

## Finger recruitment patterns during mirror movements suggest two systems for hand recovery after stroke

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### Author contributions

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*Data:* Data taken from (Xu *et al.*, 2016)

*Study design and analysis:* NE, JX, JD, JWK.

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### Open Science

Behavioural dataset available at: <https://github.com/nejaz1/mirroring2017>

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## Abstract

Accumulating behavioural and neurophysiological evidence suggests that upper-limb control relies on contributions from both cortical and subcortical motor circuits, with cortical inputs providing fine-finger function and subcortical inputs providing the ability for gross movements, respectively. During recovery of function after stroke, the relative contributions from these pathways may shift. Here we propose that mirror movements that appear after stroke provide a non-invasive assay through which relative contributions from cortical and subcortical pathways towards hand recovery can be studied. We hypothesized that mirror movements, like hand function, are generated by summed contributions from cortical and subcortical pathways, and suggest that subcortical contributions should be characterized by a broad recruitment of fingers, while cortical contributions primarily recruit the homologous finger in the passive hand. In a longitudinal stroke recovery study (Xu *et al.*, 2016), we quantified mirror movements and paretic hand function in 53 stroke patients in the year following unilateral stroke. Mirror movements in the non-paretic hand were exaggerated early after damage (week 2), with paretic finger presses broadly recruiting multiple fingers in the non-paretic hand. On average, however, mirroring in homologous fingers was 1.76 times larger than in non-homologous fingers. Over the year, mirroring in the non-paretic hand progressively normalized with a time-course that mimicked that for the fine-finger deficits in the paretic hand. In comparison, during non-paretic finger presses, the homologous component of mirroring in the paretic hand was reduced early after stroke (week 2) but progressively normalized. Altogether, we conclude that the pattern of mirror movements across homologous and non-homologous fingers reflect the summed contributions of both cortical and subcortical systems, and we discuss the implications of our results towards hand recovery after stroke.

**Key words:** mirror movements, finger movements, post-stroke hand recovery, corticospinal, reticulospinal

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## Introduction

33           Accumulating behavioural evidence suggests that upper-limb function relies on  
34 inputs from both cortical and subcortical motor circuits. While cortical contributions  
35 towards upper-limb function are well-established (Brinkman and Kuypers, 1973;  
36 Soteropoulos *et al.*, 2011), subcortical contributions have been proposed to explain why  
37 voluntary movements in response to startling acoustic cues have reaction times which are  
38 much shorter than the known conduction delays from the cortex to the upper-limb (Carlsen  
39 *et al.*, 2009; Dean and Baker, 2016; Honeycutt *et al.*, 2013). Furthermore, different aspects  
40 of upper-limb function (i.e. strength and fine-control) dissociate after stroke (Lan *et al.*,  
41 2017; Sukal *et al.*, 2007; Xu *et al.*, 2016), suggesting that these two components reflect  
42 contributions from (at least) two separate systems, originating in cortical and subcortical  
43 areas respectively (Xu *et al.*, 2016).

44           Neurophysiological studies in primates provide additional evidence for cortical and  
45 subcortical contributions towards hand function, further suggesting that inputs from each  
46 area contribute towards different aspects of hand function. The most prominent inputs to  
47 the hand come through the corticospinal tract (Porter and Lemon, 1993; Soteropoulos *et al.*,  
48 2011), which connects motor circuits in the contralateral hemisphere to the spinal cord and  
49 provides the ability to perform fine-finger function e.g. precision grip (Lawrence and  
50 Kuypers, 1968a; Rathelot and Strick, 2009; Tower, 1940). Additional input to the hand  
51 comes from phylogenetically-older, rubrospinal and reticulospinal pathways originating in  
52 the brainstem. In contrast to the corticospinal tract, these subcortical pathways are mainly  
53 involved in gross movements (e.g. whole-hand grasping) and offer only a limited ability for  
54 fractionated finger control (Lawrence and Kuypers, 1968b; Riddle *et al.*, 2009;  
55 Soteropoulos *et al.*, 2012). Since the rubrospinal pathway is largely absent in man (Nathan  
56 and Smith, 1955; 1982), the reticulo- and corticospinal pathways have been proposed to  
57 mediate gross and fine-control aspects of hand function respectively (Sukal *et al.*, 2007; Xu  
58 *et al.*, 2016).

59           Together, these cortical and subcortical pathways potentially provide a certain  
60 degree of flexibility in hand function, with one partially able to compensate for damage to  
61 the other. Indeed, changes in the relative contributions of cortical and subcortical pathways  
62 in primates is one proposed mechanism through which the hand regains function following

63 stroke (Herbert *et al.*, 2015; Zaaimi *et al.*, 2012). The extent to which changes in pathway  
64 contributions are responsible for hand recovery in man is unknown, primarily because  
65 invasive investigations like those in primates are not possible.

66 In this study, we posit that mirror movements provide a non-invasive assay through  
67 which changes in the relative contributions from cortical and subcortical systems after  
68 stroke can be studied. In health, mirror movements are unintended movements that appear  
69 in the passive hand when the active hand voluntarily moves (review, Cincotta and Ziemann,  
70 2008). Surprisingly little is known about the nature of mirroring after stroke, except that in  
71 chronic patients they are exaggerated in the non-paretic hand (Cernacek, 1961; Y. Kim *et al.*  
72 *et al.*, 2015; Y. H. Kim *et al.*, 2003; Nelles *et al.*, 1998), but slightly reduced in the paretic  
73 hand (Nelles *et al.*, 1998). While mirroring has typically been attributed to abnormally large  
74 activities in cortical sensorimotor areas (Cincotta and Ziemann, 2008; Cramer *et al.*, 1997;  
75 Y. H. Kim *et al.*, 2003; Ward *et al.*, 2003; Wittenberg *et al.*, 2000), subcortical pathways  
76 are also plausible candidates. For instance, individual reticulospinal axons project  
77 bilaterally onto the contra- and ipsilateral sections of the spinal cord (Sakai *et al.*, 2009),  
78 and activate upper-limb muscles on either side of the body (Hirschauer and Buford, 2015),  
79 potentially causing mirroring.

80 We hypothesized that mirror movements, like hand function, might be caused by  
81 summed contributions from cortical and subcortical pathways. Furthermore, we suggest  
82 that relative contributions from these pathways can be disentangled by studying the exact  
83 patterns of finger recruitment during mirroring. Subcortical contributions to mirroring  
84 should result in a broad recruitment of fingers in the passive hand, reflecting the pathway's  
85 limited ability to provide fractionated finger control (Lawrence and Kuypers, 1968b;  
86 Soteropoulos *et al.*, 2012). In contrast, we have observed that finger presses result in  
87 activation patterns in cortical sensorimotor areas that are highly similar regardless of  
88 whether the contralateral, or the homologous finger in the ipsilateral hand was used  
89 (Diedrichsen:2013hb, also see Liu *et al.*, 2010; Scherer *et al.*, 2009). Therefore, cortical  
90 contributions towards mirroring should primarily recruit the homologous finger in the  
91 passive hand, reflecting the specialized role of neocortical motor areas in providing fine-  
92 finger control (Brinkman and Kuypers, 1973; Soteropoulos *et al.*, 2011).

93 Therefore, in 53 stroke patients, we characterized the year-long changes in mirror  
94 movements after damage. After stroke, individuated finger presses with the paretic hand  
95 resulted in a broad recruitment of fingers in the non-paretic hand. On average, however,  
96 mirroring in homologous fingers was larger than in non-homologous fingers. In  
97 comparison, the homologous component of mirroring in the paretic hand was reduced early  
98 after stroke but subsequently normalized. Altogether, we conclude that mirror movements  
99 reflects contributions from (at least) two separate systems, and discuss the implications of  
100 these results on cortical and subcortical contributions towards hand recovery after stroke.

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## Materials and Methods

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### Participants

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53 patients with hemiparesis (20 female; age=57.4, SD=14.9 years) were recruited within the first week after stroke. The recovery of paretic hand function is reported in Xu et al. (2016), but clinical measures of impairment at the time of recruitment are summarized in Supplementary Figure 1. Patients were included if they had a first-time unilateral ischemic stroke within the previous 2 weeks and reported unilateral weakness of the upper extremity (Medical Research Council muscle weakness scale<5). They were excluded if age<21 years, their initial upper-limb impairment was too mild (Fugl-Meyer>63/66), or if they had cognitive deficits that could impair task comprehension and performance. Excluding aphasic patients led to a bias of right-hemispheric infarcts (36 right), in turn leading to a disproportionately higher ratio of left-handed patients (42 right-hand; according to Oldfield (1971)). A comprehensive list of inclusion/exclusion criteria is available at Xu et al. (2016).

14 neurologically-healthy participants were also recruited as healthy controls for the study (4 female; age=64.0, SD=8.2 years). Controls and patients did not differ in age ( $t_{65}=1.60$ ,  $p=0.11$ ).

Data was collected across three centres: Johns Hopkins University, University of Zurich, and Columbia University. All experimental procedures were approved by the respective local ethics committee, and written consent was obtained from all participants.

## 125 **Apparatus to measure finger forces**

126 We used a custom-built ergonomic keyboard (Fig. 1A) to measure isometric finger  
127 forces generated during the behavioural and fMRI tasks. During either experiment,  
128 participants were instructed to always keep both their hands on the 10 keys of the device.  
129 Force transducers beneath each key (Honeywell FS, dynamic range 0-25N) allowed for the  
130 sensitive measurement of finger forces in the instructed hand (Ejaz *et al.*, 2015) (Fig. 1B),  
131 as well as mirrored finger forces in the passive hand (Diedrichsen *et al.*, 2013).

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## 133 **Assessment of mirror movements during the behavioural task**

134 Mirror movements for each participant (patients and controls) were assessed over  
135 five longitudinal measurement sessions following recruitment (Table 1); weeks 2, 4, 12, 24  
136 and 52 post-stroke.

137 During each measurement session, participants performed individuated force  
138 presses in the flexion direction with the instructed finger, while mirrored forces in the  
139 fingers of the passive hand were recorded. A visual representation of all ten fingers was  
140 presented on a screen (Fig. 1A). The experiment began by estimating the strength of each  
141 finger, measuring 2 repetitions of the maximum voluntary force (MVF) of each digit on  
142 both hands.

143 All subsequent trials required the production of isometric fingertip forces at a  
144 fraction of the MVF for the instructed digit (at 20%, 40%, 60%, 80%). At the start of every  
145 trial, a force target-zone (target-force $\pm$ 25%) on a single finger was highlighted in green.  
146 This was the cue for participants to make a short force press with the instructed finger to  
147 match and maintain the target-force for 0.5s. The trial was stopped if force on the instructed  
148 digit did not exceed 2.5N in the 2s following stimulus onset. Trials were presented in  
149 sequential order, starting from the left thumb to the left little finger, and ending with the  
150 right thumb to the right little finger. Trials were grouped as blocks, with each block  
151 consisting of one measurement each for the four target-force levels across the 10 fingers (4  
152 target-force levels x 10 fingers=40 trials/block). Participant's performed 4 such blocks  
153 during each measurement session.

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## 156 Quantifying the degree of mirror movements

157 During each trial, finger presses with the instructed finger resulted in subtle forces  
158 in the fingers of the passive hand (Fig. 1B). These mirrored forces were substantially  
159 smaller than the forces produced by the instructed finger. Even at the lowest target-force  
160 levels, the trajectory of these averaged mirrored forces correlated strongly with those  
161 produced by the instructed fingers (Fig. 1C). This was true for both controls ( $r=0.63$ , 95%  
162 confidence interval: 0.53-0.72), and patients ( $r=0.61$ , 95% confidence interval: 0.56-0.65).  
163 These correlations increased monotonically as the target-forces increased, consistent with  
164 previous reports that mirrored forces are a function of the force applied with the active hand  
165 (Armatas *et al.*, 1996; Todor and Lazarus, 1986).

166 To quantify peak forces produced during mirroring, the resting baseline force on  
167 each finger prior to movement was subtracted from the subsequent force trace produced  
168 during the trial. Then the peak force  $F_{passive}$  on the passive hand was calculated as the peak  
169 averaged force on the fingers during the trial:

$$F_{passive} = \max_t \left( \frac{\sum_{p=1}^5 |\tilde{F}(t,p)|}{5} \right)$$

170  
171 where  $t$  is the duration of the trial in seconds, and  $\tilde{F}$  are the baseline corrected forces on  
172 finger  $p$  of the passive hand. Thus,  $F_{passive}$  indicates the peak averaged force in the passive  
173 hand when the active finger produces force.

174 The passive mirrored force increased approximately linearly with the force exerted  
175 by the active hand (Fig. 1D). To derive a singular metric of the degree of mirroring across  
176 the different target force levels, we conducted a regression analysis to estimate the ratio of  
177 the peak force on the instructed finger  $F_{active}$  and the peak mirrored force ( $F_{passive}$ ). First,  
178 all trials belonging to movements of the same instructed finger were grouped together. We  
179 plotted  $F_{active}$  on the x-axis and  $F_{passive}$  for corresponding trials on the y-axis and  
180 estimated the best-fit line forced through the origin that described the data points (Fig. 1D).  
181 Sensitivity to outliers was reduced by using robust regression with a b-squared weighting  
182 function. To ensure that the passive force was specific to mirroring and not due to spurious  
183 finger presses of the passive hand, we only used trials where the correlations between

184 averaged force trajectories across all fingers in the active and passive hands were  $\geq 0.2$  to  
185 estimate the linear slope.

186 Finally, to allow for the use of parametric statistics, the regression slope (i.e. the  
187 estimate of the ratio) was log-transformed to make it conform better to a normal  
188 distribution. This log-slope provides a sensitive measure of mirroring in the passive hand  
189 due to movements of the instructed finger. For each participant, the log-slopes associated  
190 with the instructed fingers on each hand were averaged to get a composite metric of the  
191 degree of mirroring.

192

### 193 **Quantifying recruitment of fingers during mirror movements**

194 The principle aim of this study was to determine how fingers of the passive hand  
195 were recruited during mirroring. To do so, we first calculated the mirroring across all 25  
196 possible combinations of instructed/non-instructed finger pairs. Mirroring across each  
197 finger pair  $(i, j)$  was computed as described in the preceding section, by computing the  
198 log-slope between the peak force in the instructed finger  $i$ , and the peak force on the non-  
199 instructed finger  $j$ . The pattern of finger recruitment during mirroring was quantified  
200 separately for each participant and measurement session, thereafter referred to as  
201 *mirroring pattern*.

202 To determine the degree of homologous mirroring, we averaged the log-slopes for  
203 homologous finger pairs  $(i = j)$  across the two hands for each participant. Non-  
204 homologous mirroring was determined by averaging log-slopes for all finger pairs where  
205  $i \neq j$ .

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### 207 **Estimating changes in mirroring patterns over time**

208 To estimate similarities between mirroring patterns for patients and controls, we  
209 first estimated the average mirroring pattern for all controls. This control pattern was then  
210 correlated with the corresponding mirroring pattern for each patient, separately for each  
211 week. The resulting correlations quantified the similarities between mirroring patterns for  
212 patients and controls during recovery. Since the mirroring patterns for controls were  
213 themselves estimated in the presence of measurement noise, even a perfect match between  
214 patient and control mirroring patterns would not result in a correlation of 1. To estimate a



215 noise ceiling for the correlations, we calculated the average correlation of each controls  
216 mirroring pattern with the group mean. As a lower bound, each control's mirroring pattern  
217 was also correlated with the group mean in which this participant was removed. These  
218 upper and lower bounds therefore specify the range of values correlations between  
219 mirroring patterns for control and patients could maximally take given measurement noise.

220

### 221 **Quantifying mirror movements in the paretic hand**

222 In addition to the non-paretic hand, we also quantified the degree of homologous  
223 and non-homologous mirroring in the paretic hand during non-paretic finger presses. Since  
224 mirroring in the paretic hand might be influenced by the loss of hand strength, we restricted  
225 our analysis to a subset of relatively mildly impaired patients. Patients were split into a  
226 mild and severe group based on whether reliable muscle potentials could be evoked on the  
227 paretic hand during transcranial magnetic stimulation (TMS) of the lesioned hemisphere.  
228 Only TMS measurements obtained within the first 2 weeks after stroke were used to  
229 categorize patients. During each measurement session, 10 single TMS pulses were applied  
230 to the hand area of the motor cortex in the lesioned hemisphere while muscle activity from  
231 the contralateral FDI muscle was recorded. Patients that demonstrated reliable muscle  
232 evoked-potentials ( $MEP \geq 50\mu V$ ) for at least 5 out of the 10 TMS pulses were placed into  
233 the mild group, while those that did not show reliable MEPs even at 100% stimulation  
234 intensity were placed in the severe group. For the TMS experiment, only a subset of 40  
235 patients (Fugl-Meyer, 16-59, 25%-75% percentile) were measured. Of these, 11 patients  
236 did not demonstrate reliable MEPs at week 2 and were thus categorized as severe, while 29  
237 patients were categorized as mild and we focused our analysis on this subgroup.

238

### 239 **Quantifying finger individuation ability**

240 In addition to the mirrored forces, individuated finger presses also resulted in  
241 enslaved forces on the uninstructed fingers of the active hand (Fig. 1B). These enslaved  
242 forces were generally much larger than the associated mirrored forces, and at high force  
243 requirements, degraded the participants ability to individuate a single finger (Z. M. Li *et al.*,  
244 1998). We quantified the degree of enslaving in the same way as for mirroring, by  
245 estimating the log-slope between the peak forces on the instructed and the passive fingers

246 on the active hand respectively. We have previously used a similar metric to quantify  
247 patients impairment in finger individuation ability after stroke (Xu *et al.*, 2016).

248

## 249 **Assessing neural activity associated with individuated finger movements** 250 **(fMRI)**

251 Cortical activity associated with finger movements was measured in controls and  
252 patients at the same time points as for the behavioural measurements, five times over the  
253 course of a 1-year period (Table 1).

254 Participants were instructed to produce individuated finger movements inside an  
255 MRI scanner in a protocol resembling the behavioural task. To reduce scanning time, only  
256 four fingers on either hand were tested (ring finger was excluded). Each trial required the  
257 production of 4 short isometric force presses with an instructed finger. Each trial began  
258 with the instructed finger highlighted in green for 2s. A green line then appeared below the  
259 finger stimulus as the go-cue for producing a short flexion force press with the instructed  
260 finger within 1.9s. This cue was repeated 4 times for a total of 4 repetitive presses with the  
261 instructed finger for that trial. A successful finger press required the production of either  
262 1.8N or 8% of the MVF for that finger, whichever was lower. The green line turned blue to  
263 signal a successful finger press. Trials were grouped as experimental runs, with each run  
264 consisting of 3 trials for the 8 fingers across the two hands (a total of  $3 \times 8 = 24$  trials/run).  
265 Trials within each run were presented in pseudo-random order, and participants performed  
266 8 runs at each measurement session.

267 Functional scans during task performance were obtained at three centers on two  
268 different 3T Philips systems (Achieva and Ingenia). Scans were obtained with a 32-channel  
269 head-coil using a two-dimensional echo-planar imaging sequence (TR=2s, 35 slices, 154  
270 volumes-per-run, slice thickness 2.5mm, 0mm gap, in-plane resolution  $2.5 \times 2.5 \text{mm}^2$ ).  
271 Within each imaging run, six rest phases lasting 10s were randomly interspersed. A T1-  
272 weighted anatomical image (3D MPRAGE sequence,  $1 \times 1 \times 1.2 \text{mm}$ ,  $240 \times 256 \times 204 \text{mm}$  FOV)  
273 was also acquired. For each participant, two diffusion tensor-imaging (DTI) images  
274 (TR=6.6s, 60 slices, 2.2mm slice thickness,  $212 \times 212 \text{mm}$  FOV) were also acquired to help  
275 quantify the size and location of stroke lesions.

276

## 277 **Imaging analysis**

278 All functional data was corrected for motion across runs (Diedrichsen and  
279 Shadmehr, 2005), and co-registered to the T1-image obtained in the participant's first  
280 measurement session (either week 2 or 4). The raw time-series data was analyzed using a  
281 generalized-linear model (GLM) with a separate regressor for each finger/hand/imaging run  
282 (4-fingers x 2-hands x 8-runs = 64-regressors). Activation for each trial was modelled using  
283 a boxcar function (10.88s) convolved with a standard haemodynamic response function.

284 Each participants T1-image was used to reconstruct the pial and white-gray matter  
285 surfaces using Freesurfer (Dale *et al.*, 1999). Individual surfaces were aligned across  
286 participants and registered to match a template using the sulcal-depth map and local  
287 curvature as minimization constraints.

288 The anatomical regions of interest (ROIs) were defined on the group surface using  
289 probabilistic cyto-architectonic maps aligned to the average surface (Fischl *et al.*, 2008).  
290 Surface nodes with the highest probability for Brodmann area (BA4) 2cm above and below  
291 the hand-knob were selected as belonging to M1. Similarly, nodes in the hand-region in S1  
292 were isolated using BA 3a, 3b, 1 and 2 (combined), again 2 cm above and below the hand  
293 knob.

294 Each participants DTI and T1-images (at first measurement) were used to estimate  
295 the size and location of lesions in two ROIs: i) cortical grey matter in the sensorimotor  
296 cortices (M1/S1) of either hemisphere, and the ii) corticospinal tract superior to the  
297 pyramids. Lesion boundaries were determined independently by radiologist (AVF) and  
298 neurologist (MB) that were blind to the patients clinical information and task performance.  
299 Detailed information about lesion distribution can be found in Xu *et al.* (2016).

300 Finally, the parameter estimates from the GLM analysis in M1 and S1 ROIs with  
301 lesion areas excluded, were identified and pre-whitened using the GLM residuals to reduce  
302 the effects of estimation noise (Walther *et al.*, 2015). These pre-whitened parameter  
303 estimates quantified the evoked-BOLD activations. As measuring participant data for all 5  
304 sessions was ambitious, we ended up with an unbalanced experimental design due to  
305 missing data across the fMRI experiment. We therefore used linear mixed-effects models  
306 for the summary plots of the fMRI experiment (Fig 5D; *lme4* package in R; (Bates *et al.*,  
307 2014)) to account for the problem of missing values.

## 308 **Statistical analysis**

309 We used 2-sided t-tests to test for differences in means either across groups, or  
310 across different time-points of recovery. To test for differences between summary statistics  
311 across groups or over time, we used linear mixed-effects models in the lme4 package in R  
312 (Bates *et al.*, 2014). In all statistical models, an intercept was included as one of the fixed  
313 effects, with each participant considered a random-effect. All data presented in the text and  
314 figures are represented as mean±standard error of the mean. All statistical tests involving  
315 correlations were performed on Fisher Z-transformed values.

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## **Results**

319

### 320 **Mirror movements appeared early after stroke and normalized over the year**

321 Using a sensitive behavioural assay, we quantified mirror movements in 53 stroke  
322 patients and 14 controls. The first measurement was within the first 2-weeks of stroke-  
323 onset, and subsequently at four sessions over the following year (Table 1). During each  
324 measurement session, patients and controls produced individuated finger presses at  
325 different target-force levels while forces in the passive hand were measured (Fig 2B). To  
326 quantify the degree of mirroring, we calculated the linear slope between the peak force  
327 produced by the instructed finger and the peak averaged force in the passive hand (Fig 1D;  
328 see methods).

329 Patients showed large time-course changes in mirroring in the year following a  
330 stroke (Fig. 2A). In the first two weeks after damage (week 2), individuated finger presses  
331 with the paretic hand resulted in large forces in the non-paretic hand, with 1N of voluntary  
332 force resulting in approximately 0.051N of averaged mirrored force. In comparison,  
333 mirroring in controls was significantly lower than patients (1N/0.004N;  $t_{51}=3.67$ ,  $p=0.001$ ).  
334 Mirroring in patients subsequently reduced over time ( $\chi^2=82.99$ ,  $p<<0.0001$ ). However,  
335 even 6-months after stroke, mirroring was still marginally larger in comparison to controls  
336 ( $t_{51}=1.75$ ,  $p=0.087$ ). There was a strong correlation between mirroring during the early and  
337 late stages following stroke  $r=0.73$  ( $p<0.001$ ), demonstrating that patients who exhibited  
338 large mirroring early after stroke continued to do so throughout recovery.

339           The longitudinal changes in mirroring were remarkably similar to those for the  
340 deficits in fine-finger function in the paretic hand (Fig. 2B). After stroke, patients' efforts to  
341 produce isometric forces with a single finger resulted in abnormally large forces in the un-  
342 instructed fingers of the paretic hand. These enslaved forces signify the loss of fine-finger  
343 control in patients (S. Li *et al.*, 2003; Xu *et al.*, 2016). Early after damage (week 2),  
344 enslaving in patients was significantly larger than controls, demonstrating a substantial loss  
345 of individuated finger control (controls 0.042N/1N; patients 0.170N/1N;  $t_{51}=4.02$ ,  
346  $p<0.001$ ). Enslaving progressively reduced over the course of the year ( $\chi^2=28.38$ ,  
347  $p<<0.0001$ ), but never fully normalized even by 6 months post stroke ( $t_{51}=3.09$ ,  $p=0.003$ ).  
348 Patients who had large enslaving early after stroke also demonstrated large mirroring at the  
349 same time-period (enslaving and mirroring at week 2,  $r=0.78$ ,  $p<<0.0001$ ), and continued to  
350 do so even by the chronic stage of recovery (enslaving week 2 and mirroring week $\geq$ 24,  
351  $r=0.66$ ,  $p=0.0001$ ).

352           Consistent with earlier findings, here we found that mirroring in the non-paretic  
353 hand was exaggerated after stroke (Y. H. Kim *et al.*, 2003; Nelles *et al.*, 1998; Wittenberg  
354 *et al.*, 2000), and appeared with a time-course that mimicked that for the fine-control  
355 deficits in the paretic hand.

356

### 357 **Mirror movements were characterized by the recruitment of multiple fingers**

358           Next, we were interested in understanding finger recruitment patterns in the non-  
359 paretic hand during mirror movements. Specifically, we wanted to determine the extent to  
360 which mirroring in the non-paretic hand was characterized by a broad recruitment of  
361 fingers. We therefore characterized mirroring patterns across all active/passive fingers in  
362 both controls and patients (see methods).

363           The degree of mirroring in each passive finger as a function of the instructed finger  
364 can be seen in Figure 3A. The overall patterns of mirroring across all active/passive finger  
365 pairs themselves were highly reliable, with split-half correlations being  $r>0.85$  for both  
366 controls and patients (Supplementary Table 1). The first immediate observation is that  
367 mirroring was not restricted to the homologous fingers (diagonal), but that substantial  
368 effects could also be observed on non-homologous fingers (off-diagonal). To quantify this

369 observation, we partitioned mirroring across the different active/passive finger pairs into  
370 their respective homologous and non-homologous components (see methods).

371 In controls, finger presses resulted in a broad recruitment of fingers in the passive  
372 hand. Finger presses in the active hand were highly individuated in nature, with 1N of force  
373 on the instructed finger resulting in 0.042N of enslaved forces (ratio of  $24.77 \pm 2.18$ ; Fig.  
374 2B). These finger presses resulted in mirroring across both homologous and non-  
375 homologous fingers pairs. While homologous mirroring was, on average, larger than the  
376 non-homologous component ( $t_{13}=5.421$ ,  $p=0.0001$ ), some finger presses resulted in near  
377 equivalent effects on both (index finger presses;  $t_{13}=1.23$ ,  $p=0.240$ , ring;  $t_{13}=0.88$ ,  
378  $p=0.398$ ). Overall, forces in the passive hand were much more evenly distributed across  
379 fingers than the forces in the active hand (Fig. 3B), with the corresponding ratio between  
380 homologous and non-homologous mirroring components ( $1.61 \pm 0.16$ ) being nearly 15 times  
381 smaller than the instructed/enslaving ratio on the active hand ( $t_{13}=28.26$ ,  $p < 0.0001$ ). Thus,  
382 mirroring was not simply due to a symmetric digit-by-digit activation of the motor system,  
383 as predicted from the exact mirroring of cortical activity patterns across hemispheres  
384 (Diedrichsen *et al.*, 2013; Liu *et al.*, 2010; Scherer *et al.*, 2009).

385 Similarly, in patients, finger presses with the paretic hand resulted in a broad  
386 recruitment of fingers in the non-paretic hand. The year-long changes in mirroring  
387 characterized earlier (Fig. 2A) were observed in both homologous and non-homologous  
388 fingers (Fig. 3C; change over weeks: homologous,  $\chi^2=71.35$ ,  $p < 0.0001$ , non-homologous,  
389  $\chi^2=78.15$ ,  $p < 0.0001$ ), with homologous mirroring being the stronger of the two ( $\chi^2=24.53$ ,  
390  $p < 0.0001$ ). Critically, despite these longitudinal changes, the ratio between homologous  
391 and non-homologous mirroring ( $1.76 \pm 0.12$ ) remained stable across weeks ( $\chi^2=1.16$ ,  
392  $p=0.885$ ) and was at the same level as healthy controls ( $\chi^2=0.10$ ,  $p=0.754$ ).

393 To summarize, finger presses in patients, like controls, resulted in a broad  
394 recruitment of fingers in the passive hand. Remarkably, when considering mirroring across  
395 all active/passive fingers irrespective of the homologous and non-homologous finger  
396 (Supplementary Figure 2), a high degree of similarity between finger recruitment patterns  
397 for patients and controls was observed. Throughout recovery, mirroring patterns for  
398 patients looked like a scaled version of the corresponding control mirroring pattern. The  
399 most parsimonious explanation for this similarity would be that a single system is

400 responsible for mirroring in controls, and it is (un)up-regulated in the non-paretic hand after  
401 stroke. However, in the next section, we characterize mirror movements in the paretic hand  
402 and provide evidence that more than one system appears to contribute towards mirroring.

403

### 404 **Homologous and non-homologous mirroring dissociated in the paretic hand**

405 After stroke, not only is mirroring exaggerated in the non-paretic hand, but a slight  
406 reduction of mirroring in the paretic hand is also observed during non-paretic hand  
407 movements (Nelles *et al.*, 1998). Mirroring in the paretic hand has to-date received little  
408 attention, consequently the cause for reduced mirroring is unknown. We hypothesized that  
409 if homologous mirroring is primarily contributed by cortical motor areas, then stroke-  
410 related damage in the lesioned hemisphere should result in reduced mirroring in the  
411 primarily the homologous fingers of the paretic hand. To test this, we partitioned mirroring  
412 across all active/passive finger pairs into their respective homologous and non-homologous  
413 components.

414 Since the degree of mirroring in the paretic hand can be influenced by a loss of hand  
415 strength, we restricted our analysis to a subgroup of mild patients who demonstrated  
416 reliable muscle-evoked potentials early after stroke (see methods). Even in the early period  
417 after stroke, these mild patients had sufficient residual strength to express mirroring at the  
418 level of controls (Fig. 4A; 1N/0.004N). Infact, even at maximal force production with the  
419 non-paretic hand (15.7N), the predicted mirrored forces on the paretic hand were small  
420 (0.07N) in comparison to the residual strength on the hand (9.0N; residual strength versus  
421 predicted mirroring at control level,  $t_{21}=6.77$ ,  $p<<0.0001$ ). Thus, these mild patients had  
422 sufficient strength to exhibit mirroring in the paretic hand.

423 However, as predicted, the ratios between homologous and non-homologous  
424 mirroring was approximately equal early after stroke (Fig. 4B; week 2; ratio for mild  
425 group= $1.11\pm 0.11$ ). Mirroring subsequently became stronger in the homologous finger pairs  
426 as the paretic hand regained fine-finger function, with the homologous/non-homologous  
427 ratio progressively increasing during recovery ( $\chi^2=21.47$ ,  $p=0.0003$ ), eventually  
428 normalizing to the control level (week $\geq 24$ ;  $t_{36}=0.48$ ,  $p=0.632$ ). This reduction in the  
429 homologous component of mirroring was also seen for the severe patients (weeks $\leq 24$ ;

430 Supplementary Figure 3), with the ratio between homologous and non-homologous  
431 remaining low even though strength recovered during this time.

432 To summarize, we demonstrate that the homologous and non-homologous  
433 components of mirroring in the paretic hand appear to dissociate, despite patients having  
434 sufficient strength in the hand. This dissociation effect is hard to attribute to a single system  
435 contributing towards mirroring. We therefore conclude that mirror movements after stroke  
436 are generated by contributions from (at least) two separate systems.

437

### 438 **No modulation of evoked-BOLD activities in the bilateral sensorimotor cortices** 439 **after stroke**

440 Finally, we consider the neurophysiological mechanisms that could cause an  
441 exaggeration of mirror movements in the non-paretic hand after stroke. One candidate  
442 mechanism could be the large activations previously reported in the primary somatosensory  
443 (S1) and motor (M1) cortices of the non-lesioned hemisphere after stroke (Cincotta and  
444 Ziemann, 2008; Cramer *et al.*, 1997; Y. H. Kim *et al.*, 2003; Ward *et al.*, 2003; Wittenberg  
445 *et al.*, 2000). These activations could potentially exaggerate mirroring directly or indirectly.  
446 In the first case, activations could be directly transmitted to the motoneurons/spinal  
447 interneurons that control the passive hand, via the crossed corticospinal pathway.  
448 Alternatively, the activations could indirectly exaggerate mirroring by up-regulating the  
449 activity of subcortical motor circuits through cortico-brainstem connections (Fisher *et al.*,  
450 2012).

451 If mirror movements after stroke were caused by over-activation of the non-lesioned  
452 sensorimotor cortex, then the time-course of these activations should resemble the time-  
453 course changes in mirroring quantified earlier (Fig. 2A). To test this idea, we used fMRI to  
454 measure evoked-activities in the hand area of S1/M1, in a smaller subset of participants  
455 from the same study cohort (Table 1, 35 patients, 12 controls). Participants performed  
456 individuated finger presses inside an MRI scanner (Fig. 5A). During paretic finger presses,  
457 patients demonstrate the same mirroring and enslaving behaviour both inside and outside  
458 the scanner environments (Fig. 5B-C; mirroring,  $r=0.89$ ,  $p \ll 0.001$ ; enslaving,  $r=0.75$ ,  
459  $p \ll 0.001$ ).



460 The resulting evoked BOLD responses in M1/S1 for patients were remarkably  
461 stable throughout recovery (Fig. 6D; statistics in Table 2). For paretic hand presses, we did  
462 not find any time-course related changes in the evoked-activities in either the contra- or the  
463 ipsi-lateral cortices, with activations in either hemisphere indistinguishable from their  
464 counterpart in controls. Patients continued to demonstrate the stereotypical pattern of  
465 evoked cortical responses seen for unimanual finger presses in health, which was  
466 characterized by an increase and reduction of BOLD responses in the contra- and ipsilateral  
467 sensorimotor cortices respectively.

468 To summarize, we report that the clear occurrence of the longitudinal changes in  
469 mirroring after stroke were not accompanied by over-activations in the sensorimotor  
470 cortices of either the non-lesioned or the lesioned hemispheres.

471

472

## Discussion

473 In this study, we present a detailed characterization of mirror movements that  
474 appear after stroke. Consistent with earlier findings, mirroring was exaggerated in the non-  
475 paretic hand (Y. H. Kim *et al.*, 2003; Nelles *et al.*, 1998; Sehm *et al.*, 2009; Wittenberg *et*  
476 *al.*, 2000). We expand upon these previous studies and demonstrate that mirroring appeared  
477 early after stroke and normalized as the hand recovered function. Despite these time-course  
478 changes in mirroring, we did not find any over-activations in the sensorimotor cortices in  
479 either hemisphere. These sensorimotor areas (M1/S1) provide the bulk of the inputs to the  
480 corticospinal pathways that provide fine-finger control (Lemon, 2008; Porter and Lemon,  
481 1993), and the lack of evoked-BOLD modulation in these areas suggests that a simple  
482 up/down regulation of overall activity is unlikely to be the mechanism which exaggerates  
483 mirroring after stroke. Although, we cannot completely rule out the possibility that BOLD  
484 responses might be insensitive to subtle changes in sensorimotor activity required to  
485 produce the small forces during mirroring, our results contradict earlier studies that have  
486 argued that exaggerated non-paretic mirroring is caused by over-activations in ipsi- or  
487 contralesional M1/S1 (Cincotta and Ziemann, 2008; Y. H. Kim *et al.*, 2003; Wittenberg *et*  
488 *al.*, 2000).

489 The main goal of this study was to better understand finger recruitment patterns  
490 during mirror movements after stroke. We did this by quantifying the distribution of

491 mirrored forces across homologous and/or non-homologous fingers, attributing  
492 homologous finger forces to cortical pathways, while attributing broad distribution of  
493 forces across all fingers to subcortical pathways instead. Our approach is analogous to the  
494 recent approach by Dean and Baker (2016) who investigated reticular contributions towards  
495 hand function using the StartReact paradigm (Valls-Solé *et al.*, 1995). The authors  
496 compared muscle activations in the hand during the presentation of intense and mild  
497 acoustic cues, predicting that intense acoustic cues would preferentially rely on  
498 contributions from the reticulospinal system and therefore elicit less fractionated muscle  
499 activity when compared to milder cues. While the authors reported no differential effect of  
500 startling acoustic cues on hand muscle activity, here we report that the distribution of  
501 mirrored forces on the passive hand are indeed less fractionated than would be predicted by  
502 the forces on the active hand that generated them. By quantifying finger recruitment  
503 patterns during mirroring in both the non-paretic and the paretic hand, we find evidence of  
504 two components of mirroring, with the two components characterized by a broad  
505 recruitment of fingers, and recruitment of the homologous finger respectively. The first  
506 mirroring component (broad finger recruitment) has to-date remained undocumented,  
507 primarily because previous studies have only focused on the homologous muscles/fingers  
508 (Armatas *et al.*, 1994; Y. Kim *et al.*, 2015; Koerte *et al.*, 2010; Mayston *et al.*, 1999). Our  
509 results therefore add to our current understanding of mirroring, both in stroke and health.

510         If the neocortex provides the ability to perform fine-finger function, then what  
511 should cortical contributions to mirror movements look like? Using data from recent fMRI  
512 studies, we argue that cortical activation patterns evoked during individuated finger presses  
513 predict mirroring primarily in the homologous finger of the passive hand. Specifically,  
514 individuated finger presses result in evoked-activities from motor areas distributed across  
515 the cortex (e.g. M1/S1, but also supplementary and premotor areas) (Diedrichsen *et al.*,  
516 2013; Ejaz *et al.*, 2015). However, the activation patterns for a finger press are highly  
517 similar across the various cortical motor areas (e.g. M1; Pearson's  $r=0.8$ ) *regardless of*  
518 *whether the contralateral, or the homologous finger in the ipsilateral hand was used*  
519 (Diedrichsen *et al.*, 2013). To the extent that these activation patterns specify the pattern of  
520 recruitment of muscles/fingers of the hand (Ejaz *et al.*, 2015), cortical contributions to  
521 mirroring should primarily recruit the homologous passive finger.

522           Although subcortical contributions towards hand function in primates has been  
523 investigated in detail (Baker, 2011b; Lawrence and Kuypers, 1968b; Riddle *et al.*, 2009;  
524 Soteropoulos *et al.*, 2012; Zaaime *et al.*, 2012), the extent to which these subcortical  
525 pathways contribute towards hand function, and indeed mirror movements, in humans  
526 remains to be determined. One clue comes from comparing the patterns of upper-limb  
527 muscle recruitment during mirroring in humans, with muscle responses measured following  
528 stimulation of subcortical pathways in primates. For instance, in young children, flexion of  
529 the elbow joint results in mirroring mostly on the extensor muscles of the opposing elbow  
530 (Missiuro, 1963). This recruitment of ipsilateral flexors and contralateral extensor shoulder  
531 muscles is a prominent muscle activity pattern observed during stimulation of neurons in  
532 the ponto-medullary reticular formation (Herbert *et al.*, 2010; Hirschauer and Buford,  
533 2015). These neurons provide input to the reticulospinal tract which has been strongly  
534 implicated as a parallel pathway involved in hand function (Baker, 2011a; Riddle *et al.*,  
535 2009; Soteropoulos *et al.*, 2012) and can therefore serve as a subcortical pathway capable  
536 of contributing towards mirroring.

537           If recovery of paretic hand function relies increasingly on the capacity of the  
538 subcortical systems to compensate for cortical damage (Xu *et al.*, 2016), and if these  
539 pathways are responsible for contributing towards mirror movements, then how does  
540 mirroring reduce over the same time while paretic hand function recovers? Recent evidence  
541 from a primate study suggests that an increased reliance on bilaterally organized subcortical  
542 systems for paretic hand recovery, can in fact occur alongside a concomitant decrease in  
543 mirroring in the non-paretic hand. In the study, neurons in the ipsi- and contralateral  
544 sections of the ponto-medullary reticular formation (PMRF) were shown to alter the  
545 strength of their outputs onto motoneurons/spinal interneurons in either half of the spinal  
546 cord independently (Herbert *et al.*, 2015). Specifically, connections between the paretic  
547 hand and cells in ipsi-PMRF were strengthened, while connections between the non-paretic  
548 hand and ipsi-PMRF cells were weakened. Therefore, such a pattern of subcortical  
549 reorganization could simultaneously facilitate recovery of the paretic hand and reduce the  
550 degree of mirroring in the non-paretic hand.

551           In conclusion, we have provided a detailed characterization of both the time-course  
552 and pattern of mirror movements following stroke. While mirroring is itself an interesting

553 phenomenon that appears after damage, we propose that it additionally offers a window  
554 into cortical and subcortical contributions towards hand recovery.

555

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561

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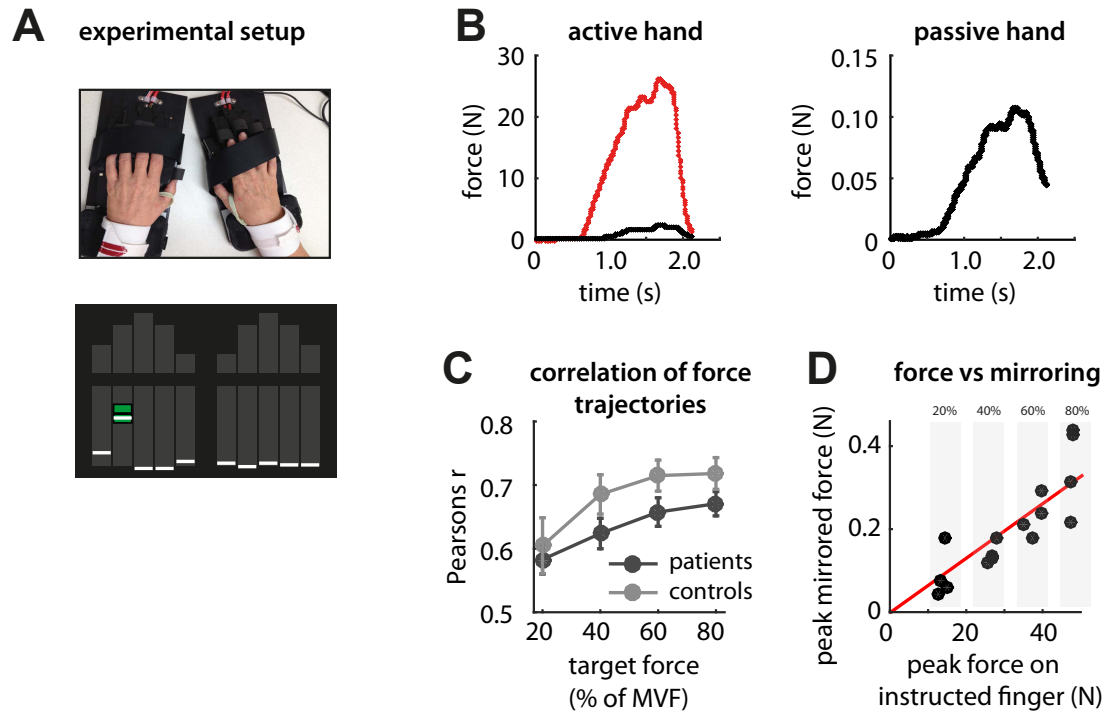
## Tables and Figures

<b>week</b>	<b>2</b>	<b>4</b>	<b>12</b>	<b>24</b>	<b>52</b>
days (mean±SD)	10 ± 4	37 ± 8	95 ± 10	187 ± 12	370 ± 9
<b><i>Behavioural experiment</i></b>	<b>53 patients, 14 controls</b>				
measured at week (%)					
controls	14 (100%)	10 (71%)	12 (86%)	12 (86%)	12 (86%)
patients	39 (74%)	39 (74%)	40 (75%)	39 (74%)	31 (58%)
Fugl-Meyer (0.25-0.75 percentile)	(16-59)	(34-64)	(52-66)	(57-66)	(59-66)
<b><i>fMRI experiment</i></b>	<b>35 patients, 12 controls</b>				
measured at week (%)					
controls	11 (92%)	10 (83)	11 (92%)	11 (92%)	11 (92%)
patients	24 (69%)	31 (89%)	27 (77%)	28 (80%)	19 (54%)
Fugl-Meyer (0.25-0.75 percentile)	(16-60)	(45-65)	(59-65)	(60-66)	(64-66)

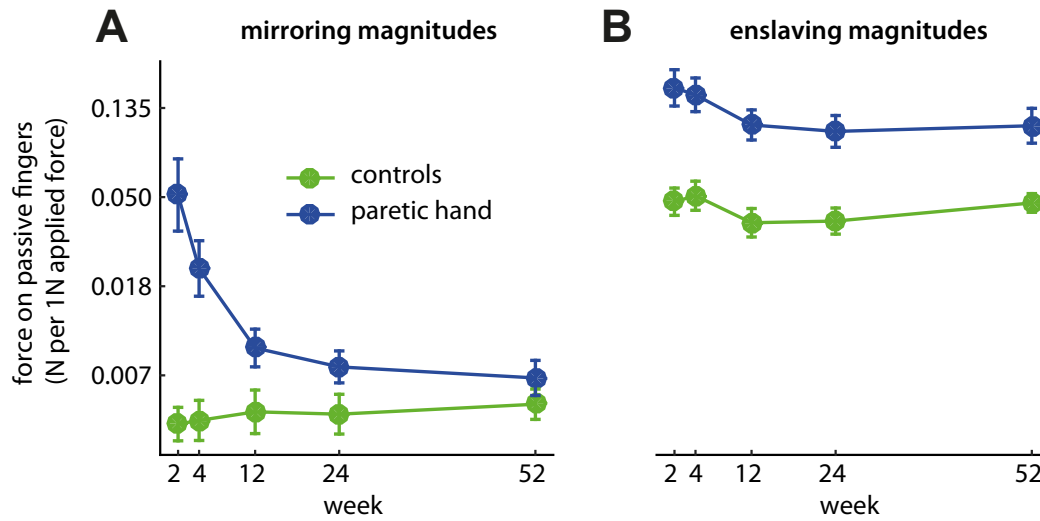
**Table 1.** Patient information and measurement schedules for the behavioural and fMRI experiments. A total of 53 patients and 14 age-matched controls were recruited for the study and measured at five different time points over the course of a year. For the behavioural experiment, each participant in the study was on average measured over at least 3 sessions (patients, 3.5±1.5 sessions; controls, 4.3±1.4), with the overall experimental data being 70.1% complete for patients and 85.7% complete for controls. For the fMRI experiment, a subset of participants from the cohort were measured (N=12 controls and N=35 patients), with the experimental data being 73.7% complete for patients and 90% for controls.

	change over weeks		patients versus controls	
	$\chi^2$	p	$\chi^2$	p
activity for paretic presses				
contra (S1)	1.410	0.842	1.160	0.282
contra (M1)	2.070	0.723	1.150	0.285
ipsi (S1)	1.860	0.761	0.813	0.367
ipsi (M1)	1.250	0.870	0.010	0.915

**Table 2.** Statistics for the fMRI experiment. Statistics are shown for differences in contralateral and ipsilateral M1/S1 activations, across weeks (first two columns) and between patients and controls (last two columns).

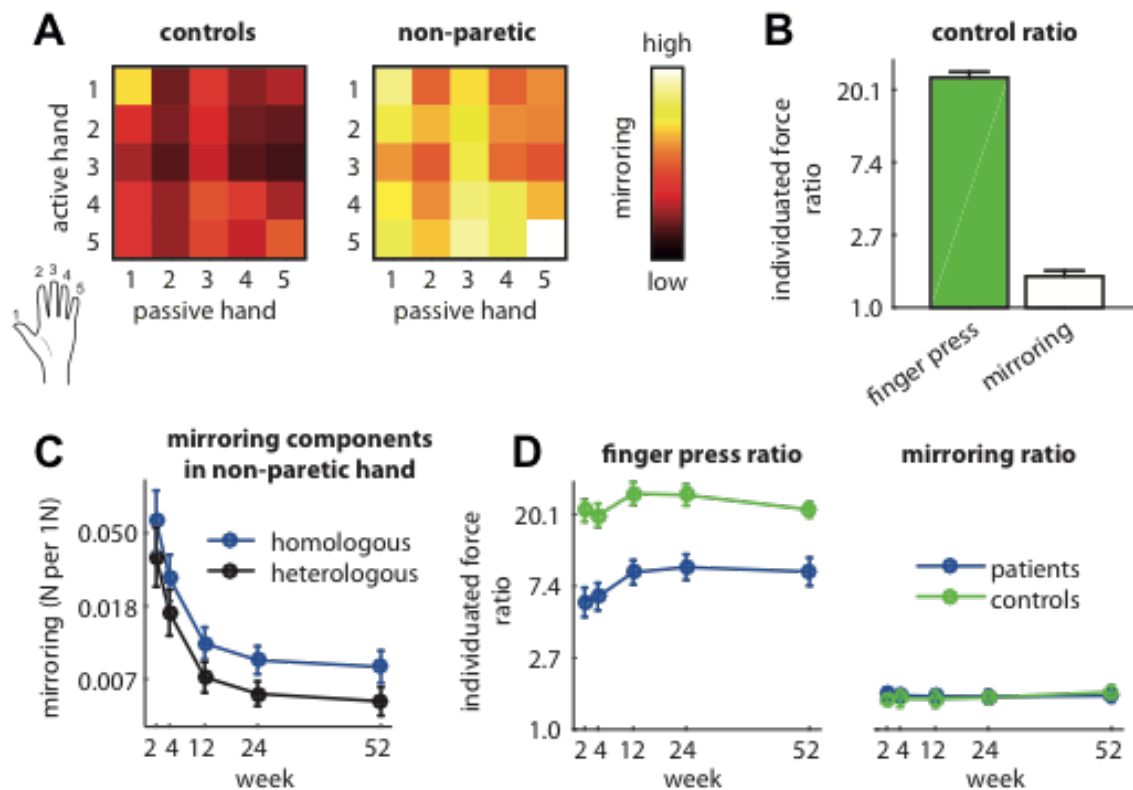


**Figure 1.** Assessment of mirror movements. (A) Both hands were strapped onto an ergonomic hand device capable of measuring isometric forces generated at the fingertips. Controls and patients were instructed to generate isometric forces by making individuated presses to bring the cursor into the target zone shown in green. During each measurement session, individuated finger presses were made at 20%, 40%, 60% and 80% of the maximum voluntary force on that finger. (B) Force presses with the instructed finger (thumb finger of right hand shown in red) resulted in involuntary forces on the passive fingers of the same hand (black), and subtle mirrored forces on the fingers of the passive hand (right panel). (C) Mirrored force trajectories were similar to that for the instructed finger, especially at higher target force levels. (D) Mirroring was quantified as the linear slope between the peak forces produced by the instructed finger and the peak averaged forces on the passive hand. The linear slope was log-transformed to allow the use of parametric statistical test, but for the purpose of clarity the raw values of the linear slope are reported in all subsequent figures.

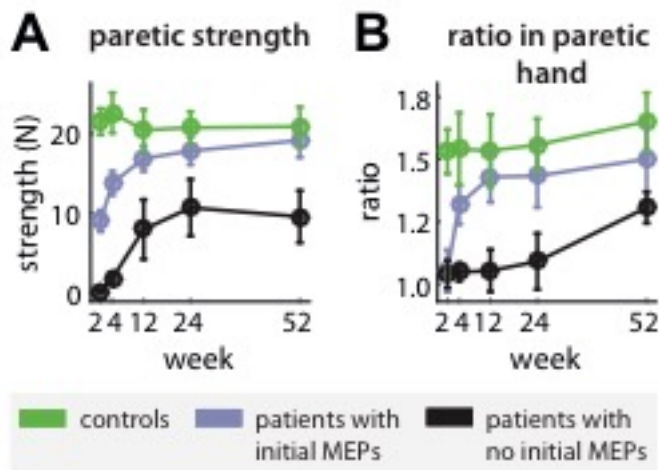


**Figure 2.** Longitudinal changes in mirror movements and fine-finger control after stroke. (A) Changes in mirroring for controls and patients measured over the course of a year. For patients, mirroring was measured in the fingers of the non-paretic hand, during active finger presses with the paretic hand. (B) Associated changes in fine-finger control on the active hand across groups. Individuated finger presses in patients and controls resulted in undesired force contractions on the uninstructed fingers of the active hand. The larger these so-called enslaved movements, the worse the degree of fine-finger control. For clarity, the raw values of the linear-slope estimates for mirroring and enslaving are plotted in (A) and (B).

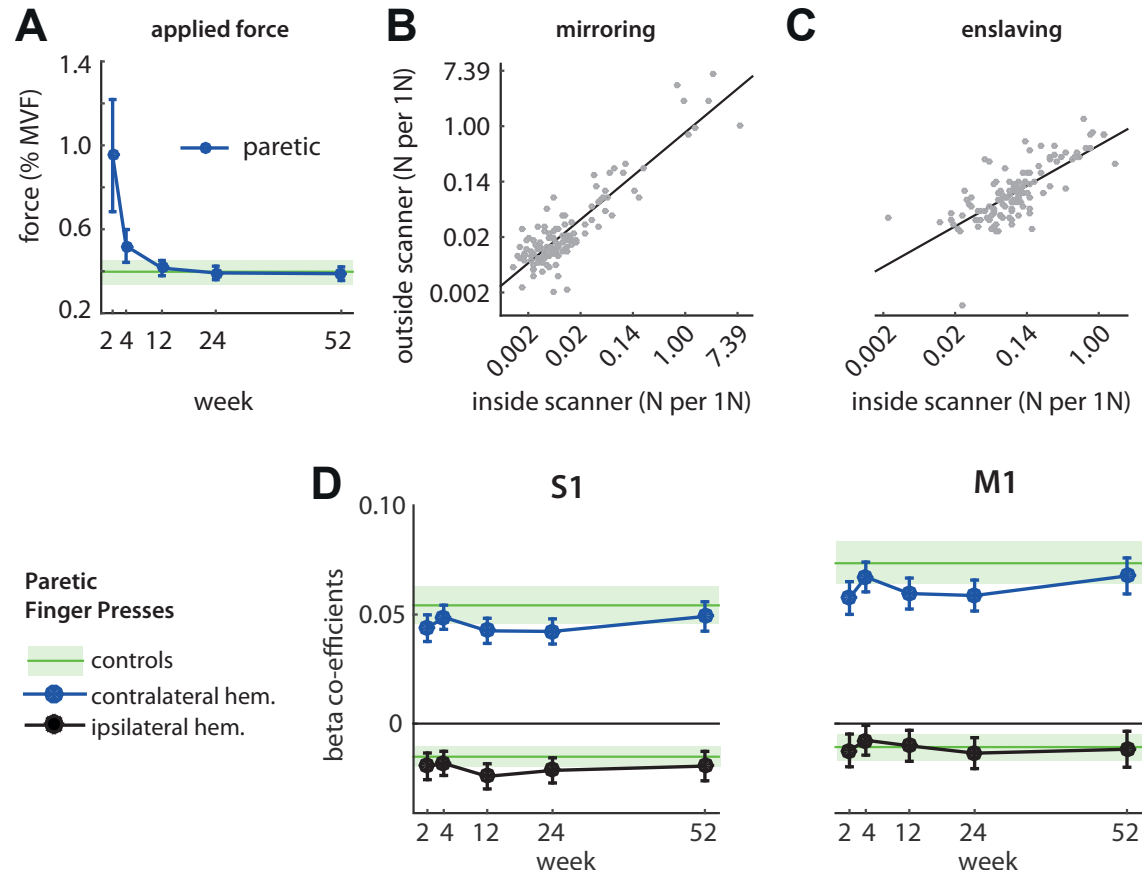




**Figure 3.** Relative contributions of homologous and non-homologous components to mirror movements on the non-paretic hand. (A) Mirroring across all possible active/passive finger pairs for controls and patients (on non-paretic hand only). Rows and columns denote which finger was pressed on the active hand, and the finger on the passive hand that mirroring was estimated on, respectively. Diagonal and off-diagonal matrix entries represent mirroring across homologous and non-homologous finger pairs. (B) Individuated finger presses by controls resulted in enslaved forces on the passive fingers of the same hand and mirrored forces across homologous and non-homologous finger pairs. The ratio between instructed/enslaved forces within the active hand is shown in green, while ratio between homologous and non-homologous mirroring components is shown in white. (C) Changes in homologous and non-homologous mirroring components on the non-paretic hand in the year following stroke. For clarity, the raw values of the linear-slope estimates for mirroring are plotted. (D) For patients, the ratios between instructed/enslaved forces on the paretic hand, and the ratio between homologous/non-homologous mirroring patterns are shown in the left and right panels respectively.



**Figure 4.** The homologous and non-homologous components of mirror movements in the paretic hand. (A) Time course of strength recovery in patients who demonstrated reliable MEPs (mild group) in the first few weeks after stroke, and those who did not (severe group). (B) Ratios between the homologous and non-homologous mirroring components across the mild and severe groups.

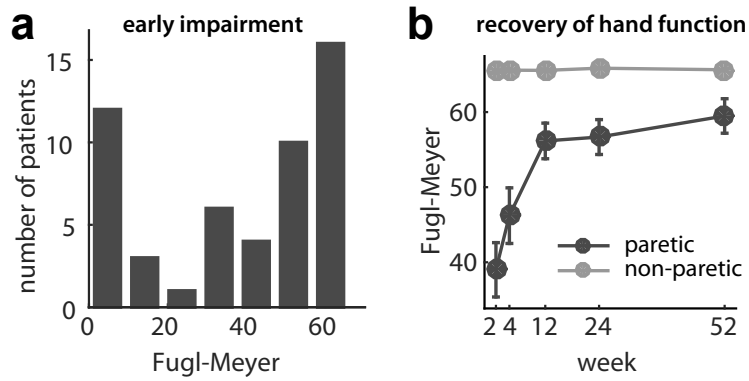


**Figure 5.** Evoked-BOLD activities for finger presses in the primary somatosensory (S1) and motor (M1) cortices. (A) During the fMRI task, patients and controls were required to produce either 1.8N or 8% of the maximum voluntary force (MVF) on the finger. Forces are expressed as a percentage of MVF. Controls produced forces at approximately 40% of MVF. From week 4 onwards, forces produced by patients and controls were not significantly different ( $\text{week} \geq 4$ ;  $\chi^2=0.02$ ,  $p=0.887$ ). (B) Measurements of mirroring on the non-paretic hand were highly correlated inside and outside the scanner environments. (C) Similarly, enslaving in the paretic hand was highly correlated for measurements inside and outside the scanner environments. Each dot in B-C represents the session measurement of a single patient. For clarity, the raw values of the linear-slope estimates for mirroring are plotted in (B-C). (D) Evoked-BOLD activities in contra- and ipsilateral S1 and M1 cortices due to paretic finger presses. Corresponding contra and ipsi activities in controls are depicted by the shaded green regions (Mean $\pm$ SE).

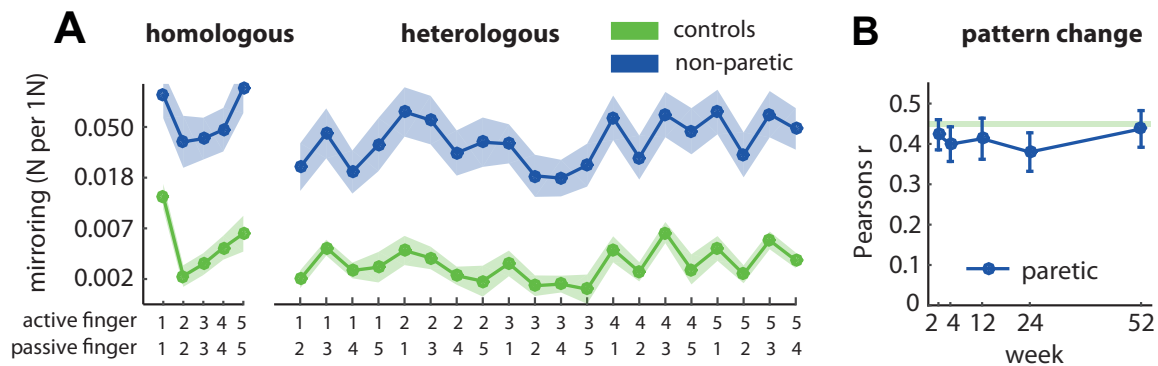
## Supplementary Material

<b>week</b>	<b>2</b>	<b>4</b>	<b>12</b>	<b>24</b>	<b>52</b>
<b><i>controls</i></b>					
mean	0.88	0.89	0.90	0.89	0.92
range	(0.82-0.92)	(0.85-0.92)	(0.85-0.94)	(0.84-0.93)	(0.88-0.94)
<b><i>non-paretic hand</i></b>					
non-paretic hand	0.86	0.89	0.89	0.90	0.89
range	(0.82-0.89)	(0.86-0.92)	(0.86-0.91)	(0.86-0.92)	(0.85-0.92)
<b><i>paretic hand</i></b>					
paretic hand	0.88	0.87	0.87	0.90	0.87
range	(0.83-0.90)	(0.84-0.90)	(0.84-0.90)	(0.88-0.92)	(0.82-0.91)

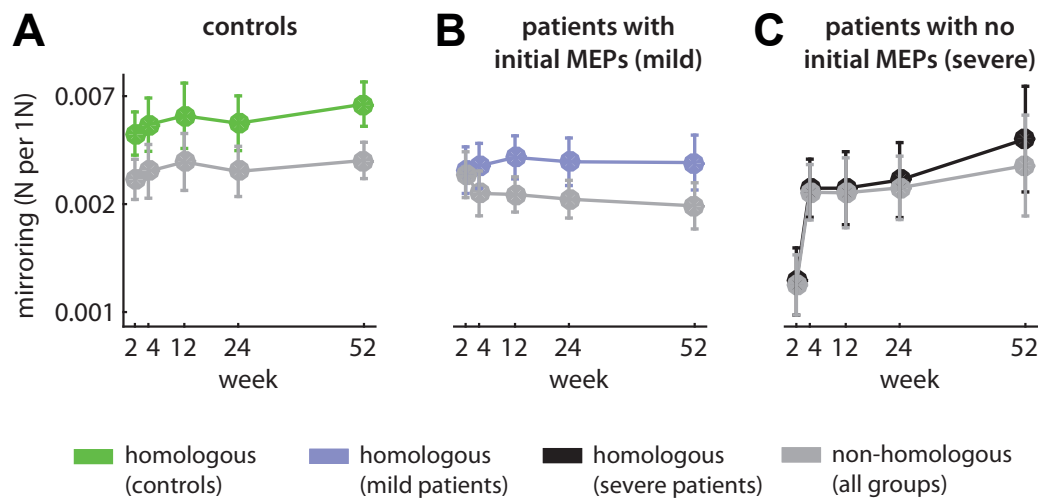
**Supplementary Table 1.** Split-half reliabilities for mirroring patterns estimated across weeks. To estimate the reliability, data from each measurement session was dividing into odd and even runs, and the corresponding mirroring patterns for each half were estimated independently. Pearson's correlation between the patterns from the two halves was then calculated to obtain the within-session or split-half reliability.



**Supplementary Figure 1.** Patient information. (a) Distribution of Fugl-Meyer measurements on paretic hand at the point of first measurement (either week 2 or 4). (b) Fugl-Meyer measurements for patients over the course of 1 year following stroke.



**Supplementary Figure 2.** Stability of mirroring pattern during stroke recovery. (A) The average mirroring patterns across all active/passive finger pairs are shown for patients (week 2) and controls. For clarity, the raw values of the linear-slope estimates for mirroring are plotted in A. Similarity between the patterns for patients and controls was high, even in the early period after stroke (week 2,  $r=0.88$ ,  $p<<0.0001$ ). (B) Correlations between mirroring patterns for patients and controls remained unchanged throughout recovery ( $\chi^2=1.87$ ,  $p=0.760$ ). The pattern correlations for patients and controls were also close to noise ceilings; i.e. the maximum possible pattern correlations possible given the measurement noise on mirroring patterns for each control (see Methods).



**Supplementary Figure 3.** The homologous and non-homologous components of mirror movements during recovery in the (A) control group, (B) in patients who demonstrated reliable MEPs at weeks $\leq$ 4 (mild group), and (C) in patients who not demonstrate reliable MEPs at weeks $\leq$ 4 (severe group).

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