger movements. Based on those previous studies, no clear and unambiguous effect of M1 activation contralateral to the mirror-viewed hand has been demonstrated. This intriguing hypothesis requires further investigation.

In the present study, we aimed to employ the general method of Praamstra et al. (2011) but using a well-practiced whole hand opening (extension) and closing (flexion) movements in which both phases we would consider to be equally automatic/intentional. This type of action is quite common in our everyday activities, for example, in grasping and releasing objects. Furthermore, whole hand movements are the more typical ones examined in previous mirror reflection studies (Altschuler et al., 1999). As mentioned above, the LRP is an event related potential (ERP) that reflects activation of the contralateral M1 in voluntary movement (Shibasaki & Hallett, 2006; Smulders & Miller, 2012). Physiological evidence has shown that the LRP is generated largely in the M1 (Coles, 1989; De Jong, Wierda, Mulder, & Mulder, 1988). Given that the LRP reflects activation of the contralateral M1 in voluntary movement, it has become a widely used index of motor preparation and execution (Smulders & Miller, 2012).

We compared LRP and its constituent components to test the hypothesis that the LRP amplitude in mirror view conditions would be lower overall than the LRP amplitude in direct view conditions based on the following logic: The MVF of the

hand movements in the mirror view conditions would reveal an increase in ipsilateral M1 activation compared to the ipsilateral M1 activation evoked by the actual hand in the direct view conditions (where ipsilateral is defined with respect to the moving hand). In the LRP calculation, if contralateral activation remains unchanged, an increase in the ipsilateral activation reduces the overall difference between the contralateral and ipsilateral M1 activation, which consequently lowers the LRP amplitude (specific calculation for LRP is described below). Thus, increased ipsilateral M1 activation in the mirror view conditions would result in lower LRP amplitude compared to the LRP amplitude of the direct view conditions. This evidence would clearly reveal the presence of motor readiness (M1 activation) evoked by *perceived* hand movement as a result of MVF in the M1 contralateral to the non-moving hand (i.e., ipsilateral to the moving hand). We would expect the effect just described to occur in both the extension and flexion phases of the movement unambiguously.

2. Methods

2.1. Participants

Fourteen students from the University of Otago (all males) between the ages of 19 and 31 years (mean age 23.44) participated. All were right-handed (Oldfield, 1971) and had normal or corrected to normal vision. They gave written informed consent and received course credit or gift vouchers (\$20) as reimbursement for their time. The experimental protocol was approved by the ethics committee of the Department of Psychology, University of Otago.

2.2. Task and procedure

Participants performed extension–flexion hand movements with one hand. A typical pattern of movement involved opening of the hand, in which the four fingers together opened away from the thumb (extension), and then closing the hand so that all fingers touched the thumb (flexion). The hand movements were paced by auditory beeps set with a random jitter between 1 Hz and 1.5 Hz so that 1 beep occurred every 1–1.5 sec. Each condition contained 90 cycles of movements.

There were four experimental conditions: *Direct view of right hand*: The extension–flexion movement described above was performed by the right hand while the participant viewed the right hand. *Direct view of left hand*: The movement was performed by the left hand while the participant viewed the left hand. *Mirror view of right hand*: The movement was performed by the right hand while the participant viewed the mirror reflection of the right hand. *Mirror view of left hand*: The movement was performed by the left hand while the participant viewed the mirror reflection of the left hand.

The experiment was conducted in a quiet laboratory. The participant was seated comfortably in a chair in front of a table, on which the mirror box (Fig. 1) was placed. The moving hand was placed in front of the mirror and the resting hand (in which no movement task was assigned) was hidden behind the mirror out of the participant's view. For each condition, 30

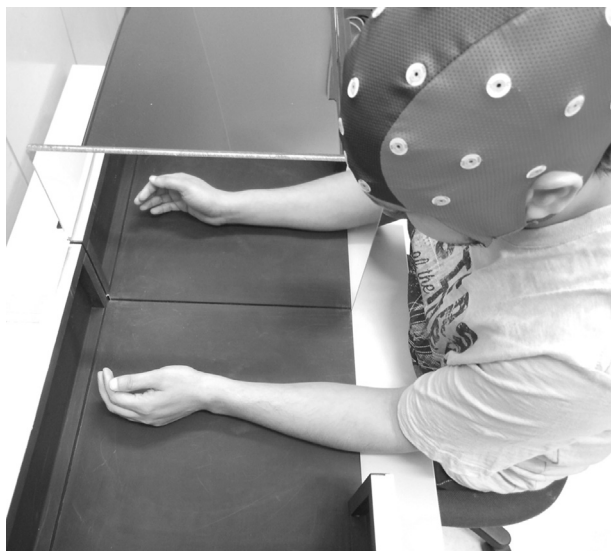


Fig. 1 – Mirror box used in this study. Picture shows the left hand and its mirror image. In the experiment, participants could see either a real hand (direct view) or the mirror image (mirror view) of a moving hand, depending on condition. The resting hand (in this case, the right hand) is hidden behind the mirror. In the experiment, a non-transparent cover was placed over the active hand (not shown here) so that only the mirror reflection was directly visible to the participant in mirror view conditions. Across conditions, each of the hands was viewed (direct view conditions), or mirrored (mirror view conditions) to make up the four experimental conditions.

cycles of movement in three series were performed in succession. There was a small pause of 5 sec between the first 2 series, and a small rest at the end of each condition prior to the next condition. Throughout the experiment, the resting hand remained behind the mirror with a dark non-transparent cover so that it was completely hidden from the participant's view. In the mirror conditions, a dark non-transparent cover was placed over the moving hand to avoid direct view of that hand (and so that its mirror reflection was the only hand view the participant had). In the direct view conditions, the mirror was shielded to prevent participants having peripheral vision of the mirror image.

3. Data collection and analysis

3.1. Electroencephalography (EEG) recording

Continuous EEG was recorded with a 32-channel ANT machine (ANT B.V., Enschede, The Netherlands). EEG electrodes were mounted on an Ag/AgCl sintered ANT WaveGuard cap according to the international 10–20 montage system. The mathematical average of both mastoid electrodes was used as a reference. Data were sampled at 1024 Hz. Impedances were kept below 5 K Ω . EMG data from each hand were recorded (in

parallel with EEG) using surface electrodes attached to the right and left forearm extensor muscles. EMG signals were analyzed offline to detect the onset time of the individual movements. Subsequently, the EMG onset time was used as the trigger or event marker for EEG analyses.

3.2. EEG pre-processing

EEG data were offline processed with EEGLAB (version 12.0.2.5b), an open source EEG analysis toolbox (Delorme & Makeig, 2004). EMG onset was detected by visual inspection. EEG signals were first resampled at 512 Hz and were band-pass filtered (FIR) from .01 to 40 Hz. Independent component analysis was performed on continuous EEG data to decompose the data into independent components (ICs). The EEG data were then epoched relative to EMG onset into fixed lengths of 800 msec (300 msec before and 500 msec after each movement onset) and re-referenced to the average reference. The artefactual ICs, which include ocular artefacts (eye blinks, vertical, and horizontal eye movements), and generic discontinuity, were removed by a completely automatic algorithm that identifies such components by combining stereotyped artefact-specific spatial and temporal features (Mognon, Jovicich, Bruzzone, & Buiatti, 2011). To further exclude eye movement artefacts, the frontal electrodes were visually inspected to remove epochs containing eye blinks, vertical eye movements (FP1, FPZ, FP2) and horizontal eye movements (F7, F8). Further artefact rejections were carried out using the criterion of absolute voltage. Individual trials with EEG amplitudes higher than +100 μ V or lower than –100 μ V were rejected. After exclusion of all artefacts, the remaining epochs were baseline corrected (from –300 msec to –200 msec). Epochs related to each condition were averaged time-locked to the EMG-onset. Further analyses were performed in order to compute ERP, LRP and the scalp distribution of ERP potentials. All grand averaged data were low-pass filtered at 20 Hz to display in the figures.

3.3. LRP computation

There are two methods of computing LRP: (1) subtraction, which is $[(C_3-C_4)_{\text{right hand}} - (C_3-C_4)_{\text{left hand}}]$, and (2) average, which is $[(C_4-C_3)_{\text{left hand}} + (C_3-C_4)_{\text{right hand}}]/2$; where C_3 is the left M1 site and C_4 is the right M1 site. The two methods are interchangeable given they are equally sensitive to one hemisphere (contralateral) becoming more activated than the other (ipsilateral) for unilateral movements (Smulders & Miller, 2012). We computed response-specific LRP according to the subtraction method. LRPs were calculated with ERPLAB (version 4.0.3.1), an open source ERP analysis toolbox (Lopez-Calderon & Luck, 2014). Individual trials were averaged at C3 and C4 separately for each condition and participant to compute ERPs. A two-step subtraction was performed on ERP data in which C3–C4 was first calculated for each hand. Second, the C3–C4 for the left hand was subtracted from the C3–C4 for the right hand. Using this procedure, the direct view left hand condition was subtracted from the direct view right hand condition. Similarly, the mirror view left hand condition was subtracted from the mirror view right hand condition.

4. Results

4.1. EMG data

EMG data were averaged across left and right hands separately for the moving and resting hands. The EMG waveforms revealed similar patterns for moving hands and also for resting hands in both direct and mirror view conditions (Fig. 2A). Importantly, in all conditions EMG revealed no overt movements of the resting (hidden) hand. Absence of overt movement of the hidden hand confirms that any LRP amplitude difference between direct and mirror view conditions is not due to differences in muscle activity of the resting (hidden) hand. Separate paired t-tests were conducted to compare the mean EMG amplitude difference between the hands in each experimental condition. There was no significant difference in EMG amplitude of the moving hands for direct view compared to mirror view conditions, $[t(1,13) = -.053, p = .958]$. Similarly, the mean EMG amplitude difference between the resting hands in direct and mirror view conditions was not significant, $[t(1,13) = -.836, p = .418]$.

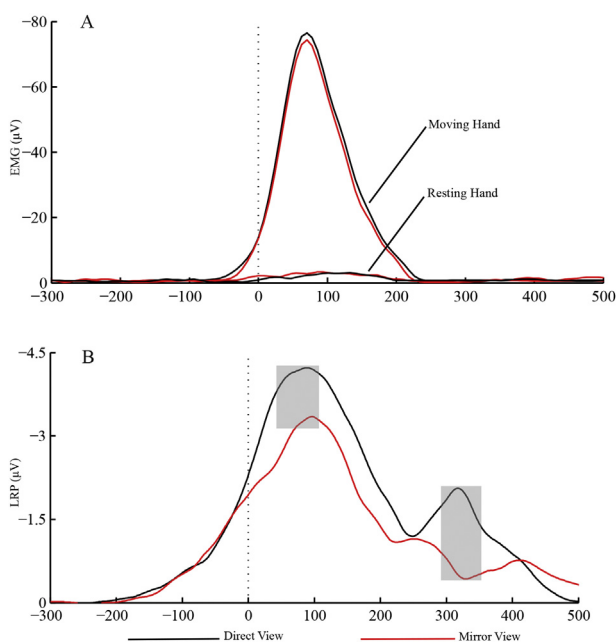


Fig. 2 – A. Grand averaged EMG for moving and resting (hidden) hands. Time 0 indicates the time of movement onset. EMG data are shown averaged across left and right hands. Around the peak of the EMG (mean peak latency 77 msec) coincides with the extension phase of the movements; the final portions (200–500 msec) coincide with the flexion phase. B. Grand averaged LRP for direct view conditions and mirror view conditions measured at C3/C4 electrode sites which overlie (left and right) M1. Shaded regions show time intervals with statistically-significant differences between the two conditions, with the first region reflecting the extension phase (40–100 msec), and the second region (300–340 msec) reflecting the flexion phase at the end of the movement.

4.2. LRP data

Mean LRP amplitude was statistically analyzed at each 20 msec time window ranging from –200 msec to 500 msec. As a standard practice of our lab, an effect was considered as significant only if 2 consecutive 20 msec time intervals reached conventional significance levels (.05 or smaller); those satisfying this criterion are described as being smaller or larger (< or >) than the t or p value for the consecutive time intervals for ease of presentation (Franz & Miller, 2002; Fu & Franz, 2014).

As can be seen in Fig. 2B, mean LRP amplitude is smaller in the mirror view condition compared to the direct view condition. At the extension phase of the movement, LRP amplitudes between direct view and mirror view conditions differed significantly (time intervals: 40–100 msec corresponding to the extension phase) $[t(1,13) > -3.063, p < .009]$. LRP amplitudes again differed significantly between 300 and 340 msec, corresponding to the flexion phase $[t(1,13) > -3.432, p < .004]$. The mirror view LRP in both the extension and flexion phases was attenuated in comparison to the direct view LRP. This reduced amplitude in mirror view conditions reveals the influence of MVF on M1 activation. Further analysis (as will be shown below) demonstrated that the lower LRP amplitude in mirror view conditions was due to increased activation in M1 ipsilateral to the moving hand (contralateral to the non-moving/hidden hand). The increased ipsilateral activation produced the effect of reducing the overall LRP in the mirror view conditions.

4.3. Contralateral and ipsilateral ERP data

Given that the LRP calculation depends on contralateral and ipsilateral activation differences, we further analyzed the contralateral and ipsilateral ERP data in both direct view and mirror view conditions. We separately compared the right contralateral (C3) and left contralateral (C4) ERP data for both viewing conditions. Similarly, the right ipsilateral (C4) and left ipsilateral (C3) data were compared for both viewing conditions. The ERP data revealed a bilateral distribution of motor activation, with higher amplitudes contralateral to the moving hand in both direct view and mirror view conditions. This ERP activity is consistent with the bilateral distribution of movement related EEG potentials reported in previous studies (Gerloff et al., 1997; Kičić, Lioumis, Ilmoniemi, & Nikulin, 2008; Rao et al., 1993; Shibasaki et al., 1993). Fig. 3A shows the averaged contralateral and ipsilateral ERP waveforms of the right and left hands for direct and mirror view conditions. The mean amplitude across 20 msec time bins for contralateral and ipsilateral datasets was compared for the time windows where significant LRP amplitudes were found (as in Fig. 2B).

It is clear that the mean amplitude of contralateral ERP waveforms at the earlier intervals corresponding to movement extension (40–100 msec) showed no hint of a difference between the direct and mirror view conditions for the right hand $[t(1,13) > -1.078, p < .301]$ or the left hand $[t(1,13) > .191, p < .851]$. Similarly, the mean amplitudes of the contralateral ERP waveforms around the end of the movement (300–340 msec) also showed no hint of any differences between the direct and mirror conditions for the right hand

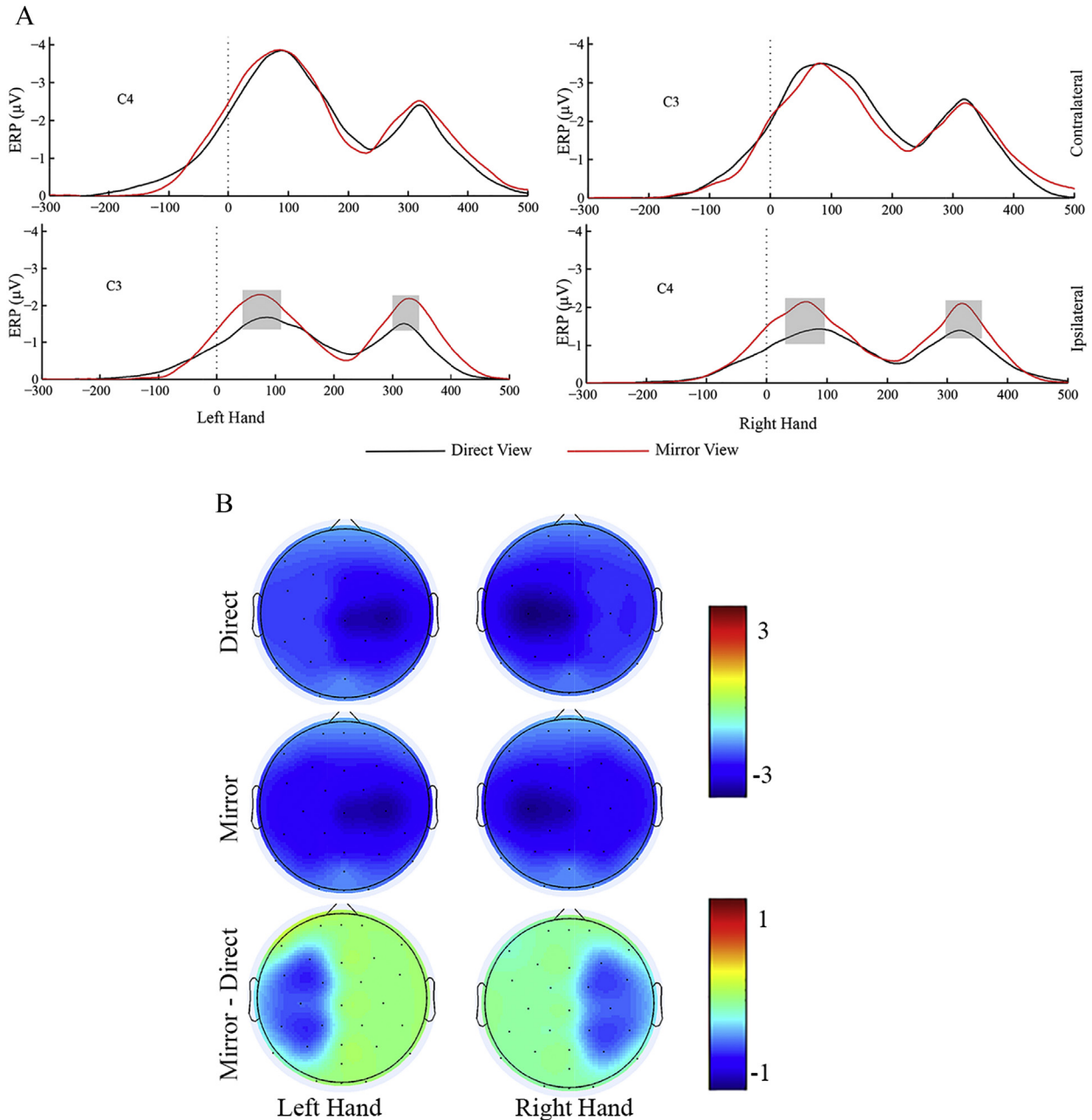


Fig. 3 – A. Mean ERP data averaged at right and left contralateral (top row) and ipsilateral (second row) electrode sites are displayed in the upper panel. One clearly sees the bilateral distribution of motor activation in both conditions, but with overall larger amplitude at the contralateral sites. Contralateral waveforms show similar activation for direct view and mirror view conditions. Ipsilateral waveforms show increased activation in mirror view compared to direct view conditions as hypothesized. Both the contralateral and ipsilateral waveforms show two separate peaks coincident with, respectively, extension (left-peak) and flexion (right-peak) of the movements. Shaded regions indicate time intervals (40–100 msec and 300–340 msec) where LRP amplitude differences were found when comparing mirror versus direct view conditions. **B.** Scalp distributions of ERPs elicited for each condition, when the left hand performs the required movement and when the right hand performs the required movement. Lowest panel shows subtraction of activation of the two experimental conditions (Mirror minus Direct). After subtraction, clear activation remains on the cortical side ipsilateral to movement.

$[t(1,13) > -.129, p < .900]$ or left hand $[t(1,13) > .248, p < .808]$. In marked contrast, the ipsilateral ERP amplitude of the mirror view conditions is clearly higher than that of direct view conditions (Fig. 3A). This effect was highly significant for the

extension phase (40–100 msec) in both the right hand comparison $[t(1,13) > 5.117, p < .001]$ and the left hand comparison $[t(1,13) > 2.988, p < .010]$. Similar comparisons at the 300–340 time window also revealed significant differences for right

hand conditions [$t(1,13) > 3.443, p < .004$] and left hand conditions [$t(1,13) > 5.550, p < .001$].

The higher ipsilateral amplitude in the mirror view conditions provides strong evidence in support of our hypotheses and for the interpretation that the MVF induced additional activation in M1 ipsilateral to the moving hand (M1 contralateral to the mirror-hand). This higher ipsilateral activation reduced the contralateral–ipsilateral activation difference, thereby attenuating LRP amplitude in the mirror view conditions.

5. Discussion

The main objective of the present study was to investigate M1 activity associated with the perception of MVF of a hand movement. A standard mirror box was used to reflect a moving limb while the other limb remained still and hidden from the participant's view. The primary hypothesis was that perception of the mirror-hand (the visually-apparent hand which is perceived by mirror reflection only) will evoke activity in the M1 contralateral to that perceived hand, which is the hemisphere ipsilateral to the moving hand. Thus, the direct prediction was that the overall LRP amplitude of the mirror view conditions would be lower than the overall LRP amplitude of the direct view conditions (due to the nature of the calculation of LRP, described earlier). A related hypothesis was that these effects would be unambiguously present in association with extension and flexion phases of the moving hand.

Results strongly support our hypotheses, with a clear demonstration of smaller LRP amplitude in mirror view conditions compared to direct view conditions, and the effect is unambiguous to flexion and extension phases. Data analyses further revealed that activation of the M1 contralateral to the moving hand does not fundamentally differ between direct and mirror view conditions. Rather, it is clearly the M1 ipsilateral to the moving hand that reveals significant differences between the two viewing conditions, with ipsilateral activation higher in the mirror view conditions. The higher ipsilateral activation (defined here with respect to the actual moving hand) led to a reduction in overall LRP amplitude in the mirror view conditions. The present study clearly isolates activity ipsilateral to the moving hand as the main effects of interest, thereby confirming such effects in the hemisphere opposite the mirror viewed hand. This alone is quite compelling, given that the LRP is traditionally regarded as a neural measure associated with activation of the M1, and in particular, is a widely used index of motor preparation and execution; yet, in this study, the LRP is modulated by activation of the M1 associated with a hand that is actually stationary.

From earlier research, we know that the M1 ipsilateral to a unilateral movement reveals increased activity with increasing force of muscle contraction (Liepert, Dettmers, Terborg, & Weiller, 2001; Muellbacher, Facchini, Boroojerdi, & Hallett, 2000; Perez & Cohen, 2008). If this were the cause of our effects due to the mirror manipulation, we would expect more force output in mirror view conditions compared to direct view conditions. However, our EMG results suggest that this explanation is very unlikely. We recorded EMG

continuously with EEG from moving and resting hands in both direct view and mirror view conditions. The EMG analysis (Fig. 2A) shows an identical EMG pattern with no significant differences in EMG amplitudes between the moving hands in direct and mirror view conditions.

We suggest that MVF facilitates the increased ipsilateral M1 excitation in mirror conditions by reducing inhibitory activity in the ipsilateral hemisphere. A sound basis for this notion comes from previous research which has suggested that both preparation and execution of voluntary unilateral movement activate inhibitory networks in the ipsilateral hemisphere's motor areas (Franz & Fahey, 2007; Kikić et al., 2008; Pinet, Hamamé, Longcamp, Vidal, & Alario, 2015; Shen & Franz, 2005; Vidal, Grapperon, Bonnet, & Hasbroucq, 2003). This inhibition is proposed as a mechanism serving to allow execution of voluntary movement without interfering movement signals from the ipsilateral hemisphere (Franz & Fahey, 2007; Franz, 2012; Kikić et al., 2008; Shen & Franz, 2005). Embracing those findings, we further suggest that with use of a mirror reflection there is reduced activation of inhibitory networks in the ipsilateral hemisphere, perhaps in association with more visual information directly impacting motor processes as is known to occur with observation of movement. Previous studies have shown that action observation reduced intracortical inhibition and increased activation in the M1 contralateral to the limb involved in the observed movement (Patuzzo, Fiaschi, & Manganotti, 2003; Schütz-Bosbach, Avenanti, Aglioti, & Haggard, 2008; Strafella & Paus, 2000). In our mirror conditions, we blocked the participant's vision of the moving hand by use of a shield (only MVF of the moving hand was visible). According to our hypothesis, we would expect heightened activity in association with MVF to occur primarily or only in the hemisphere contralateral to the mirror-view hand (the hemisphere ipsilateral to the moving hand). Our findings support the reduction of inhibitory activation in the ipsilateral hemisphere, with heightened activity in the ERP waveform associated with the ipsilateral side (ipsilateral to the moving hand) only. This occurs in association with both the flexion and extension phases of the movement. We therefore suggest that the increased activation in M1 contralateral to the mirror reflected hand (ipsilateral to the actual moving hand) found in this study resulted from reduction of inhibitory activity in M1 associated with the mirror-reflected (i.e., perceived-moving) hand.

The present study followed similar methods as those proposed and applied by Praamstra et al. (2011), although using a whole-hand movement task rather than the finger extension–flexion task used in their study. In contrast to the modest effects of MVF found by Praamstra et al. (2011) which were specific to the flexion phase of finger movement only, the present study demonstrates clear and robust effects of MVF for both the flexion and extension phases of movement (as demonstrated by comparing mirror vs direct conditions for each hand). Our earlier study suggests that the effects of the mirror reflection are immediate and automatic and do not depend on feedback from the effectors (Franz & Packman, 2004). The hand movement task of this study was well-learned, with both flexion and extension phases proposed to be similar in degree of automaticity. While this might be the reason for identical effects of MVF on both phases of the

movement, our findings do not provide support for the suggestion of Praamstra et al. (2011) that flexion and extension phases differently recruit ipsilateral corticospinal pathways; whether that applies to just finger movements (as used in Praamstra et al., 2011) remains to be elucidated. Our findings are therefore consistent with the view that visual information of one's own perceived moving hand directly affects motor activation at the level of central representation, even though not reflected in peripheral muscle activity (of the hidden hand). This is consistent with findings from earlier work that implicates central representational processes as being modulated even without peripheral input from movement (Franz & Ramachandran, 1998).

As with the findings of Praamstra et al. (2011), our findings are not consistent with those of Touzalin-Chretien & Dufour (2008), Touzalin-Chretien et al. (2009, 2010). Ipsilateral amplitude in the mirror view conditions was clearly larger in the present study in comparison to ipsilateral amplitude in direct view conditions. However, ERP data of the present study consistently showed larger amplitude at electrode sites contralateral to the movement hand compared to the amplitude at electrode sites ipsilateral to the movement hand in both experimental conditions. We, therefore, agree with Praamstra et al. (2011) that MVF induces additional excitation in the ipsilateral M1 of the moving hand but contrary to Touzalin-Chretien & Dufour (2008), Touzalin-Chretien et al. (2009, 2010) this additional excitation does not exceed the contralateral activation.

6. Conclusion

In summary, the present study utilized the well-known LRP, which is known to reflect movement readiness of the M1 associated with an impending voluntary movement. Using direct and mirror-reflected views of a moving hand, this study provides clear evidence of increased activity of the M1 associated with a visually-perceived (non-moving) hand, which is the hemisphere ipsilateral to a moving hand reflected in a mirror. The increased ipsilateral activation modulated LRP in the mirror conditions showing an actual cortical-movement-related activation occurring in the absence of real movement.

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