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ABSTRACT

Aim

To investigate the neuronal basis for the effects of mirror therapy in stroke patients.

Methods

Twenty-two stroke patients participated in this study. We used functional magnetic resonance imaging to investigate neuronal activation patterns in two experiments. In the unimanual experiment, patients moved their unaffected hand, either while observing it directly (no-mirror condition), or while observing its mirror reflection (mirror condition). In the bimanual experiment, patients moved both hands, either while observing the affected hand directly (no-mirror condition) or while observing the mirror reflection of the unaffected hand in place of the affected hand (mirror condition). A two-factorial analysis with movement (activity versus rest) and mirror (mirror versus no mirror) as main factors was performed to asses neuronal activity resultant of the mirror illusion.

Results

Data of 18 participants were suitable for analysis. Results showed a significant interaction effect of movement x mirror during the bimanual experiment. Activated regions were the precuneus and the posterior cingulate cortex ($p<.05$ FDR).

Conclusion

In this first study on the neuronal correlates of the mirror illusion in stroke patients we showed that during bimanual movement the mirror illusion increases activity in the precuneus and the posterior cingulate cortex, areas associated with awareness of the self and spatial attention. By increasing awareness of the affected limb the mirror illusion might reduce learned non-use. The fact that we did not observe mirror-related activity in areas of the motor or mirror neuron system questions popular theories that attribute the clinical effects of mirror therapy to these systems.

INTRODUCTION

Mirror therapy was first introduced by Ramachandran and co-workers to alleviate phantom limb pain in amputees.[1] By showing patients the reflection of their unimpaired arm in a mirror, they retrieved the sensation of their amputated arm without pain. Since then, the paradigm of mirror therapy has also been studied in other pain related syndromes (especially chronic regional pain syndrome) [2] and motor related syndromes (stroke, hand surgery).[3,4] The focus of these studies has been on potential clinical effects; reduction of pain and improvement of motor function. Relatively little research has focussed on the mechanisms that underlie the effects of mirror therapy.

Presumably, different working mechanisms are behind the effects of mirror therapy on pain and motor symptoms. For the latter category, the focus of the current study, a number of mechanisms have been proposed. Ramachandran originally hypothesised that paralysis following stroke might have a 'learned' component, which could possibly be 'unlearned' by means of the mirror illusion.[5] Others suggested that mirror therapy might be a form of visually guided motor imagery.[6] Motor imagery itself has proven to be effective in the rehabilitation of patients with hemiparesis [7] and the mirror induced visual feedback of the imagined movement might further facilitate this. In addition, it has been hypothesized that the observation of the mirror illusion might trigger the mirror neuron system (MNS).[3] Mirror neurons were initially discovered by Di Pelligrino and co-workers in monkeys[8] and are a particular type of neurons that discharge both with performance of a motor action and with observation of another individual performing similar motor actions.[9] As single cell studies are not normally performed in the human brain, there is not yet direct evidence for the existence of a mirror neuron system in humans. However, brain imaging data do suggest the existence of a similar system.[10,11] Previous research has indicated the potential of the MNS in motor recovery by showing that the observation of movements performed by others improves motor performance in stroke patients.[12] It is conceivable that observing one's own mirrored movement promotes recovery in a similar way.

A number of studies have evaluated the neuronal correlates of mirror therapy by examining the observation of the mirror reflection of a moving hand in healthy subjects. These studies were based on the hypothesis that the mirror illusion would increase excitability or activity in primary motor areas in the hemisphere ipsilateral to the moving hand. Using transcranial magnetic stimulation (TMS) [13-15], magnetoencephalography (MEG) [16], electroencephalography (EEG) [17] and functional

magnetic resonance imaging (fMRI) [18] the authors compared neuronal activity or excitability ipsilateral to the moving hand with or without observing its mirror reflection. The MEG study reported the mirror illusion to suppress 20-Hz activity, indicating increased activation of the primary motor cortex [16], while the EEG study reported that the mirror illusion of movement induced lateralized readiness potentials, indicating cortical motor preparation for the non-moving hand.[17] On the other hand, the TMS studies either found no effect of the mirror illusion on motor cortex excitability [13,14] or indicated that the mirror illusion needs to be combined with motor imagery in order to increase motor cortex excitability.[15] Finally, an fMRI study from our research group [18] found no increased activity in sensorimotor areas as a result of the mirror illusion, but did find an increase in activity in the superior temporal sulcus (STS), presumed to be due to involvement of the MNS.[19]

So far, no studies on the neuronal correlates of the mirror illusion have been performed in patient groups. It seems obvious that caution has to be taken when generalizing results from mirror studies in healthy participants to stroke patients. Patients have a damaged hemisphere, and alteration of activity within that hemisphere might not be as easily achieved as in healthy participants. Furthermore, stroke patients performing mirror therapy are generally instructed to practice bi-manually, moving affected and un-affected limb together.[3,20,21] As stroke patients move asymmetrically, placing a mirror between their hands will give them a sudden illusion of normal movement of the involved hand, creating an incongruence between task performance and visual feedback. This situation can not be created similarly in healthy controls, and is conceptually different from the experiments in which healthy controls only move one hand.

In summary, while clinical trials have presented promising results of mirror therapy in several patients groups, the working mechanisms have not yet been investigated in patients. Additionally, results of the studies on the working mechanisms in healthy participants have not been conclusive and effects that have been found in these studies cannot be generalized to stroke patients. In the present study we therefore investigated the neuronal correlates of the mirror illusion in stroke patients. We used fMRI to compare two different sets of conditions: 1) moving the unaffected hand while observing it directly versus moving the unaffected hand while observing its mirror reflection and 2) moving both hands while observing the affected hand directly versus moving both hands while observing the mirror reflection of the unaffected hand in place of the affected hand. We hypothesised that observing the mirror reflection would increase neuronal activity in the affected hemisphere.

MATERIALS & METHODS

Participants

Patients that took part in this experiment were selected participants of a randomized controlled trial (RCT) investigating the effects of a rehabilitation program of mirror therapy (www.trialregister.nl NTR1052). In this trial, 40 stroke patients were included and randomly assigned to either an experimental (mirror) group or a control group. Patients from the trial that were eligible to be scanned in an MRI scanner were asked to take part in the present study. This study took place ahead of the start of the clinical trial, before patients had been allocated to a treatment group. Inclusion criteria for the RCT were knowledge of the Dutch language, a Brunnstrom Score for the upper-extremity between III and V, home dwelling status and at least one year post stroke. Patients with neglect, co-morbidities that influenced upper-extremity usage or who had suffered multiple strokes were excluded from participation. For patients to be able to take part in the present study, the following additional inclusion criteria applied: a Brunnstrom score of IV or V and standard MRI exclusion criteria. Application of these criteria resulted in a total of 22 eligible patients. The study was approved by the Medical Ethics Committee of the Erasmus MC Rotterdam and all patients gave written informed consent before participating in the study. Before the fMRI experiment started the Fugl Meyer [22] assessment of upper-extremity function was administered to all participants for descriptive purposes.

fMRI experiment

The fMRI paradigm we used was based on one previously designed in our laboratory.[18] We performed two separate experiments each involving two conditions within a single scanning session. In the first experiment patients were instructed to only move their unaffected hand (unimanual), either while looking directly at it (no mirror condition) or while observing its reflection in a mirror (mirror condition). In the second experiment patients were instructed to move both their hands (bimanual) either while looking directly at their affected hand (no mirror condition) or while observing the mirror reflection of their unaffected hand in place of their affected hand (mirror condition) (see Figure 1). In all four conditions, patients could see two hands. In the no mirror conditions of both experiments, patients had a direct view of both their affected and their unaffected hand. In the mirror conditions, patients had

a direct view of their unaffected hand and saw the reflection of their unaffected hand in place of their affected hand, also leading to visual feedback of two hands.

During scanning, patients lay on their back in the scanner with their upper arms comfortably resting on the scanner table alongside their torso and their elbows flexed in such a way that their hands were 20 centimetres apart above their waists. By means of two mirrors attached to the head coil above the head, patients were able to look in the direction of their feet and could thus view both their hands.

All four conditions were performed using a block design, consisting of 10 alternating 30s periods of 5 rest blocks and 5 active blocks. In the active blocks patients had to open and close either their unaffected hand or both hands, in the rest blocks patients had to hold their hands still. Patients were instructed to pace the opening of their hands to a metronome with a rhythm of 0.5 Hz. The onsets of the rest and active conditions were indicated verbally using simple words (start, rest) generated by a computer program (Matlab 7.1; Mathworks, Sherborn, Mass). Auditory stimuli were presented to the patients through MRI compatible headphones. The hand movement was practiced before the scan session started.

The four conditions were presented to the patients in random order. During the mirror conditions, a large mirror was placed between the subjects' hands in such a way that the mirror image of the unaffected hand was superimposed on the position of the affected hand. The large mirror was made of MRI-compatible material (plexiglass) and was shaped in such a way that it fitted inside the scanner bore and fully obstructed the view of the hand behind the mirror (see Figure 2). In this way, a visual illusion of two normal hands was created. Before the scanning session, patients practiced outside the scanner with a regular mirror as used during mirror therapy in order to make sure they experienced the visual illusion. While it is hard to objectively quantify the presence or strength of the illusion, all subjects reported that the illusion of seeing the affected hand moving in an unimpaired fashion was similar to their experience during the mirror exercises outside the MRI scanner.

Imaging was performed on a 3T MR system (HD platform, GE Healthcare, Milwaukee, Wis). For anatomical reference, a high-resolution, 3-dimensional, inversion recovery, fast spoiled gradient echo, T1-weighted image was acquired (TR/TE/TI 10.7/2.2/300 ms, 18° flip angle, matrix 416×256, and field of view 250×175 mm^2). For functional imaging, a single-shot, T2*-weighted, gradient echo echo-planar imaging (EPI) sequence was used (TR/TE 3000/30 ms, 75° flip angle, matrix 64×96, field

of view 220×220 mm^2). An fMRI acquisition lasted for 5m15s, including 15 seconds of dummy scans that were discarded. For each of the four conditions 100 volumes were collected. The imaging volume covered the entire brain including the cerebellum.

Statistical analyses

The imaging data were analyzed using statistical parametric mapping software (SPM5, Wellcome Department of Cognitive Neurology, University College London, UK) implemented in MATLAB version 7.1 (Mathworks, Sherborn, MAS).

All functional images for each participant were realigned to the first scan of each condition and then coregistered to the T1-weighted anatomical scan. Subsequently, images were transformed to standard Montreal Neurologic Institute space. To prevent warping around the lesions, we used a segmentation-based normalization approach.[23] Finally, normalized images were spatially smoothed by using a Gaussian filter of 8-mm FWHM.

Preliminary analyses showed that the realignment parameters estimated during spatial preprocessing were sometimes correlated with the task design. Therefore, we decided not to model the realignment parameters in the design matrix as regressors of no interest, as this would have resulted in cancelling out task-related activation. Instead, we used the ArtRepair Toolbox [24], which evaluates all volumes, detects the ones most affected by movement, and deweights these in the general linear model estimation. The experimental block design was convolved with the canonical hemodynamic response function, and the resulting model was estimated using a high-pass filter at 128 s in order to remove low-frequency artifacts.

In the first-level analysis, statistical maps were calculated for each of the four task blocks (i.e. movement with mirror, movement without mirror, rest with mirror, rest without mirror) for each patient and each experiment (bimanual and unimanual) separately. Statistical maps of patients with left-sided lesions were flipped about the midsagittal plane, so that the affected hemisphere corresponded to the right side of the brain for all patients. The statistical maps were used for second level analyses.

Second level analysis

We performed a two factorial analysis with movement (activity versus rest) and mirror (mirror versus no mirror) as main factors for both the unimanual and the bimanual experiments separately. Main effects of movement and mirror as well as the interaction between movement and mirror were investigated. Significance was set at $p<.05$ (FDR corrected) with a minimum cluster size of 20.

RESULTS

Four patients were discarded from further analysis, one due to scanner failure, and three due to scanner artefacts in their data sets. The remaining analyses were thus conducted using data sets of 18 patients. The characteristics of these patients are presented in Table 1.

Table 1

Patient characteristics of the study participants

Characteristic	**Total***
No. of patients	18
Age (years)	54.7 ± 9.9
Time since stroke (years)	5.2 ± 3.6
Sex (male/female)	10/8
Affected side dominant/nondominant)	6/12
Type of stroke (infarct/haemorrhage)	16/2
Location of stroke lesion	
- Cortical (with or without subcortical)	13
- Subcortical	3
- Brainstem†	2
FM score	41.9 ± 11.3

*Values are mean ± standard deviation

† Brainstem lesions are located in the pons, above the crossing of the cortico-spinal tract

In a two-factorial design, we examined main effects of movement (task condition versus rest), mirror (mirror condition versus no mirror condition), and the interaction effect between movement and mirror for both experiments. Observed activation patterns for the main effect of movement were in accordance with the expected activation for uni- and bimanual hand motor tasks. Activity was observed in the pre- and postcentral gyrus (primary motor and sensory cortex), the medial superior

frontal gyrus (SMA), at the junction of the superior frontal sulcus and the precentral sulcus (premotor cortex) and in the cerebellum.

Table 2

Areas of activation (unimanual experiment: main effect of movement)

Anatomical location	Side	Cluster size	Z-score	MNI		
				x	y	z
Pre- and Post central Gyrus	Unaffected	2103	7.57	-34	-26	54
Cerebellum	Unaffected	1287	7.28	16	-56	-20
Middle Occipital/Temporal gyrus	Affected	612	6.18	42	-64	4
Medial Frontal Gyrus, Superior Frontal Gyrus, Cingulate Gyrus	Affected, Unaffected	448	6.17	-6	-6	56
Middle Occipital/Temporal gyrus	Unaffected	491	5.98	-48	-70	-2
Precentral Gyrus	Unaffected	36	5.72	-52	0	8

Areas of activation (bimanual experiment: main effect of movement)

Anatomical location	Side	Cluster size	Z-score	MNI		
				x	y	z
Pre- and Post central Gyrus	Unaffected	853	7.11	-42	-20	52
Medial Frontal Gyrus, Superior Frontal Gyrus, Cingulate Gyrus	Unaffected	331	6.43	-6	-4	58
Pre- and Post Central Gyrus, Medial and Superior Frontal Gyrus, Cingulate Gyrus	Affected	665	6.36	36	-16	56
Middle Occipital gyrus, Inferior Temporal gyrys	Affected	33	5.63	44	-72	0
Middle Occipital/Temporal gyrus, Inferior Temporal gyrys	Unaffected	55	5.35	-46	-68	0

Areas are tresholded at $p < .05$ (FDR corrected) with a minimum cluster size of 20 voxels. MNI = Montreal Neurological Institute.

Analysis of the main effect of mirror (mirror versus no mirror) showed no significant areas of activation in either of the two experiments. The interaction of mirror x movement showed no significant activation for the unimanual experiment but it did show significant activation in the bimanual experiment; in the precuneus and the posterior cingulate cortex. Post-hoc analysis revealed that this was caused by increased activity in the movement with mirror condition versus the movement without mirror condition. Table 3 and Figure 3 show the activated clusters for the interaction effect of movement x mirror in the bimanual experiment.

Table 3

Areas of activation (bimanual experiment: interaction movement x mirror)

Anatomical location	Side	Cluster size	Z-score	MNI		
				x	y	z
Precuneus	Affected, Unaffected, Central	78	5.28	2	-58	58
Posterior Cingulate Cortex	Unaffected	117	4.68	-6	-36	8

Areas are tresholded at p < .05 (FDR corrected) with a minimum cluster size of 20 voxels. MNI = Montreal Neurological Institute.

DISCUSSION

In an attempt to unravel the working mechanism of mirror therapy, this study investigated the neuronal correlates of the mirror-induced visual illusion in stroke patients. In this first study, to our knowledge, in which stroke patients participated instead of healthy volunteers, we showed increased activity as a result of the mirror illusion during bimanual movement in two areas: the precuneus and the posterior cingulate cortex. We found no differential effect on neuronal activity of the mirror illusion during unimanual movement, nor did we find evidence for the mirror illusion to increase activity in motor areas or the mirror neuron system.

A network including both the precuneus and posterior cingulate cortex is reported to be associated with mental representation of the self.[25] More specifically, research showed that the precuneus is activated when actions are being interpreted as being controlled by the self as well as during self centred mental imagery strategies [26] whereas the cingulate cortex becomes activated during spatial navigation [27] and has been found to process information about the spatial positions of the limbs in monkeys.[28] The mirror illusion of a normal moving affected hand thus seems to increase alertness and spatial attention towards this hand. The fact that we did not find this activation during the unimanual condition, suggests that it is not so much the illusion of a virtual moving hand that causes this activation, but the mismatch between the movement one performs and the movement that is

observed. Research showing that the cingulate cortex becomes activated during conflict monitoring, specifically during action conflicts, supports this.[29]

Two previous studies in healthy participants have reported increased neuronal activity in similar areas as a result of an incongruence between movement observation and action.[30-32] Dohle et al.[32] found that such incongruence increased activation in occipital and posterior parietal areas, amongst them the precuneus, which they suggest to play a decisive role during mirror therapy.[21] In an earlier experiment Fink et al.[30] also reported on the neural correlates of a conflict between visual and proprioceptive information. Using positron emission tomography (PET) they investigated the effect of the mirror illusion during either in-phase movements or out-of-phase movements that are perceived as in-phase movements due to the mirror. Their results showed an effect of the mirror in the dorsolateral prefrontal cortex (DLPCF) and in the superior posterior parietal cortex (Brodmann's area (BA) 7). BA 7 is a point of convergence between vision and proprioception and plays a role in visuo-motor coordination. The precuneus, which in our study became activated during the bimanual mirror condition, is part of BA 7 [26] but is located more medial than the area of activation reported by Fink et al. The main difference between our study and Fink et al.'s is that in the latter participants actively had to create the motor-sensory conflict (by moving out-of-phase), while in our patient group this resulted from the involved arm not being able to perform similar movements as the non-involved arm. The situation created by Fink et al. likely induces a larger cognitive burden for the participants, which may explain increased DLPCF activation, while the main effect of the mirror they observed in BA 7 is in line with our findings of precuneus activation in the presence of a motor-sensory conflict, albeit under different experimental settings.

The question is how the involvement of the areas we found activated by the mirror illusion relates to the reported improvements in motor function following mirror therapy.[3,21] Possibly, by increasing the spatial attention towards the affected limb the mirror illusion might help in overcoming the learned non-use phenomenon [21,33], and as a result of the ensuing increased use of the limb improve motor performance. An alternative hypothesis, supported by the fact that we only observed increased cortical activation during the bimanual experiment, might be that the effects of the mirror lie in an enhancement of spatial coupling between limbs. It is well known that when two arms move simultaneously, movements become more temporally and spatially stable.[34] In stroke rehabilitation, this phenomenon has been exploited in the form of bimanual training programs. Several studies have

shown that bimanual training strategies have a favourable effect over unimanual training [35], demonstrating that spatial coupling can cause the affected limb to take on the properties of the non-effected limb, thereby improving motor performance. The hypothesis that the mirror illusion enhances this spatial coupling is supported by studies on healthy volunteers, showing that the mirror illusion increased the tendency of one limb to take on the spatial properties of the other limb.[36,37]

So far, several reviews and clinical studies have attributed the effects of mirror therapy to activation of motor areas or the mirror neuron system (MNS).[3,38-40] As mentioned, in the present study we did not observe activation resulting from the mirror illusion in these areas (e.g. M1, PMC, SMA, Broca's area), neither in the unimanual experiment nor in the bimanual experiment. Research performed in healthy subjects has so far also been unable to provide convincing evidence for the activation of these areas by the mirror illusion, only the fMRI study of Matthys et al. showed some evidence for MNS activation by reporting increased activation within STS.[18] However, although STS is reported to be related to the MNS [19], this area has been associated with many different behaviours and its exact function remains poorly understood.[41] Matthys et al. also reported activation in the superior occipital gyrus, an area connected with the PPC trough the dorsal stream. Activation of this area may reflect increased attentional demands for the integration of vision and proprioception induced by the mirror, which is in line with our present results. It has to be noted that the analysis strategy of Matthys et al. differed from the strategy employed in the present paper. Contrary to our approach, Matthys et al. did not apply an ANOVA design and thus did not examine the effect of the mirror, the hand motor performance and its interaction separately. As a final note on the proposed activation of the MNS or motor system by the mirror illusion, a previous study showed that whereas observation of actions attributed to another individual activated the motor system, observation of identical actions linked to the self did not.[42] The MNS thus seems to distinguish between observing actions linked to the self and actions linked to others. This finding further undermines the notion that the mirror illusion of self-performed movements might trigger the motor or mirror neuron system.

We acknowledge that our study has some limitations. In general, detecting study-related effects in fMRI experiments in stroke patients is difficult as the neuronal circuitry may be distorted and heterogeneous between subjects. Some authors try to get around this issue by including only patients with minor lesions, which is a major source of selection bias. In the current study, in order to enlarge

the contrast between mirror and no mirror conditions in the bimanual experiment, we explicitly enrolled patients with larger motor deficits. Consequently, the within-group variability was considerable, which may have decreased the power to detect differences between conditions. Another issue, related to the severity of their motor deficit, is that some patients had problems keeping their head still during the experimental task. As these movements were task-related, we could not simply regress out head motion-related activation as this would have cancelled out task-related activation as well. However, we used an alternative, sensitive method to deal with this issue (see Methods section), and activation patterns we observed are in accordance with the expected activation for uni- and bimanual hand motor tasks, implicating the validity of our analysis. A general limitation of this and similar studies is that it is difficult to objectify the strength of the illusion patients experience when inside the scanner. To maximize the mirror illusion during scanning, all patients practiced with a standard mirror used for mirror therapy outside the scanner, and they all reported similar illusion strength during the measurements inside the scanner as outside.

In conclusion, the present study showed that during bimanual movement, the mirror illusion alters neuronal activation in the precuneus and posterior cingulate cortex, areas related to alertness and spatial-awareness. We found no differential effect on neuronal activity of the mirror illusion during unimanual movements, nor did we find evidence for the mirror illusion to increase activity in motor areas. By increasing awareness of the affected limb, possibly due the mismatch between action and observation, the mirror illusion might reduce learned non-use. The fact that we did not observe any activation in areas belonging to the motor or mirror neuron system questions popular theories that contribute the clinical effects of mirror therapy to these systems. As research into the working mechanism of mirror therapy has so far mainly focussed on these systems, we suggest that future research should adopt a broader perspective, amongst other things taking the ideas as proposed in this paper into account. Since a better understanding of why and how mirror therapy works may lead to a more effective application and might help in selecting patients for which mirror therapy will be most effective, it is important that efforts to unravel the neuronal correlates of mirror therapy continue.

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Figure 1

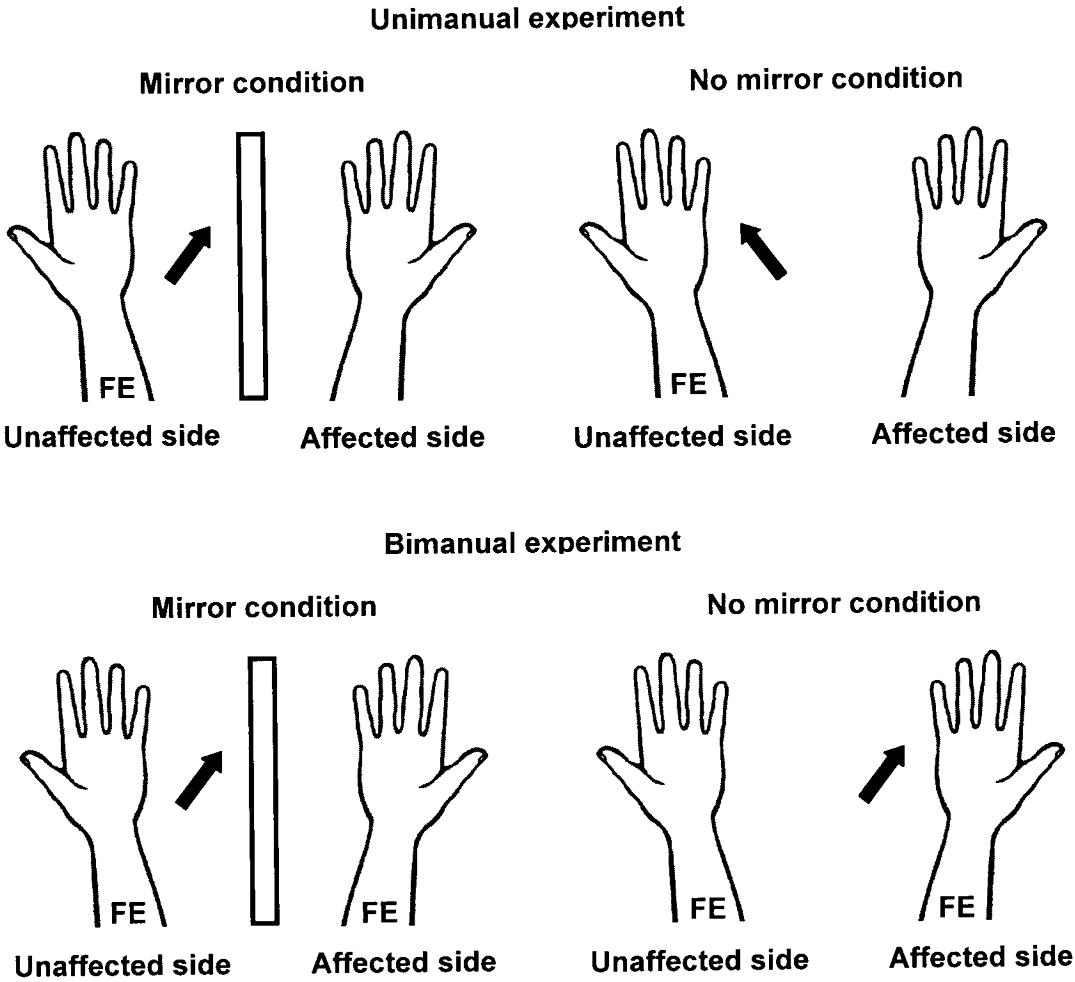
Schematic representation of the four conditions. FE indicates which hands perform the flexion-extension movements, and the arrow is used to indicate the direction of gaze in each condition.

Figure 2

Participant lying in the scanner during the mirror condition. The unaffected hand is not visible, as it is positioned in front of the mirror.

Figure 3

Activation map of the interaction effect of movement x mirror for the bimanual experiment ($p<.05$, FDR corrected, minimum cluster size 20). Label A: posterior cingulate cortex; Label B: precuneus.


Unimanual experiment
Mirror condition
No mirror condition
FE
FE
Unaffected side
Affected side
Unaffected side
Affected side
Bimanual experiment
Mirror condition
No mirror condition
FE
FE
FE
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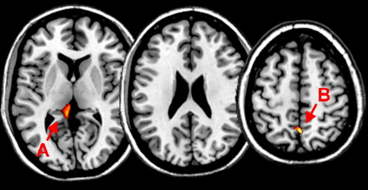
Affected side
Unaffected side
Affected side


A
B