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1 **The neuronal correlates of mirror therapy: an fMRI study on mirror induced visual illusions in**
2 **stroke patients**

3

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32

33 **Key words:** Stroke, Upper-Limbs, Rehabilitation, fMRI, Mirror Therapy

34

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36

37 **ABSTRACT**

38

39 **Aim**

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

41 **Methods**

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

50 **Results**

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

54 **Conclusion**

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

61

62

63 **INTRODUCTION**

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

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

88 A number of studies have evaluated the neuronal correlates of mirror therapy by examining
89 the observation of the mirror reflection of a moving hand in healthy subjects. These studies were
90 based on the hypothesis that the mirror illusion would increase excitability or activity in primary motor
91 areas in the hemisphere ipsilateral to the moving hand. Using transcranial magnetic stimulation (TMS)
92 [13-15], magnetoencephalography (MEG) [16], electroencephalography (EEG) [17] and functional

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

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

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

123 **MATERIALS & METHODS**

124

125 **Participants**

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

141

142 **fMRI experiment**

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

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

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

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

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

177 Imaging was performed on a 3T MR system (HD platform, GE Healthcare, Milwaukee, Wis).
178 For anatomical reference, a high-resolution, 3-dimensional, inversion recovery, fast spoiled gradient
179 echo, T1-weighted image was acquired (TR/TE/TI 10.7/2.2/300 ms, 18° flip angle, matrix 416×256,
180 and field of view 250×175 mm²). For functional imaging, a single-shot, T2*-weighted, gradient echo
181 echo-planar imaging (EPI) sequence was used (TR/TE 3000/30 ms, 75° flip angle, matrix 64×96, field

182 of view 220×220 mm²). An fMRI acquisition lasted for 5m15s, including 15 seconds of dummy scans
183 that were discarded. For each of the four conditions 100 volumes were collected. The imaging volume
184 covered the entire brain including the cerebellum.

185

186 **Statistical analyses**

187 The imaging data were analyzed using statistical parametric mapping software (SPM5, Wellcome
188 Department of Cognitive Neurology, University College London, UK) implemented in MATLAB version
189 7.1 (Mathworks, Sherborn, MAS).

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

195 Preliminary analyses showed that the realignment parameters estimated during spatial
196 preprocessing were sometimes correlated with the task design. Therefore, we decided not to model
197 the realignment parameters in the design matrix as regressors of no interest, as this would have
198 resulted in cancelling out task-related activation. Instead, we used the ArtRepair Toolbox [24], which
199 evaluates all volumes, detects the ones most affected by movement, and deweights these in the
200 general linear model estimation. The experimental block design was convolved with the canonical
201 hemodynamic response function, and the resulting model was estimated using a high-pass filter at
202 128 s in order to remove low-frequency artifacts.

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

208

209

210 **Second level analysis**

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

215

216 **RESULTS**

217 Four patients were discarded from further analysis, one due to scanner failure, and three due to
218 scanner artefacts in their data sets. The remaining analyses were thus conducted using data sets of
219 18 patients. The characteristics of these patients are presented in Table 1.

220

221 **Table 1**

222 **Patient characteristics of the study participants**

Characteristic	Total*	
No. of patients	18	223 224
Age (years)	54.7 ± 9.9	226
Time since stroke (years)	5.2 ± 3.6	227
Sex (male/female)	10/8	228
Affected side dominant/nondominant)	6/12	229
Type of stroke (infarct/haemorrhage)	16/2	230
Location of stroke lesion		231
- Cortical (with or without subcortical)	13	232
- Subcortical	3	233
- Brainstem [†]	2	234
FM score	41.9 ± 11.3	235

237 *Values are mean ± standard deviation

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

239

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

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

247

248 **Table 2**

249 **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

250

251

252 **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 gyrus	Affected	33	5.63	44	-72	0
Middle Occipital/Temporal gyrus, Inferior Temporal gyrus	Unaffected	55	5.35	-46	-68	0

253

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

256

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

264

265 **Table 3**

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

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

267

268 Areas are thresholded at $p < .05$ (FDR corrected) with a minimum cluster size of 20 voxels. MNI =

269 Montreal Neurological Institute.

270

271 **DISCUSSION**

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

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

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

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

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

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

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

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

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

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

374

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382

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384

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391

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488

489

490 **Figure 1**

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

493

494 **Figure 2**

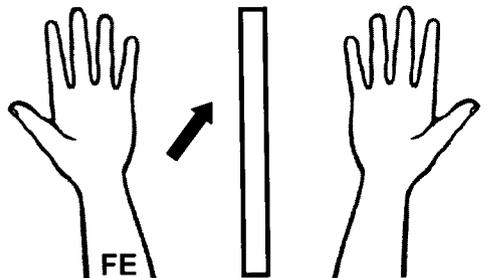
495 Participant lying in the scanner during the mirror condition. The unaffected hand is not visible, as it is
496 positioned in front of the mirror.

497 **Figure 3**

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

Unimanual experiment

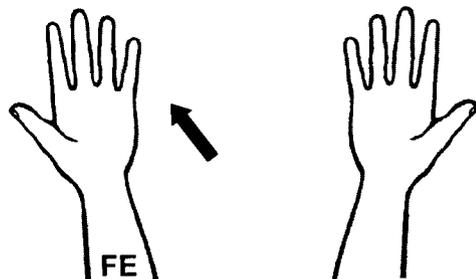
Mirror condition



Unaffected side

Affected side

No mirror condition

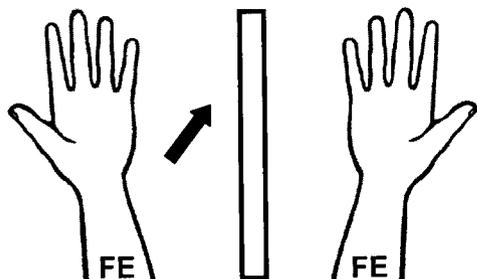


Unaffected side

Affected side

Bimanual experiment

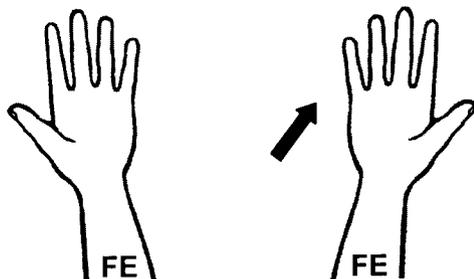
Mirror condition



Unaffected side

Affected side

No mirror condition



Unaffected side

Affected side



