

1 **No evidence for motor recovery-related cortical reorganization after**
2 **stroke using resting-state fMRI**

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24 **Abstract**

25 Cortical reorganization has been suggested as mechanism for recovery after stroke. It has been
26 proposed that a form of cortical reorganization (changes in functional connectivity between brain
27 areas) can be assessed with resting-state fMRI. Here we report the largest longitudinal data-set
28 in terms of overall sessions in 19 patients with subcortical stroke and 11 controls. Patients were
29 imaged up to 5 times over one year. We found no evidence for post-stroke cortical reorganization
30 despite substantial behavioral recovery. These results could be construed as questioning the
31 value of resting-state imaging. Here we argue instead that they are consistent with other
32 emerging reasons to challenge the idea of motor recovery-related cortical reorganization post-
33 stroke when conceived as changes in connectivity between cortical areas.

34

35 **Keywords: stroke recovery, upper extremity impairment, resting state, cortical reorganization, functional**
36 **connectivity**

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39 **1. Introduction**

40 Spontaneous neurological recovery occurs in almost all stroke patients within the first
41 months after the insult. While the underlying physiological changes that accompany spontaneous
42 motor recovery in humans remain largely unknown, data from animal models have been
43 interpreted as showing that cortical reorganization is a potential key mechanism mediating
44 recovery (Dancause & Nudo, 2011; Grefkes & Ward, 2014; Nudo, 2006).

45 In the literature, the term cortical reorganization has been loosely defined and used to
46 refer to any number of structural and physiological changes that follow injury. These changes

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47 can span the micro-, meso- and macro-scale, including synaptogenesis, axonal sprouting, and
48 changes in cortical activation maps. We have argued elsewhere that the term functional
49 reorganization should be reserved for those changes, including new cortico-cortical connections,
50 that are causally related to or at least correlated with motor recovery (Krakauer & Carmichael,
51 2017). It should be added that reorganization has also been taken as a qualitative event,
52 exemplified by the idea that one cortical area “takes over” another, which implies a change in the
53 tuning of neurons, for example, when touching the face activates the hand area of sensory cortex
54 in amputees. We argue elsewhere that a qualitative change in cortical representation need not be
55 invoked to explain this result (Krakauer & Carmichael, 2017), but we will not use this definition
56 here.

57 Evidence for functional reorganization after stroke comes primarily from studies of
58 axonal sprouting. For example, Overman and colleagues (2012), in a mouse cortical stroke
59 model, generated sprouting of axonal connections within ipsilesional motor, premotor and
60 prefrontal areas by blocking of an axonal growth inhibitor (epinephrine A5). Similar results were
61 reported for the neuronal growth factor GDF10 (Li *et al.*, 2015). Critically, however, in both
62 studies no direct test of the relevance of axonal sprouting for motor improvement was performed,
63 indeed not even a correlation with the degree of sprouting and behaviour was examined. In
64 addition, most studies describing axonal sprouting after stroke found that it was cortico-
65 subcortical instead of cortico-cortical connectivity changes that were linked to motor recovery
66 (see e.g. Lee, 2004; Wahl *et al.*, 2014). Other studies that argue for a role of cortico-cortical
67 connectivity changes underlying stroke recovery are limited by cross-sectional approaches or do
68 not report behavior at all (Dancause *et al.*, 2005; Frost *et al.*, 2003; Liu & Rouiller, 1999;
69 Napieralski *et al.*, 1996).

70 Despite the weak evidence for behaviorally-relevant new cortical connections in animal
71 models post-stroke, these models have nevertheless led to widespread interest in identifying
72 similar processes of functional reorganization in the human brain. One prominent non-invasive
73 method is to measure inter-regional connectivity with resting-state fMRI (rs-fMRI; Biswal *et al.*,
74 1995; Fox & Raichle, 2007). This method relies on correlations between time-series of fMRI
75 activity recorded while the subject is lying in the scanner without performing a task. Most often
76 these correlations are computed between a set of pre-defined regions of interest (ROIs). The
77 underlying assumption is that regions with connected neuronal processing show stronger
78 statistical dependency of their spontaneous neuronal fluctuations. These correlations are
79 commonly regarded as a measure of “functional connectivity”, which has been closely linked to
80 structural connectivity (Friston, 2011; van der Heuvel *et al.*, 2009). In the context of stroke
81 recovery, it has been suggested that reorganization can be detected as a change in such
82 correlations/functional connectivity patterns (van Meer *et al.*, 2010). Specifically, for post-stroke
83 recovery of hemiparesis, the advantage of task-free resting-state over task-based fMRI is that it
84 avoids the performance confound (Krakauer, 2004, 2007); the connectivity measures are not
85 biased by the inability of patients to match control performance due to motor impairment.

86 To date, results from rs-fMRI studies of functional connectivity changes after stroke have
87 been mixed. Although, rs-fMRI studies have frequently found changes in interhemispheric
88 connectivity patterns after stroke (Carter *et al.*, 2010; Chen & Schlaug, 2013; Golestani *et al.*,
89 2013), the direction of these changes and their correlations with behavior have been inconsistent.
90 One study found a positive correlation between motor function and increased functional
91 connectivity between the lesioned M1 and contralateral heterologous cortical areas (Park *et al.*,
92 2011), another study reported that interhemispheric homologous connectivity was associated

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93 with lower degrees of motor impairment but only for infratentorial strokes (Lee *et al.*, 2018). Yet
94 another study showed that an increase in M1-M1 connectivity correlated negatively with motor
95 function (Wang *et al.*, 2014).

96 There are many potential reasons for these inconsistencies in rs-fMRI findings.
97 If patients with cortical lesions are included in the study design, it is possible to confuse changes
98 in connectivity measures as a direct consequence of the lesion (e.g. the damaged area becomes
99 disconnected from the brain) with changes associated with true reorganization. Additionally,
100 most studies use different analysis protocols and measures to quantify changes in connectivity,
101 making integration of evidence across studies difficult. Third, the majority of currently available
102 studies have been cross-sectional but it is essential to evaluate changes in connectivity across the
103 time-course of recovery.

104 To address these issues, we here report the results of a longitudinal rs-fMRI study of
105 stroke recovery in patients with hemiparesis after subcortical stroke. Only patients with
106 subcortical lesion locations were included in this study so that any changes in cortical
107 connectivity could not be attributed to the presence of the lesion itself. We provide a detailed
108 characterization of inter- and intrahemispheric connectivity between five cortical motor areas.
109 Because of considerable variation of analysis approaches in the existing literature, in addition to
110 our primary analysis, we also compared results after using two different pre-processing
111 procedures, report results from an individual M1-M1 ROI analysis, and replicated the analysis
112 approach from the largest longitudinal resting-state stroke study published to date (Golestani *et*
113 *al.*, 2013).

114

115 **2. Results**

116 The main goal of this study was to determine whether motor impairment recovery following
117 stroke was associated with systematic changes in cortical connectivity. Our two main questions
118 were: 1) Is there a mean difference in the connectivity pattern between five motor regions (S1,
119 M1, PMv, PMd, SMA) when comparing patients and age-matched controls at any time-point
120 during stroke recovery? 2) Is there a change in patients' connectivity patterns over time that is
121 related to motor impairment?

122 We analyzed data from 19 patients with subcortical stroke and 11 healthy controls.
123 Behavioral assessments and resting-state images were obtained at five different time-points over
124 one year. Each patient completed on average 4.5 ± 0.7 sessions, with the overall experimental
125 data being 89.5% complete (see also Table S1 for demographics and completed sessions in the
126 supplemental material). We begin by quantifying the extent of impairment and recovery of upper
127 extremity deficits in our patients in the year following stroke.

128

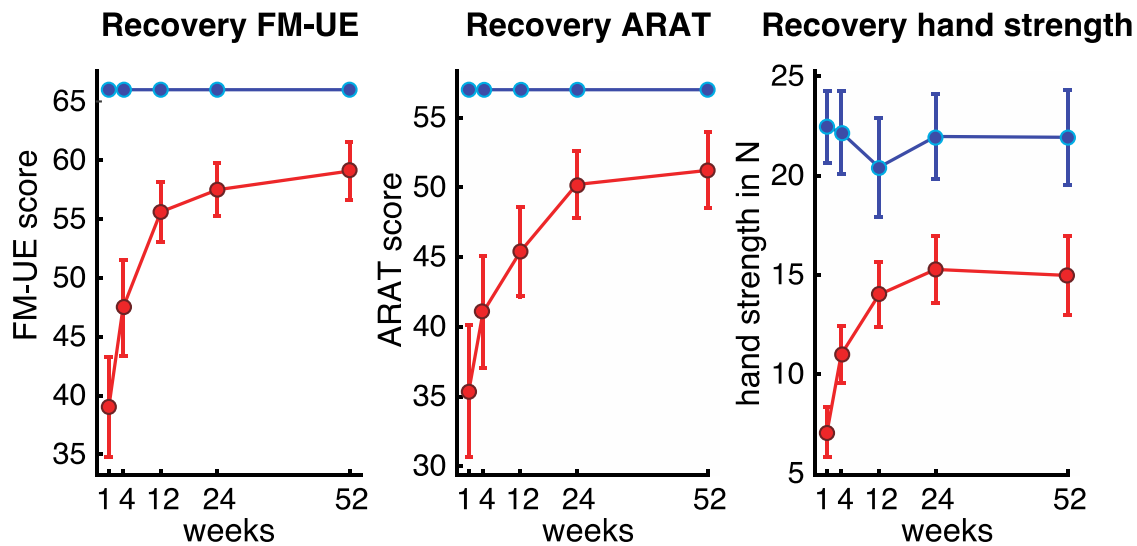
129 **2.1. Patients showed substantial clinical recovery after stroke**

130 We measured initial impairment and subsequent recovery of the upper extremity using the upper
131 extremity portion of the Fugl-Meyer score (FM-UE), the Action Research Arm Test (ARAT),
132 and hand strength (Xu *et al.*, 2017).

133 At the acute stage, all behavioral measures indicated impairment of the upper extremity for
134 patients relative to controls (FM-UE: $t(28)=3.706$, $p=0.001$, ARAT: $t(28)=2.315$, $p=0.028$,
135 strength: $t(28)=5.195$, $p<0.001$, Figure 1). These deficits recovered substantially over the course
136 of one year, with the largest changes observed within the first three months (Week effect for FM-
137 UE: $\chi^2=24.865$, $p<0.001$; ARAT: $\chi^2=13.942$ $p=0.007$; hand strength: $\chi^2=13.419$, $p=0.009$). No
138 significant changes were observed in controls for any of the three measures.

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140

141 *Figure 1: Recovery of upper extremity deficits after stroke over one year. For all behavioral*
142 *assessments, the largest changes in recovery were seen within the first three months. Patients*
143 *reached a plateau at 6 months and, on average, remained impaired compared to controls at all*
144 *time-points. Note that patients had moderate to severe upper extremity impairment in the acute*
145 *stage. Red lines = patients, blue lines = controls, FM-UE = Fugl-Meyer score Upper Extremity,*
146 *ARAT = Arm Research Action Test.*

147

148 **2.2. Connectivity patterns across sensorimotor areas were reliable and stable in controls**

149 Next, we looked at changes in connectivity patterns (pattern of ROI-ROI connectivity
150 weights) between five key sensorimotor areas to determine if and how connectivity between
151 these sensorimotor areas changed alongside behavior during recovery. To determine the
152 connectivity patterns, we calculated pairwise correlations between the averaged time-series of
153 BOLD activities between all possible ROI pairs to get a 10×10 matrix of connectivity weights
154 (see Methods). An average connectivity pattern for patients and controls is shown in Figure 2a.

155 Connectivity patterns were highly reliable for both groups with high intrasession
156 reliabilities (*all connections*, controls: $R=0.66$, CI 0.62–0.71, patients: $R=0.70$, CI 0.66–0.74; see
157 supplementary material for inter- and intrahemispheric connections, Figure S2). An unbalanced

158 mixed-effects ANOVA (see Methods) showed that the intrasession reliability was not
159 significantly different between groups ($\chi^2(1)=1.0782$, $p=0.2991$) and showed no changes over
160 time (controls: $\chi^2(4)=6.174$, $p=0.187$; patients: $\chi^2(4)=1.922$, $p=0.75$).

161 Furthermore, connectivity patterns for controls were stable, showing no significant
162 change over time (*all connections*: Δ week acute_W4=0.841, confidence interval (CI) 0.597–
163 2.727; acute_W12=0.689, CI 0.582–2.412; acute_W24=1.079, CI 0.687–2.821;
164 acute_W52=1.059, CI 0.611–2.531). Thus, for all subsequent analyses connectivity patterns for
165 controls were averaged over time-points.

166 We also confirmed that the connectivity pattern for controls reflected known anatomical
167 connectivity (Damoiseaux & Greicius, 2009). Within one hemisphere, the highest correlations
168 were found between S1-M1 (0.91 ± 0.47 , Fisher-Z transformed), while the weakest correlation
169 was found between M1-PMv (0.58 ± 0.39). Between hemispheres, S1_{right}-S1_{left} demonstrated the
170 highest correlation (0.9 ± 0.43), while M1_{right}-PmV_{left} showed a weaker correlation (0.59 ± 0.37).
171 For correlations between hemispheres, homologous ROIs (e.g. M1-M1 or S1-S1) showed higher
172 correlations of the BOLD time series compared to heterologous ROI-ROI connectivity weights
173 (e.g. M1_{right}-PmV_{left} or S1_{left}-Pmd_{right}) as expected from interhemispheric neural-recordings
174 (Asanuma & Okamoto, 1959, see supplemental results and Figure S3 for comparison of
175 homologous versus heterologous interhemispheric connectivity).

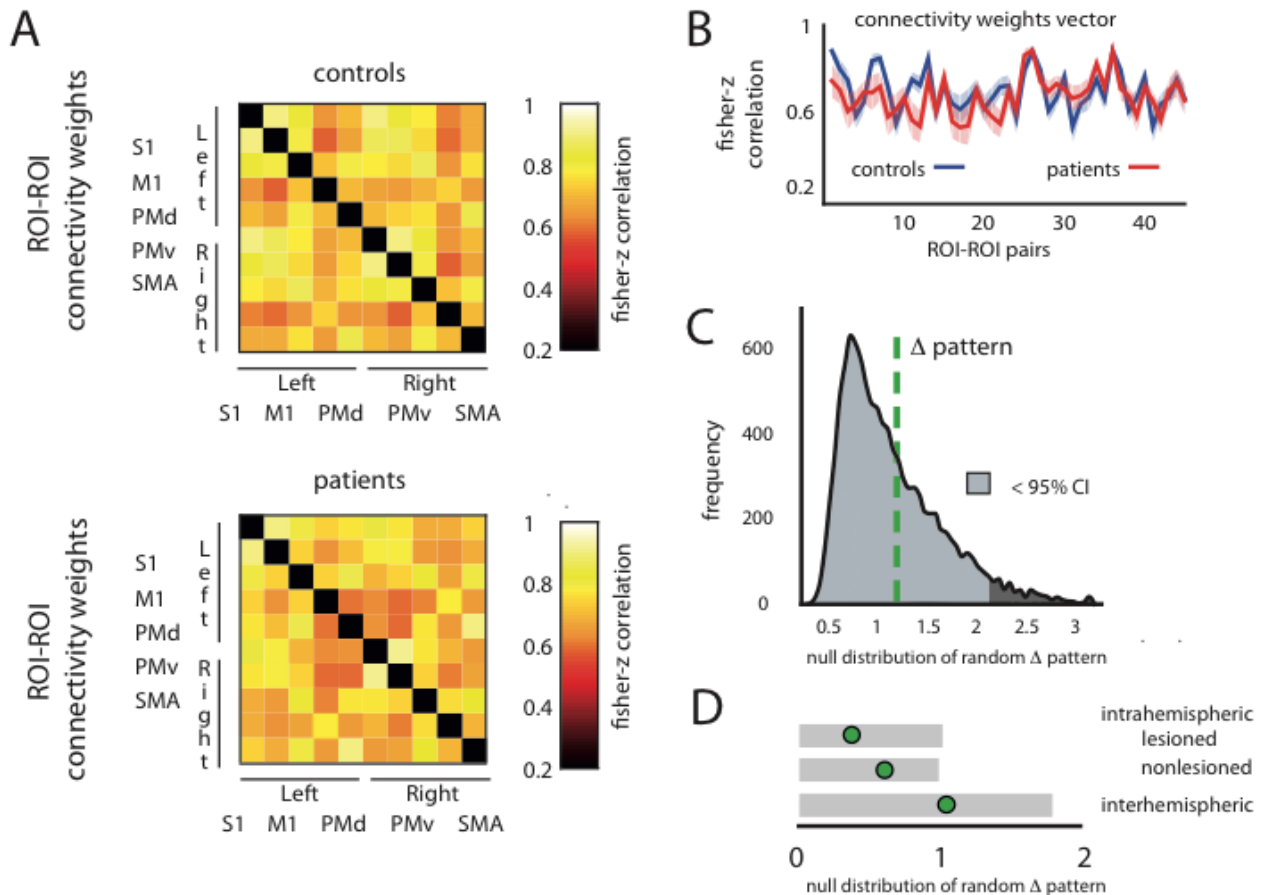
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177 **2.3. There were no systematic changes in connectivity patterns in the acute recovery** 178 **period**

179 If disruption of the cortical projections through subcortical stroke leads to an acute
180 reorganization of cortical circuits, one would expect that (on average) acute connectivity patterns

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181 of patients and controls would be different. Connectivity patterns for patients and controls were
182 highly correlated in the early period after stroke (acute stage: $R=0.69$, $p=0.0002$; see connectivity
183 matrices in Figure 2A and also Figure S4). To statistically test for significant differences
184 between connectivity patterns, we used the Euclidian distance between the two groups' mean
185 patterns and compared it to a null-distribution obtained by a permutation test (Figure 2c). We
186 found no systematic difference between patients and controls at the acute stage ($\Delta\text{pattern}=1.246$,
187 CI 0.575–2.467). This was also true when only considering intrahemispheric connections of
188 either the lesioned ($\Delta\text{pattern}=0.367$, CI 0.205–1.109) or non-lesioned side ($\Delta\text{pattern}=0.603$, CI
189 0.196–1.1) or interhemispheric connections ($\Delta\text{pattern}=1.027$, CI 0.394–1.968).
190



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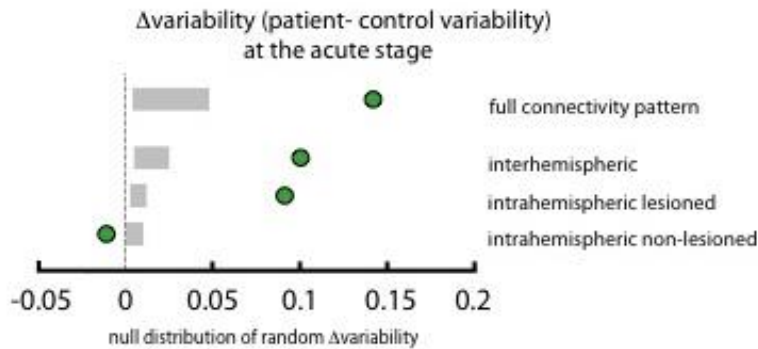
192 *Figure 2: No systematic differences in connectivity patterns of patients and controls in the acute*
 193 *recovery period (week 1-2). (A) Heat map representation of average connectivity weights for*
 194 *controls and patients at the acute stage after stroke. The y- and x-axis show the five ROIs (S1,*
 195 *M1, Pmd, PMv, SMA) for the left and right hemisphere creating a connectivity matrix. One small*
 196 *square represents the connectivity weight for the respective ROI pairing. The diagonal (black) is*
 197 *missing, as it is the correlation of a ROI with itself. (B) Vectorized upper triangular part of the*
 198 *correlation matrix for the average full connectivity pattern of controls (blue line) and patients*
 199 *(red line). (C) To quantify the differences between connectivity patterns for controls and*
 200 *patients, we calculated the Euclidian distance between the two pattern vectors (Δ pattern, dashed*
 201 *green line). The Euclidian distance is sensitive to differences of shape and scaling of patterns.*
 202 *The measured distance was then tested against the expected distribution if there were no*
 203 *differences between the two groups. To generate an empirical estimate of this distribution, we*
 204 *randomly shuffled group assignments and repeatedly computed the Euclidean distance (x10.000*
 205 *times, histogram with frequency on the y-axis and absolute value of the Euclidean distance on the*
 206 *x-axis). For the acute stage after stroke, the Δ pattern lay within the lower 95% percentile (grey*
 207 *shaded area) of the null-distribution. (D) The measured Δ patterns (green circle) for the*
 208 *intrahemispheric lesioned, non-lesioned or interhemispheric ROIs also always fell within the*
 209 *lower 95% range (grey boxes).*

210

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211 Even though the averaged connectivity patterns for patients and controls were
212 indistinguishable at the acute stage, the heterogeneity in lesion locations for different patients
213 might result in idiosyncratic shifts in connectivity patterns that in the whole group would be
214 reflected as higher variability in patterns. To measure this within-group variability, we calculated
215 the average Euclidian distance of each patient's pattern to the patient group mean pattern and did
216 likewise for controls. The average within-patient distance was 2.955, whereas the average
217 within-control distance was 2.813, resulting in a difference of 0.142 (Δ variability). We compared
218 this value to a null distribution of Δ variability generated with permutation testing. We found that
219 resting-state connectivity patterns of patients showed a higher idiosyncratic, non-systematic
220 variability compared to controls: The difference between the variability lay outside the 2.5% –
221 97.5% confidence interval generated by permutation testing (CI 0.018–0.051, Figure 3). Note
222 that the confidence interval was not symmetric around zero, as the N for controls was smaller
223 than for patients.

224 The difference in variability for intrahemispheric lesioned and interhemispheric
225 connections was also higher for patients. For intrahemispheric non-lesioned connections, we
226 found higher variability in controls (intrahemispheric lesioned: Δ variability=0.091, CI 0.002–
227 0.023; non-lesioned: Δ variability=-0.01, CI -0.003–0.015; interhemispheric: Δ variability=0.1, CI
228 0.008–0.05, Figure 3).



229

230 *Figure 3: Patients showed a higher unsystematic variability compared to controls at the acute*
231 *stage (Δ variability = green circle, 2.5%-97.5% range = grey boxes). Only for intrahemispheric*
232 *non-lesioned ROI's patients showed a lower variability.*

233

234 Thus, overall, while connectivity patterns for patients were more variable, patient
235 connectivity patterns were indistinguishable from control patterns at the acute stage.

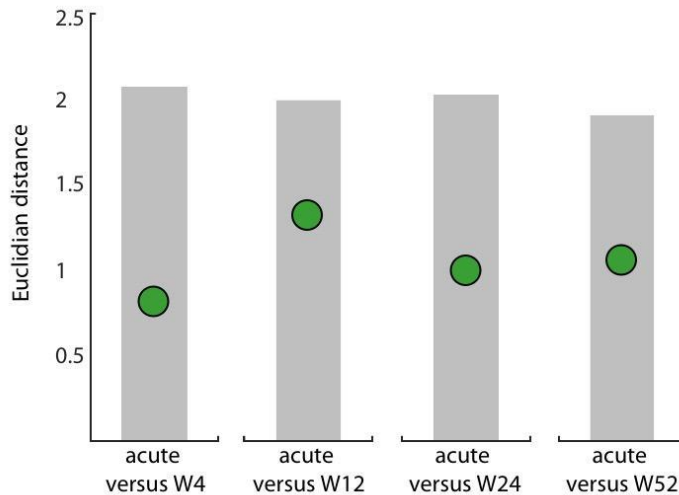
236

237 **2.4. There were no changes in patients' connectivity patterns over time**

238 Even though there were no systematic differences between connectivity patterns of
239 patients and controls at the acute stage, we might expect to find changes in patient connectivity
240 patterns over time as they recover from impairment.

241 We therefore quantified Euclidean distances between the average connectivity patterns at
242 the acute stage as reference versus all other weeks (Δ week). Surprisingly, patients showed no
243 increase in Euclidian distances between the acute stage and consecutive weeks (Figure 4 and
244 Table 1).

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245

246 *Figure 4: No significant change from patients' acute connectivity pattern compared to time-*
 247 *points at the subacute or chronic stage.*

248 *We computed the Euclidian distance between the average connectivity pattern of patients at the*
 249 *acute stage and all consecutive weeks (W4, W12, W24, W52; Δweek = green circles). Range of*
 250 *the expected distribution if there were no differences between the two groups (grey shaded area).*

251

252

Patients	acute_W4	acute_W12	acute_W24	acute_W52
All connections	Δweek: 0.814, (0.467 - 2.066)	Δweek: 1.322, (0.488 - 1.994)	Δweek: 0.994, (0.471 - 2.024)	Δweek: 1.063, (0.512 - 1.898)
Interhemispheric	Δweek: 0.636 (0.309 - 1.695)	Δweek: 1.018 (0.3255 - 1.627)	Δweek: 0.665 (0.315 - 1.589)	Δweek: 0.77 (0.343 - 1.616)
Intrahemispheric lesioned	Δweek: 0.353 (0.241 - 1.246)	Δweek: 0.413 (0.237 - 1.169)	Δweek: 0.457 (0.252 - 1.324)	Δweek: 0.558 (0.274 - 1.158)
Intrahemispheric non- lesioned	Δweek: 0.367 (0.152 - 0.859)	Δweek: 0.735 (0.157 - 0.886)	Δweek: 0.579 (0.158 - 0.919)	Δweek: 0.474 (0.174 - 0.805)

253

254 *Table 1: Euclidian distances between the connectivity pattern of the acute stage compared to all*
 255 *subsequent time-points in patients for only interhemispheric, intrahemispheric lesioned, or non-*
 256 *lesioned subsets.*

257

258 As it could be expected from these results, patients showed reliably high correlations of

259 their connectivity patterns with controls at the subacute or chronic stage (W4: R=0.74, p<0.0001;

260 W12: R=0.76, p<0.0001; W24: R=0.87, p<0.0001; W52: R=0.80, p<0.0001) and no significant

261 difference to control patterns 9 (Table 2). The analyses for intra- or interhemispheric connections
 262 alone found the same result (Table 1 & 2 and Figure S4).

263

patients versus controls'	W4	W12	W24	W52
All connections	Δ pattern: 1.203 (0.53 - 2.482)	Δ pattern: 1.795 (0.57 - 2.208)	Δ pattern: 0.885 (0.563 - 2.249)	Δ pattern: 1.653 (0.575 - 2.07)
Interhemispheric	Δ pattern: 1.102 (0.366 - 1.986)	Δ pattern: 1.671 (0.387 - 1.797)	Δ pattern: 0.663 (0.387 - 1.755)	Δ pattern: 1.354 (0.402 - 1.706)
Intrahemispheric lesioned	Δ pattern: 0.412 (0.2 - 1.202)	Δ pattern: 0.44 (0.198 - 0.998)	Δ pattern: 0.404 (0.213 - 1.122)	Δ pattern: 0.802 (0.216 - 0.892)
Intrahemispheric non- lesioned	Δ pattern: 0.253 (0.184 - 1.097)	Δ pattern: 0.486 (0.192 - 0.955)	Δ pattern: 0.415 (0.201 - 1.039)	Δ pattern: 0.505 (0.206 - 0.822)

264

265 *Table 2: Difference between the connectivity pattern of patients compared to controls at Week 4,*
 266 *Week 12, Week 24, and Week 52 for only interhemispheric, intrahemispheric lesioned, or non-*
 267 *lesioned subsets.*

patients	acute_W4	acute_W12	acute_W24	acute_W52
	$F(3,36) = 0.09, p = 0.9678$			
All connections	Δ week_variability: 2.474 \pm 1.6	Δ week_variability: 2.607 \pm 1.022	Δ week_variability: 2.424 \pm 0.96	Δ week_variability: 2.642 \pm 0.778
	$F(3,36) = 0.15, p = 0.9276$			
Interhemispheric	Δ week_variability: 1.9 \pm 1.4	Δ week_variability: 2.058 \pm 0.782	Δ week_variability: 1.78 \pm 0.697	Δ week_variability: 1.932 \pm 0.61
	$F(3,36) = 0.25, p = 0.859$			
Intrahemispheric lesioned	Δ week_variability:	Δ week_variability:	Δ week_variability:	Δ week_variability:

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	1.099 ±0.524	1.071 ±0.529	1.214 ±0.485	1.228 ±0.461
Intrahemispheric non-lesioned	F(3,36) = 0.32, p = 0.814			
	Δ week_variability: 1.08 ±0.688	Δ week_variability: 1.133 ±0.547	Δ week_variability: 1.083 ±0.518	Δ week_variability: 1.284 ±0.3519

268 By examining Euclidian distances between the individual connectivity patterns to the
 269 average connectivity pattern, we found a greater non-systematic variability in patients than in
 270 controls at the acute stage. However, the idiosyncratic variability of patients themselves did not
 271 change from the acute stage compared to the following time-points (Table 3).

272
 273 *Table 3: Difference in connectivity pattern variability in patients over time for all connections,*
 274 *interhemispheric, intrahemispheric lesioned, or non-lesioned subsets.*
 275

276 In summary, we found no evidence for a mean difference of connectivity patterns between
 277 patients within one year. More importantly, patients did not show any significant longitudinal
 278 change in connectivity patterns either systematically or regarding their group variability.

279 **2.5. Comparison between alternative metrics for M1-M1 connectivity**

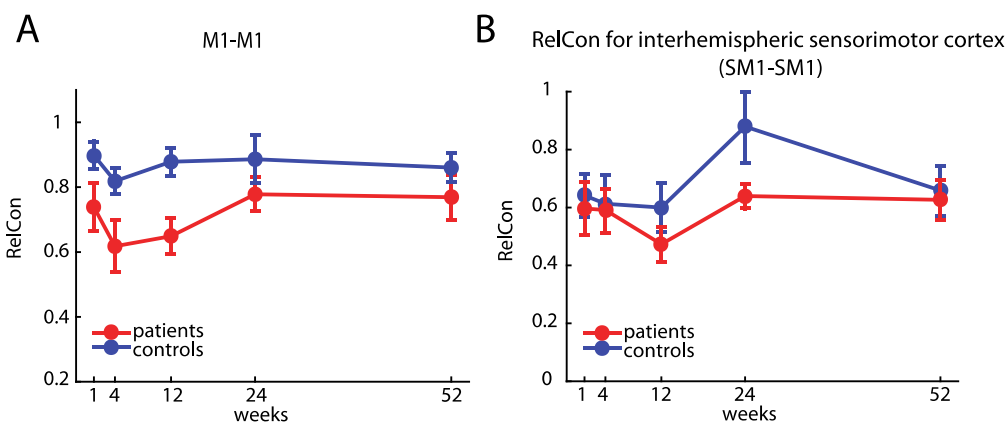
280 Above we looked at the entire connectivity pattern between five sensorimotor areas
 281 within and across hemispheres and found no changes for patients either longitudinally or when
 282 compared to controls. In contrast, some previous studies have focused on individual ROI-to-ROI
 283 connections and have reported changes after stroke (Thiel & Vahdat, 2015). Specifically,
 284 changes in interhemispheric connectivity between the two motor cortices have been frequently
 285 reported (Carter *et al.*, 2010; Chen & Schlaug, 2013; Golestani *et al.*, 2013; Park *et al.*, 2011).

286 To test this finding, we investigated changes of interhemispheric M1-M1 connectivity
 287 weights over time and between patients and controls in our data set. The analysis showed a
 288 significant difference between patients and controls, with patients having a slightly lower

289 average correlation between motor cortices (Figure 5a; *mixed model, group effect*: $\chi^2(1)=5.759$,
290 $p=0.016$). Congruent with our other results, however, we found no longitudinal changes either
291 for patients (*patient_week*: $\chi^2(4)=5.836$, $p=0.212$) or controls (*control_week*: $\chi^2(4)=0.4.723$,
292 $p=0.317$).

293 Our results also contrast with another published finding that used an alternative metric of
294 connectivity to assess changes in functional connectivity after stroke. Golestani and colleagues
295 (2013) used a relative connectivity (RelCon, see Methods) measure between the two sensory-
296 motor cortices and reported lower relative interhemispheric sensorimotor (SM1 RelCon)
297 connectivity in stroke patients with a motor deficit compared to controls and stroke patients
298 without impaired motor function.

299 Similarly, our patients had a lower RelCon for SM1-SM1 compared to controls at all time-
300 points. Using a mixed-model, we found a significant difference between the groups
301 ($\chi^2(1)=5.2457$, $p=0.022$). However, consistent with our results reported above, we did not find a
302 change over time for RelCon SM1-SM1 in neither controls ($\chi^2(4)=2.8087$, $p=0.5903$) nor in
303 patients ($\chi^2(4)=8.2243$, $p=0.0837$; Figure 5b).



304

305 *Figure 5: A) M1-M1 connectivity in our dataset. In patients, interhemispheric connectivity*
306 *between the two motor cortices was systematically lower than compared to controls at all time-*
307 *points. However, no changes of M1-M1 connectivity over time were found. B) Relative*
308 *Connectivity of SM1-SM1 in controls and patients. While there was a significant difference in*

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309 *SMI-SMI connectivity between the two groups, with lower RelCon for patients, there was no*
310 *significant change over time.*

311

312 **3 Discussion**

313 Here we report, that there were no longitudinal changes in resting-state functional
314 connectivity (rsFC) between cortical motor areas despite substantial motor recovery over the
315 same time period in a cohort of patients with subcortical stroke. In addition, at no stage of
316 recovery were rsFC patterns different from healthy, age-matched controls.

317 Whenever results are negative, concerns will be raised about the power of the study (addressed
318 below) and the biological validity of the method in general.

319 There have been more than 500 rs-fMRI studies of brain connectivity (Buckner *et al.*, 2013).
320 Recent reports have described the close relationship between resting-state networks and
321 structural connectivity assessed with other methods e.g. magnetoencephalography (van den
322 Heuvel *et al.*, 2009; Brooks *et al.*, 2011). Most notably for our purposes, the sensitivity of rsFC
323 to changes in experience-dependent neural plasticity appears to be quite high, as even short
324 periods of training yield statistically significant changes of functional connectivity in small *n*
325 studies in healthy subjects (Mawase *et al.*, 2017; Vahdat *et al.*, 2011). For example, Censor and
326 colleagues (Censor *et al.*, 2014), in a comprehensive multimodal approach combining
327 behavioral, brain stimulation, and rs-fMRI data, they demonstrated that changes in performance
328 after training on a five-digit sequence task led to reliable changes in corticostriatal functional
329 connectivity. When motor memory formation after training was disrupted using rTMS, changes
330 in functional connectivity predicted the modification of memory recall on the next day.

331 Given such results, why were we not able to detect rsFC changes in the setting of stroke
332 recovery? Injury ostensibly triggers functional reorganization, which arguably should be a more

333 dramatic cause of connectivity change as it is associated with structural alterations, e.g.
334 sprouting, and not just learning-related changes in pre-existing connections. There are two
335 potential answers to this question, one is the possibility that the idea that changes in cortico-
336 cortical connections promote motor recovery after stroke is ill-conceived, the second is that there
337 are methodological limitations to rs-fMRI. We shall discuss both of these concerns.

338

339 A large number of animal studies, in rodents and non-human primates, have described numerous
340 structural and physiological changes in cortical areas around and beyond the infarct core. These
341 changes have collectively been called reorganization, but in only a small subset of cases have
342 they been correlated with motor recovery, which suggests that most are likely just reactive
343 (Carmichael, 2016). We reasoned that as spontaneous biological recovery is similar for cortical
344 and subcortical strokes (Zarahn et al., 2011) then recovery-related cortical reorganization, if not
345 just reactive, should still occur in patients with isolated subcortical lesions. Indeed, we know that
346 corticospinal integrity assessed with TMS is a good predictor of recovery in patients with
347 subcortical stroke (Radliska et al., 2010; Byblow et al. 2015), i.e., cortical output is required for
348 recovery from subcortical stroke just like it is for cortical stroke. In addition, changes in cortical
349 maps are seen not just with cortical lesions but with spinal and peripheral lesions as well
350 (Florence *et al.*, 1998; Moxon *et al.*, 2014, Krakauer & Carmichael, 2017). Here, however, we
351 found no evidence for systematic rsFC changes between cortical motor regions. In the light of
352 these results, previously reported cortical connectivity changes could be reactive rather than
353 reparative, e.g. confounded by the presence of a cortical lesion.

354

355 The question must now be asked why it was ever conjectured that changes in connections

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356 between cortical regions would enhance recovery from hemiparesis, which is caused by
357 interruption of descending pathways out of a particular region(s). One could rephrase this to ask
358 why would there be a “horizontal” solution to a “vertical” problem? This question is related to
359 the increasing awareness of the questionable relevance of cortical map changes to recovery
360 (Krakauer & Carmichael 2017), changes which have hitherto been taken as electrophysiological
361 evidence for reorganization (Dancause & Nudo, 2011; Warraich & Kleim, 2010; Wittenberg,
362 2010). Overall, it is increasingly apparent both from recent and previous work in non-human
363 primates and rodents that recovery after stroke relates to changes in the strengths of descending
364 projections to the brainstem and spinal cord from individual motor cortical areas rather than to
365 changes in the connections *between* them (Lin *et al.*, 2018; Starkey *et al.*, 2012; Wahl *et al.*,
366 2014; Zaaimi *et al.*, 2012). That said, it could be postulated that cortico-cortical drive, for
367 example of premotor cortex onto primary motor cortex (M1) could facilitate remaining CST
368 descending projections out of M1, as studies have shown such cortico-cortical facilitation in
369 healthy non-human primates (Cerri *et al.*, 2003; Shimazu *et al.*, 2004). Consistent with what we
370 found here, however, there is little evidence for this as a recovery mechanism after stroke in any
371 animal.

372

373 While our results are congruent with similar observations in a smaller cohort (Nijboer *et al.*,
374 2017), they are seemingly contradicted by a recently published paper that reported results for
375 resting-state changes in a similarly sized cohort of patients with subcortical stroke. In this study,
376 Lee and colleagues obtained six connectivity measures between 40 supra- and infratentorial
377 ROIs in 21 stroke patients measured at two time-points post-stroke (2 weeks and 3 months), and
378 found differences in two of the measures. Specifically, they found lower overall strength in

379 interhemispheric connectivity and higher network distance compared to healthy controls at 2
380 weeks, but neither measure changed at 3 months. Even if one overlooks the unmentioned
381 comparisons problem and the fact that they had more variables (six measures, 40 ROIs) than
382 subjects, their results showed no connectivity measure *changing* as the patients improved, which
383 is consistent with our results.

384

385 Although we favor the view that the absence of connectivity change in our study is a true
386 negative result both in terms of the power of the study and the biological validity of rsFC (van
387 Meer *et al.*, 2010), an alternative explanation would relate to methodological limitations of rs-
388 fMRI.

389 Methodological problems with e.g. regard to reproducibility of imaging analysis in general and
390 rs-fMRI, in particular, have long been a topic of discussion (Baker, 2016; Ioannidis *et al.*, 2014;
391 Macleod *et al.*, 2014). So far, there is no consensus about the optimal way to analyze rs-fMRI
392 data, which poses a fundamental challenge regarding the generalizability and comparability of
393 reported findings. In face of a low signal to noise ratio, missing consensus in analysis steps and
394 statistical methods (promoting the risk of conscious and unconscious p-hacking; Nuzzo, 2015),
395 and frequent absence of an *a priori* hypothesis (which can lead to so-called HARKing; Kerr,
396 1998), the imaging literature is especially vulnerable to false-positive or -negative results
397 (Munafò *et al.*, 2017). For example, converging evidence highlights that the choice of different
398 pre-processing strategies needs to be considered as an important confound in rs-fMRI (Cole *et*
399 *al.*, 2010; He & Liu, 2012; Weissenbacher *et al.*, 2009).

400

401 We addressed this problem by providing measures of data reliability, comparing two different

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402 pre-processing procedures, and by reanalyzing our data set with regard to individual M1-M1
403 changes using a previously reported metric for resting-state imaging analysis (Golestani *et al.*,
404 2013). Here we provide, to the best of our knowledge, the most methodologically complete study
405 to date of stroke recovery using rs-fMRI. Additionally, open science efforts including data
406 sharing have been identified as a major tool to secure transparency and reproducibility of
407 reported results, allowing for external validation of results, detection of mistakes, and generation
408 of alternative interpretations (Nosek *et al.*, 2015). In an effort to increase the transparency and
409 reproducibility of our results, the complete data set as well as the custom-written MATLAB and
410 R scripts are made publicly available to invite further analysis.

411

412 **Conclusion**

413 In the present study, we investigated longitudinal changes in functional connectivity after
414 subcortical stroke. Despite substantial recovery from motor impairment over one year, we found
415 no differences in functional connectivity between patients and controls, nor any changes over
416 time. Assuming that rs-fMRI is an adequate method to capture connectivity changes between
417 cortical regions after brain injury, the results presented here, provide reason to doubt that post-
418 stroke cortical reorganization, conceived as changes in cortico-cortical connectivity, is the
419 relevant mechanism for promoting motor recovery after stroke. We suggest instead that it is
420 facilitation of residual cortical descending pathways that are likely to be more causally relevant.
421 It is perhaps time for the field to change its emphasis from changes in “horizontal” connections
422 to changes in “vertical” ones.

423 **4 Materials and methods**

424 The resting-state data set presented here was acquired from a natural history study investigating
425 upper extremity recovery after stroke (Study of Motor Acute Recovery Time course after Stroke;
426 SMARTS). As part of the study, a range of behavioral, physiological, and imaging
427 measurements were obtained. Details of the behavioral characterization of the patients have been
428 published elsewhere (Cortés *et al.*, 2017; Ejaz *et al.*, 2018; Xu *et al.*, 2017).

429

430 **4.1. Patients**

431 Since we were interested in cortical connectivity changes after stroke, in order to avoid
432 confounding results due to cortical damage, only a subset of 19 patients with lesions restricted to
433 subcortical areas was considered (6 females; mean age 59 ± 12 years, 15 right-handed). Major
434 inclusion criteria were: first-ever clinical apparent ischemic stroke, proven by a positive DWI
435 lesion within the previous 2 weeks; unilateral upper extremity weakness (Medical Research
436 Council muscle weakness scale < 5); ability to give informed consent. Patients were excluded for
437 one or more of the following reasons: initial impairment too mild (Fugl-Meyer score Upper
438 Extremity $> 63/66$), age ≤ 21 years, hemorrhagic stroke (Xu *et al.*, 2017). The selected patients
439 had lesions either in the corona radiata, the internal capsule or in the cortico-spinal tract above
440 the crossing in the pyramid. Demographics are described in Table S1; more detailed information
441 about lesion distribution is shown in Figure S1.

442 Additionally, 11 healthy age-matched control participants (4 females; mean age 65 ± 8
443 years; all right-handed), were tested at the same time-points.

444 The study was carried out in accordance with the Declaration of Helsinki and approved
445 by the respective local ethics committee of the participating recruiting centers of SMARTS

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446 (Johns Hopkins University, USA, Columbia University, USA, University Hospital Zurich,
447 Switzerland). All participants gave written informed consent.

448

449 **4.2. Study design**

450 Patients were enrolled in the study within the first two weeks after stroke and followed up
451 over a one-year period at five time-points: acute stage: week 1-2 (10 ± 4 days), W4: week 4-6 (37
452 ± 8 days), W12: week 12-14 (95 ± 10 days), W24: week 24-26 (187 ± 12 days), and W52: week
453 52-54 (370 ± 9 days). During each visit, the following clinical parameters were assessed: Fugl-
454 Meyer score Upper Extremity (FM-UE, max. score 66, Fugl-Meyer *et al.*, 1975), Action
455 Research Arm Test (ARAT, max. score 57, Yozbatiran *et al.*, 2008). Hand strength and
456 individuation ability were measured using a custom-made hand-device (Xu *et al.*, 2017). The
457 FM-UE and ARAT are widely used to assess motor deficits after stroke and can capture different
458 aspects of recovery: higher FM-UE scores represent normal reflex activity, fewer muscular
459 coactivations, coordination and higher joint mobility thought to be equal to “true” resolution of
460 impairment; higher ARAT scores are achievable with compensatory strategies, thus correlating
461 closer with activities of daily living. Measuring hand strength offers a third dimension of
462 recovery that is only partially captured within the FM-UE and ARAT.

463

464 **4.3. Image Acquisition**

465 Participants were scanned with an 3T Achieva Philips system. Scans were obtained with
466 a 32-channel head coil, using a two-dimensional echo-planar imaging sequence (TR=2.00s, 35
467 slices, 210 volumes/run, slice thickness 3mm, 1mm gap, in-plane resolution $3 \times 3 \text{mm}^2$). Each

468 resting-state scan was 8min long. Participants were instructed to lie still and visually fixate on a
469 central white cross displayed on a computer monitor.

470 Structural images for atlas transformation and lesion definition were acquired with a T1-
471 weighted anatomical scan (3D MPRAGE sequence, TR/TE=8/3.8ms, FOV 212×212mm, matrix
472 96×96, 60 slices, slice thickness 2.2mm). Finally, for each participant, a diffusion weighted
473 imaging (DWI) image (TR=2.89s, 30 slices, 5mm slice thickness, 240x240mm FOV), was
474 acquired to define lesion boundaries.

475

476 **4.4. Imaging analysis**

477 4.4.1. Preprocessing of rs-fMRI time series

478 Rs-fMRI has a relatively low signal-to-noise ratio. Non-neuronal processes, such as sensor noise,
479 head motion, cardiac phase, and breathing, account for a considerable part of the variance of the
480 raw signal (Birn, 2012). It has been argued that markers for the reliability of the sampled rs-
481 fMRI data are missing and that the choice of preprocessing steps is often not justified (Bennett &
482 Miller, 2010; Zuo & Xing, 2014). We therefore conducted two different procedures for noise
483 reduction and then compared split-half reliability for the whole connectivity pattern in controls to
484 determine which steps provided higher reliability (see supplementary material).

485 4.4.2. Lesion definition

486 Lesion boundaries were defined as an intensity increase of $\geq 30\%$ on DWI images, and in a
487 second step manually modified by a neuroradiologist and a neurologist using RoiEditor, see
488 Figure S1 for averaged lesion distribution map.

489

490 4.4.3. ROI definition

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491 We chose five motor areas (S1=primary somatosensory cortex, M1=primary motor cortex,
492 PMd=dorsal premotor cortex, PMv=ventral premotor cortex, SMA=supplementary motor area)
493 as regions of interest that have been widely accepted as being associated with motor function and
494 motor recovery (Miyai *et al.*, 1999, 2002; Rehme *et al.*, 2012). Individual T1-images were used
495 to delineate pial-grey matter and grey matter-white matter boundaries using FreeSurfer software
496 (Dale *et al.*, 1999). The cortical surfaces were aligned across participants based on the sulcal-
497 depth and local curvature maps. Probabilistic cyto-architectonic maps (Fischl *et al.*, 2008)
498 aligned to the group average surface were then used to define ROIs first on the individual
499 surface, and then back-projected into the subject-native space.

500 The ROIs were defined as follows, M1: surface nodes with the highest probability for
501 Brodmann area (BA) 4. To increase specificity for processes related to recovery of hand
502 function, this ROI was limited to 2cm above and below the hand-knob (Yousry, 1997). S1: nodes
503 in the hand-region in S1 were isolated using BA 3a, 3b, 1 and 2.2cm above and below the hand
504 knob. PMd: nodes with highest probability in BA6, above middle frontal sulcus, but on the
505 lateral surface of the hemisphere. PMv: nodes with the highest probability in BA6, above middle
506 frontal sulcus. SMA: nodes with the highest probability in BA6 on the medial surface of the
507 brain. This ROI therefore includes SMA and preSMA (Picard & Strick, 1996).

508

509 **4.5. Functional connectivity analysis**

510 For each ROI, the time series for all voxels within the ROI were extracted and averaged,
511 resulting in a single BOLD time-course vector for each of the 10 ROIs across the two
512 hemispheres (left-S1, left-M1, left-PMd, left-PMv, left-SMA, right-S1, right-M1, right-PMd,
513 right-PMv, right-SMA). Pairwise correlations between averaged BOLD time-course vectors for

514 the different ROIs were computed and Fisher-Z transformed to conform better to a normal
515 distribution, resulting in a 10×10 matrix of connectivity weights (Figure 2). The matrix thus
516 represents the connectivity weights between all possible ROIs for a patient: 10 intrahemispheric
517 ROI pairs, each *within* the lesioned and non-lesioned hemispheres, respectively, and 25
518 interhemispheric ROI pairs *between* the lesioned and non-lesioned hemispheres (overall 45
519 connectivity weights for all ROI pairs). For the rest of this manuscript, this vectorized, Fisher-Z
520 transformed correlation matrix will be referred to as the full connectivity pattern, while the
521 corresponding intra- and interhemispheric subsets of the matrix will be referred to as the
522 intrahemispheric non-lesioned (1×10 vector), intrahemispheric lesioned (1×10 vector), and
523 interhemispheric connectivity patterns respectively (1×25 vector). These connectivity patterns
524 were estimated independently for each session and patient. Connectivity patterns for controls
525 were estimated similarly, with the exception that intrahemispheric connectivity patterns were
526 averaged across both hemispheres.

527

528 **4.6. Changes in connectivity patterns in the acute recovery period**

529 In the early acute recovery period (week 1-2), stroke-related damage could alter connectivity
530 patterns in patients in two distinct ways: 1) the connectivity pattern could remain the same but
531 overall connection strengths might be increased or decreased, resulting in connectivity patterns
532 in patients DC-shifted but otherwise identical to control patterns. This would indicate that a
533 canonical pattern of connectivity between motor ROIs in healthy people is simply up or down-
534 regulated post-stroke either due to maladaptation or compensation for damage. 2) stroke-related
535 damage might alter connectivity weights among only a few select ROIs, e.g. either between
536 ROIs within one hemisphere or across hemispheres. This would alter the shape of the

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537 connectivity patterns in patients in comparison to controls. Since we wanted to be sensitive to
538 both kinds of connectivity pattern change, the appropriate statistical test would be a MANOVA
539 between patient and control connectivity patterns. However, due to insufficient degrees of
540 freedom in performing such an analysis (the number of connectivity weights exceeds the number
541 of patients and controls), we instead opted for a permutation test with Euclidean distance as a
542 measure of dissimilarity between patient and control connectivity patterns as it is sensitive to
543 *shape and scaling* changes of connectivity patterns (for details see supplementary material).

544

545 While, on average, connectivity patterns for patients might not differ from controls in the
546 acute recovery stage, individual patients might exhibit idiosyncratic connectivity patterns owing
547 to the heterologous distribution of lesions locations in the cohort. Thus, acute stage changes in
548 connectivity patterns might result in an increase in variability in within-group connectivity
549 patterns. To determine whether this was the case in the acute stage, we computed the average
550 Euclidean distances between each patient's connectivity pattern and the patients' mean
551 connectivity pattern (acute P_variability). Similarly, we computed the average Euclidean
552 distance between each individual control pattern and the controls' mean connectivity pattern
553 (acute C_variability). The differences between these two served as a measure of increased or
554 decreased variability in the patients ($P_variability - C_variability = \Delta variability$). We then repeated
555 the permutation test (for details see supplementary material) to generate a null distribution of the
556 difference in variability to test the significance of $\Delta variability$.

557

558 **4.7. Changes in connectivity patterns over time during recovery**

559 Since patients in our cohort demonstrated substantial improvements of upper extremity deficits
560 in the year after stroke (Figure 1), we were interested to see whether there were concomitant
561 longitudinal changes in connectivity patterns. To determine this, we performed two separate but
562 related analyses. First, we independently compared differences in patient connectivity patterns
563 from the acute stage to all consecutive weeks (Δ week from acute to week 4, week 12, week 24,
564 and week 52) to determine how far connectivity patterns diverged over the year from the pattern
565 in the acute post-stroke stage. The same was done for control connectivity patterns to establish
566 intersession reliability. Second, we compared patient's connectivity patterns for all five
567 measurement sessions against the control connectivity patterns to determine how patient patterns
568 changed longitudinally in reference to controls (Δ pattern for acute, week 4, week 12, week 24
569 and week 52). Both these analyses were performed using Euclidean distance and permutation
570 testing in the same way as for estimating differences in connectivity patterns at the acute
571 recovery stage.

572 To assess if individual idiosyncratic patterns might show a change over time that could underlie
573 recovery, we analyzed individual connectivity pattern changes for a subgroup of patients with all
574 time-points (10 patients) by comparing pattern variability in the acute stage against all other
575 time-points (Δ week_variability for acute_week 4, acute_week 12, acute_week 24, and
576 acute_week 52) and performing an ANOVA with the factor Weeks.

577

578 **4.1. Alternative metrics to calculate functional connectivity**

579 Because changes in functional connectivity between the two primary motor cortices have been
580 reported more consistently than other connectivity changes after stroke, we also explicitly looked
581 at changes of M1-M1 connectivity weights.

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582

583 We additionally analyzed our dataset using a metric of functional connectivity that was proposed
584 in the to-date largest longitudinal resting-state stroke study with cortical and subcortical lesion
585 location, which reported changes of M1 interhemispheric connectivity. The metric has been
586 called Relative connectivity (RelCon) and is claimed to have low sensitivity to the temporal
587 signal-to-noise ratio and signal amplitude fluctuations while maintaining a high sensitivity to
588 meaningful signal changes, therefore offering an advantage e.g. in the analysis of data sets
589 acquired with different scanners (Golestani & Goodyear, 2011). RelCon looks at
590 interhemispheric connectivity of M1 in relation to intrahemispheric connectivity of M1 (for
591 details see supplementary material).

592

593 Based on the reported methods, we calculated the RelCon for interhemispheric SM1 connections
594 in our dataset.

595

596 *Statistical analysis*

597 Changes of behavioral measures in patients over time were analyzed using a mixed-effects
598 ANOVA, with Week (acute – W52) as a fixed factor, and Subject as a random factor. As
599 approximately 11% of the sessions were missing, we used the lme4 toolbox in R (Bates et al.,
600 2015) to fit the unbalanced mixed-effects design. Rather than F-values, statistical tests for main
601 effects and interactions are reported using a χ^2 approximation. Behavioral measures of patients
602 and controls at the acute stage were compared with a two-tailed t-test.

603 Intrасession reliability was analyzed by computing split-half correlations (Pearson's correlation)
604 for each single week and individual patient/control, as well as looking at the averaged split-half

605 correlation for all weeks together. Reliability between groups was compared using a mixed-
606 effects ANOVA, with Group (patients vs. controls) and Week (acute – W52) as fixed, and
607 Subject as a random factor. This was done for all connections, as well as subsets only including
608 interhemispheric, intrahemispheric lesioned or non-lesioned ROIs.

609 Changes of interhemispheric M1-M1 connectivity weights over time between patients and
610 controls were analyzed using a mixed-effects ANOVA, with Group (patients vs. controls) and
611 Week (acute – W52) as fixed, and Subject as a random factor, alternative metrics reported in
612 Golestani *et al.* were analyzed in the same way.

613 Results were considered significant at $p < 0.05$. Means values are reported \pm standard deviation
614 unless stated otherwise.

615

616 *Data availability*

617 The complete data set will be openly available in a public repository upon publication. All
618 analysis was performed using built-in and custom-written MATLAB and R scripts that will be
619 made publicly available upon publication.

620 **5 Acknowledgement**

621 We like to thank Susumu Mori & Andreia Faria from the Department of Neuroradiology, Johns
622 Hopkins University for their support regarding imaging analysis.

623 **6 Competing interests**

624 The authors report no competing interests.

625

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626 **7 Supplemental Material**

627 **Methods**

628 **Permutation test and Bootstrapping**

629 To perform a permutation test, we first identified patients and controls that had estimates of
630 connectivity patterns within the first two weeks after stroke. We estimated Δ pattern as the
631 Euclidean distance between the average connectivity pattern for patients and the average
632 connectivity pattern for controls. We then shuffled group assignment labels for connectivity
633 patterns 10,000 times, randomly assigning connectivity patterns to “controls” or “patients”. From
634 the shuffled data, we again calculated the Euclidean distance between the average connectivity
635 pattern for patients and controls based on this new assignment. By repeatedly shuffling and
636 computing Euclidean distances, we obtained an estimate of the empirical null distribution of
637 Δ pattern – e.g. the expected distribution if there was no real difference between the two groups.
638 The measured Δ pattern was then compared against this null distribution, and the relative
639 proportion of simulations that showed a larger distance was used as a p-value - the probability
640 that the distance between the mean control and patient pattern would be equal or larger than the
641 measured distance by pure chance. This analysis was carried out independently for the full,
642 intrahemispheric lesioned, intrahemispheric non-lesioned, and interhemispheric connectivity
643 patterns.

644

645 **RelCon**

646 To calculate the interhemispheric RelCon for ipsilesional and contralesional sensorimotor cortex
647 (SM1) the correlation between time-series of all possible pairs of voxels is calculated (all voxels
648 $SM1_{ipsilesional-contralesional}$). The average of the interhemispheric connectivity for $SM1_{ipsilesional-$

649 *contralesional* is then calculated relative to the within connectivity of the ipsilesional SM1 (divided
650 by the average correlation of all voxel within SM1_{ipsilesional}).

651 This metric was tested on different real and simulated data sets and showed superior results
652 compared to other *absolute* connectivity measures (absolute meaning connectivity measures that
653 do not relate interhemispheric ROI-to-ROI connectivity weights to the average within correlation
654 of the ipsilesional ROI itself).

655

656 Results

657

ID	age	gender	handedness	lesion side	first FM-UE	first ARAT	session
2310	57	m	right	left	58	56	5
2365	53	f	right	right	0	57	4
2395	65	m	right	right	30	21	4
2450	66	m	right	right	66	56	3
2531	66	f	right	right	60	55	5
2565	71	m	right	right	4	0	3
2652	46	m	left	left	4	0	4
2654	46	m	right	right	49	52	5
2663	67	f	right	left	16	2	4
2789	56	m	right	right	64	57	4
2925	59	f	right	left	60	57	5
3176	64	m	left	right	63	57	4
3239	74	m	left	left	5	0	5
3240	80	f	right	left	9	56	5
3241	64	f	right	right	58	39	5
3243	22	m	right	left	63	56	5
3246	53	m	left	left	30	39	5
3247	54	m	right	right	59	57	5
3248	58	m	right	right	61	56	4

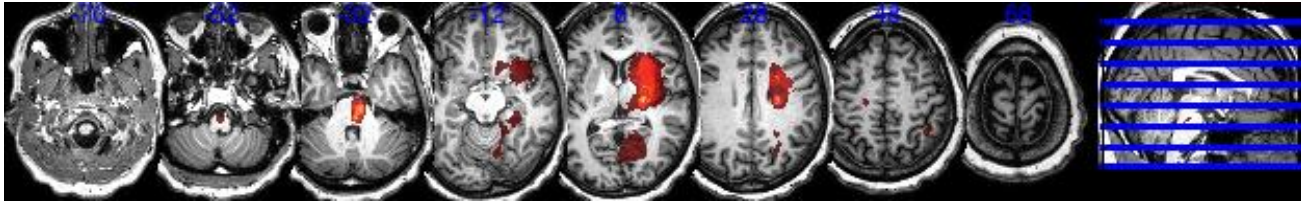
658

659 *Table S1: Patient demographics and overall session count. First FM-UE = first recorded Fugl-*
660 *Meyer score Upper Extremity, first ARAT = first recorded Arm Research Action Test.*

661

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662 Lesion distribution map



664 Figure S1: Lesion distribution of patients (N = 19). Averaged lesion distribution mapped to MNI
665 space with lesion flipped to one hemisphere.

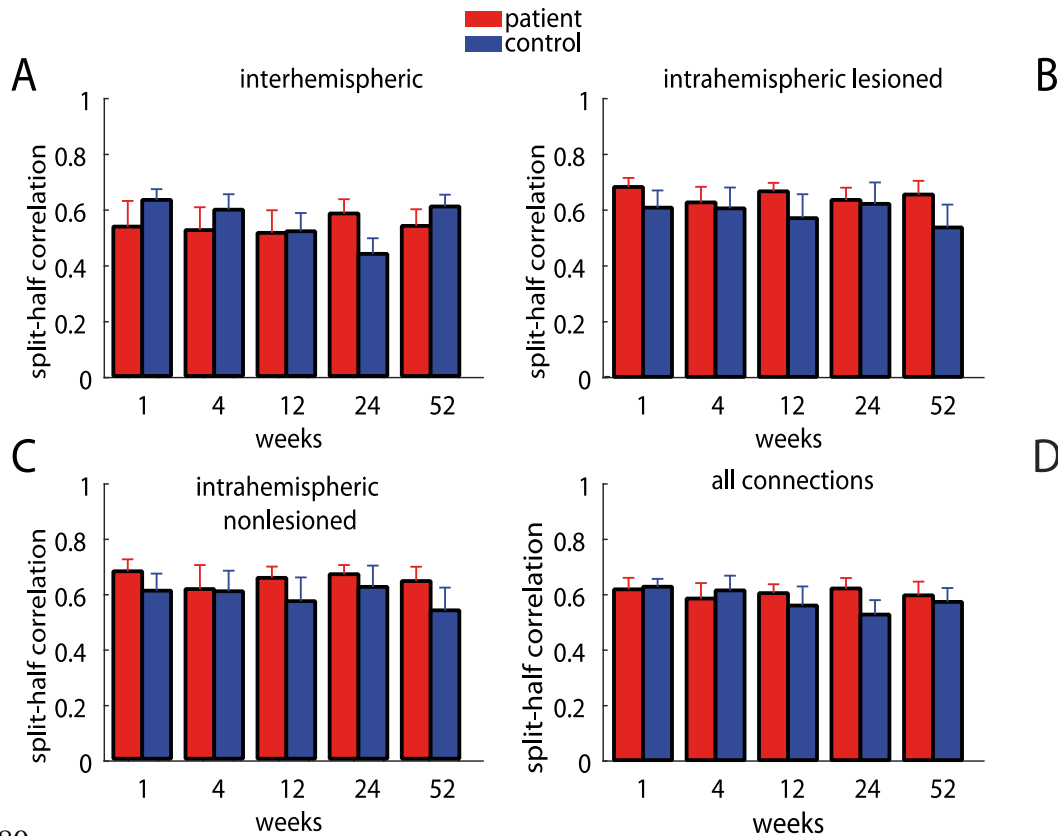
666

667 2.6 Data reliability and Preprocessing comparison

668 To estimate the reliability of our measurements within sessions, connectivity patterns were
669 computed as described above for the first 100 volumes and the second 100 volumes
670 independently and correlated with each other to calculate split-half reliabilities.

671 As seen for overall connectivity, intra- and interhemispheric split-half reliabilities were highly
672 reliable for controls and patients (controls: *intrahemispheric*: $r = 0.67$ (95% Confidence Interval,
673 $0.61-0.74$), *interhemispheric*: $r = 0.64$ (CI $0.59-0.69$), patients: *intrahemispheric lesioned*: $r =$
674 0.78 (CI $0.75-0.81$), *non-lesioned*: $r = 0.77$ (CI $0.73-0.82$), *interhemispheric*: $r = 0.69$ (CI $0.66-$
675 0.74), see Figure S1 for split-half reliability of each week). Split-half reliability was not different
676 between groups for *interhemispheric*: ($\chi^2(1) = 0.0239$, $p = 0.8771$) and *intrahemispheric non-*
677 *lesioned* connections: ($\chi^2(1) = 3.5634$, $p = 0.0591$), but was different for *intrahemispheric*
678 *lesioned* connections ($\chi^2(1) = 4.2337$, $p = 0.0396$).

679



680

681 Figure S2: Intrasection split-half reliability for patients and controls at each week. For each
682 individual patient or control participant, the BOLD time series of the first 100 volumes of the
683 scan were correlated with the last 100 volumes. Each Panel shows the results for a different
684 condition. Patients always had slightly higher intrasection reliability than although this
685 difference was not significant and was possibly driven by outlier in the control group.

686 The reliability measurement also allowed us to compare two different pre-processing
687 procedures:

688

689 Preprocessing procedure (P1): We removed the first 10 volumes of the functional data, then
690 performed correction for the timing of slice acquisition, motion correction, brain extraction,
691 linear trend removal, and temporal filtering (band pass, 0.01-0.08 Hz) using FSL (FMRIB

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692 Software Library (FSL), Oxford University, Oxford, UK). Our analysis was carried out in the
693 native space, and no spatial smoothing was applied. Linear regression was used to remove signal
694 correlated with the global mean signal, and the average time series in the cerebral white matter
695 and cerebrospinal fluid (Fox *et al.*, 2006).

696 Preprocessing procedure (P2): Here, we used an independent component analysis (ICA)
697 approach using FSL MELODIC for artifact reduction (Smith *et al.*, 2004). Again, we removed
698 the first 10 volumes of the functional data. We applied motion correction and brain extraction.
699 Probabilistic independent component analysis was conducted to denoise individual data by
700 removing components such as head motion, scanner artifacts, and physiological noise. Noise
701 components were classified using FMRIB's ICA-based Xnoiseifier (Salimi-Khorshidi *et al.*,
702 2014), which attempts to auto-classify ICA components into "good" vs. "bad" components. The
703 "bad" components were then removed from the functional data.

704 To determine which procedure would provide a more stable result, we calculated the
705 split-half reliability of the ROI-ROI connectivity weights for the whole connectivity pattern over
706 time in controls only.

707 Both procedures lead to good intrasession reliability on average (P1 = 0.64, CI 0.60–0.66;
708 P2 = 0.62, CI 0.57–0.66) but showed no significant difference ($\chi^2(1) = 1.231$, $p = 0.267$), while
709 no consistent change over time was found for either procedure by itself (P1: $\chi^2(4) = 2.834$, $p =$
710 0.684 ; P2: $\chi^2(4) = 3.007$, $p = 0.557$). Because of the nominal higher intrasession reliability we
711 conducted all subsequent analyses after noise correction using the P1 procedure.

712

713 As for overall connectivity, the intersession reliability for controls showed no significant
714 change over time for intra- or intrahemispheric (*intrahemispheric lesioned*: Δ week acute_W4 =

715 0.36, CI 0.217–1.308; acute_W12 = 0.323, CI 0.225–1.119; acute_W24 = 0.567, CI 0.259–
716 1.333; acute_W52 = 0.527, CI 0.228–1.118; *intrahemispheric non-lesioned*: Δ week acute_W4 =
717 0.36, CI 0.216–1.286; Δ week = 0.323, CI 0.221–1.121; acute_W24 = 0.567, CI 0.26–1.331 ;
718 acute_W52 = 0.527, CI 0.23–1.136; *interhemispheric*: , Δ week acute_W4 = 0.669, CI 0.445–
719 2.062; acute_W12 = 0.516, CI 0.419–1.876; acute_W24 = 0.721, CI 0.519–2.127; acute_W52 =
720 0.751, CI 0.45–1.991).

721

722 **7.2.1 Homo- versus Heterologous ROI connectivity**

723 The physiological plausibility of the recorded BOLD signal fluctuations was further examined by
724 comparing functional connectivity of homologous versus heterologous interhemispheric ROI-
725 ROI connectivity weights using a linear mixed-model with participants as random factor and
726 type (homo- or heterologous), week and group (control vs patients) as fixed factors,
727 supplemental results Figure S3.

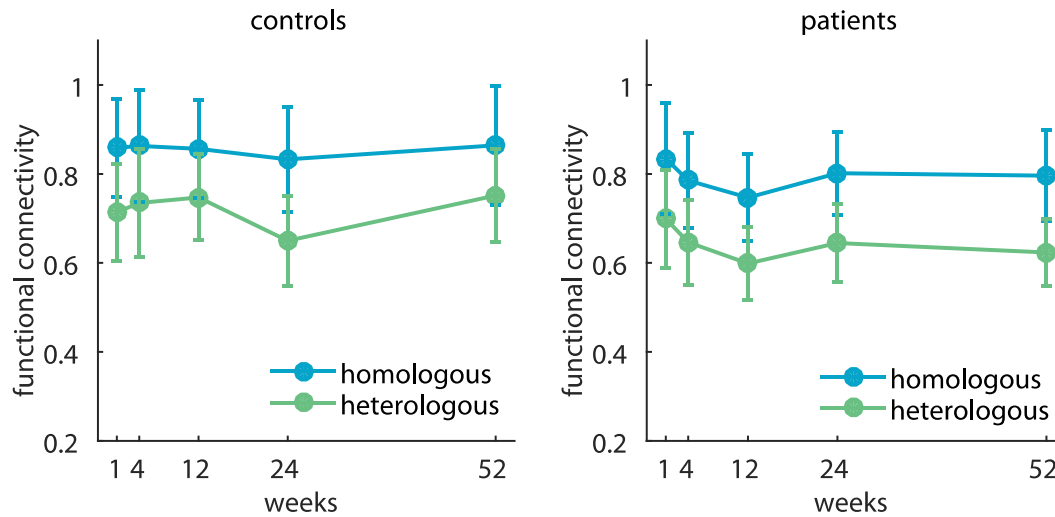
728

729 **Homo- versus Heterologous ROI connectivity**

730 We examined the differences in connectivity between homo- and heterologous ROI connection.
731 Homologous connectivity was significantly higher than connections between heterologous ROIs
732 ($\chi^2(1) = 108.38$, $p < 0.001$) and this effect showed no changes over time $\chi^2(4) = 5.8993$, $p =$
733 0.207), Figure S1. Furthermore, we found no differences for this effect between patients and
734 controls (type*group $\chi^2(1) = 2.2701$, $p = 0.132$ and type*week*group $\chi^2(1) = 2.2187$, $p = 0.136$),
735 Figure S3.

736

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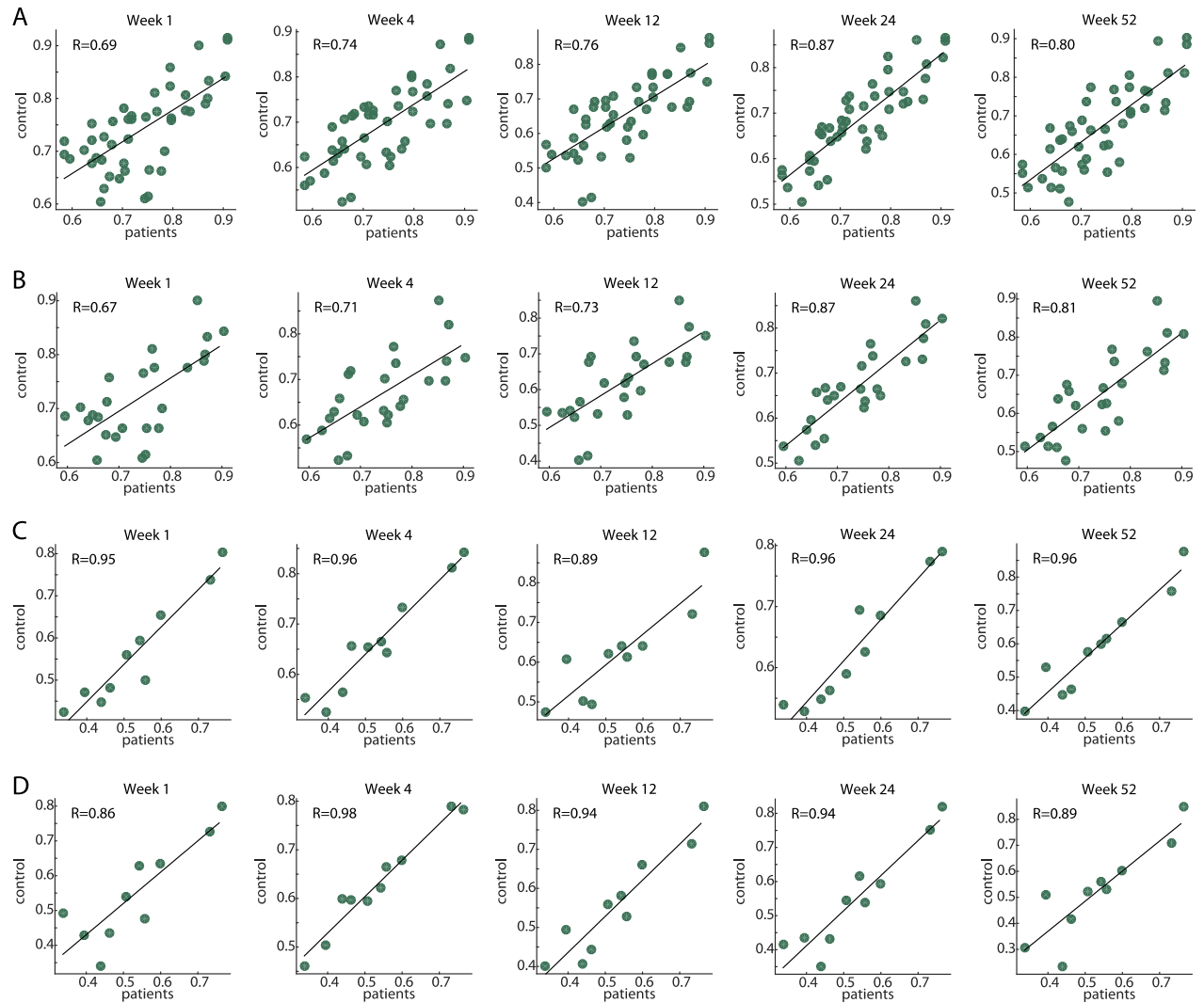


737

738 Figure S3: Average connectivity of interhemispheric homologous versus heterologous ROI-ROI
739 connectivity weights. Homologous regions (e.g. M1-M1, S1-S1, blue line) were higher
740 correlated than heterologous regions (e.g. M1-PmV, PmV-S1, green line). This did not change
741 over the course of a year and no systematic difference was found between both groups (patients
742 right panel, control left panel).

743 7.2.2 Correlations between patient and control connectivity patterns

744 Connectivity patterns for patients and controls were highly correlated in the early period after
745 stroke as well as at all subsequent measured time-points over the year (*all connections*: W1: R =
746 0.69, $p = 0.0002$; W4: R = 0.74, $p < 0.0001$; W12: R = 0.76, $p < 0.0001$; W24: R = 0.87, $p = 0.0001$;
747 W52: R = 0.80, $p < 0.0001$; *interhemispheric*: W1: R = 0.67, $p = 0.0002$; W4: R = 0.71, $p < 0.0001$;
748 W12: R = 0.73, $p < 0.0001$; W24: R = 0.87, $p < 0.0001$; W52: R = 0.81, $p < 0.0001$; *intrahemispheric*
749 *lesioned*: W1: R = 0.95, $p < 0.0001$; W4: R = 0.96, $p = 0.0088$; W12: R = 0.89, $p = 0.0006$; W24:
750 R = 0.96, $p = 0.0129$; W52: R = 0.96, $p < 0.0001$; *intrahemispheric non-lesioned*: W1: R = 0.86, p
751 $= 0.0014$; W4: R = 0.98, $p = 0.0089$; W12: R = 0.94, $p < 0.0001$; W24: R = 0.94, $p = 0.0001$; W52:
752 R = 0.89, $p = 0.0006$; Figure S4).



753

754 Figure S4: Correlations of connectivity patterns for patients (x-axis) and controls (y-axis) at each

755 week. A) all connections, B) interhemispheric, C) intrahemispheric lesioned, D) intrahemispheric

756 non-lesioned connectivity patterns.

757

758 8 References

759 Asanuma H & Okamoto K. (1959). Unitary study on evoked activity of callosal neurons and its
760 effect on pyramidal tract cell activity on cats. *The Japanese Journal of Physiology*.

761 Baker, M. (2016, May 26). 1,500 scientists lift the lid on reproducibility. *Nature*, pp. 452–454.

Cortical reorganization after stroke

- 762 <http://doi.org/10.1038/533452a>
- 763 Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models
764 Using lme4. *Journal of Statistical Software*, 67(1). <http://doi.org/10.18637/jss.v067.i01>
- 765 Bennett, C. M., & Miller, M. B. (2010). How reliable are the results from functional magnetic
766 resonance imaging? *Annals of the New York Academy of Sciences*, 1191(1), 133–155.
767 <http://doi.org/10.1111/j.1749-6632.2010.05446.x>
- 768 Birn, R. M. (2012). The role of physiological noise in resting-state functional connectivity.
769 *NeuroImage*, 62(2), 864–870. <http://doi.org/10.1016/j.neuroimage.2012.01.016>
- 770 Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the
771 motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in*
772 *Medicine*, 34(4), 537–541.
- 773 Brookes, M. J., Woolrich, M., Luckhoo, H., Price, D., Hale, J. R., Stephenson, M. C., et al.
774 (2011). Investigating the electrophysiological basis of resting state networks using
775 magnetoencephalography. *Proceedings of the National Academy of Sciences of the United*
776 *States of America*, 108(40), 16783–16788. <http://doi.org/10.1073/pnas.1112685108>
- 777 Buckner, R. L., Krienen, F. M., & Yeo, B. T. T. (2013). Opportunities and limitations of intrinsic
778 functional connectivity MRI. *Nature Neuroscience*, 16(7), 832–837.
779 <http://doi.org/10.1038/nn.3423>
- 780 Byblow, W. D., Stinear, C. M., Barber, P. A., Petoe, M. A., & Ackerley, S. J. (2015).
781 Proportional recovery after stroke depends on corticomotor integrity. *Annals of Neurology*,
782 78(6), 848–859. <http://doi.org/10.1002/ana.24472>
- 783 Carmichael, S. T. (2016). Plasticity of Cortical Projections after Stroke. *The Neuroscientist*, 9(1),
784 64–75. <http://doi.org/10.1177/1073858402239592>
- 785 Carter, A. R., Astafiev, S. V., Lang, C. E., Connor, L. T., Rengachary, J., Strube, M. J., et al.
786 (2010). Resting interhemispheric functional magnetic resonance imaging connectivity
787 predicts performance after stroke. *Annals of Neurology*, 67(3), 365–375.
788 <http://doi.org/10.1002/ana.21905>
- 789 Censor, N., Horowitz, S. G., & Cohen, L. G. (2014). Interference with existing memories alters
790 offline intrinsic functional brain connectivity. *Neuron*, 81(1), 69–76.
791 <http://doi.org/10.1016/j.neuron.2013.10.042>
- 792 Cerri, G., Shimazu, H., Maier, M. A., & Lemon, R. N. (2003). Facilitation from ventral premotor
793 cortex of primary motor cortex outputs to macaque hand muscles. *Journal of*
794 *Neurophysiology*, 90(2), 832–842. <http://doi.org/10.1152/jn.01026.2002>
- 795 Chen, J. L., & Schlaug, G. (2013). Resting state interhemispheric motor connectivity and white
796 matter integrity correlate with motor impairment in chronic stroke. *Frontiers in Neurology*,
797 4, 178. <http://doi.org/10.3389/fneur.2013.00178>
- 798 Cole, D. M., Smith, S. M., & Beckmann, C. F. (2010). Advances and Pitfalls in the Analysis and
799 Interpretation of Resting-State fMRI Data. *Frontiers in Systems Neuroscience*, 4.
800 <http://doi.org/10.3389/fnsys.2010.00008>
- 801 Cortes, J. C., Goldsmith, J., Harran, M. D., Xu, J., Kim, N., Schambra, H. M., et al. (2017). A
802 Short and Distinct Time Window for Recovery of Arm Motor Control Early After Stroke
803 Revealed with a Global Measure of Trajectory Kinematics. *Neurorehabilitation and Neural*
804 *Repair*, 31(6), 552–560. <http://doi.org/10.1177/1545968317697034>
- 805 Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation
806 and surface reconstruction. *NeuroImage*, 9(2), 179–194.
807 <http://doi.org/10.1006/nimg.1998.0395>

- 808 Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: a review of
809 studies combining structural connectivity and resting-state functional connectivity. *Brain*
810 *Structure & Function*, 213(6), 525–533. <http://doi.org/10.1007/s00429-009-0208-6>
- 811 Dancause, N., & Nudo, R. J. (2011). Shaping plasticity to enhance recovery after injury. *Progress*
812 *in Brain Research*, 192, 273–295. <http://doi.org/10.1016/B978-0-444-53355-5.00015-4>
- 813 Dancause, N., Barbay, S., Frost, S. B., Plautz, E. J., Chen, D., Zoubina, E. V., et al. (2005).
814 Extensive cortical rewiring after brain injury. *The Journal of Neuroscience: The Official*
815 *Journal of the Society for Neuroscience*, 25(44), 10167–10179.
816 <http://doi.org/10.1523/JNEUROSCI.3256-05.2005>
- 817 Ejaz, N., Xu, J., Branscheidt, M., Hertler, B., Schambra, H., Widmer, M., et al. (2018). Evidence
818 for a subcortical origin of mirror movements after stroke: a longitudinal study. *Brain: a*
819 *Journal of Neurology*, 141(3), 837–847. <http://doi.org/10.1093/brain/awx384>
- 820 Fischl, B., Rajendran, N., Busa, E., Augustinack, J., Hinds, O., Yeo, B. T. T., et al. (2008).
821 Cortical folding patterns and predicting cytoarchitecture. *Cerebral Cortex (New York, N.Y.:*
822 *1991)*, 18(8), 1973–1980. <http://doi.org/10.1093/cercor/bhm225>
- 823 Florence, S. L., Taub, H. B., & Kaas, J. H. (1998). Large-scale sprouting of cortical connections
824 after peripheral injury in adult macaque monkeys. *Science*, 282(5391), 1117–1121.
- 825 Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with
826 functional magnetic resonance imaging. *Nature Reviews. Neuroscience*, 8(9), 700–711.
827 <http://doi.org/10.1038/nrn2201>
- 828 Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous
829 neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of*
830 *the National Academy of Sciences of the United States of America*, 103(26), 10046–10051.
831 <http://doi.org/10.1073/pnas.0604187103>
- 832 Friston, K. J. (2011). Functional and effective connectivity: a review. *Brain Connectivity*, 1(1),
833 13–36. <http://doi.org/10.1089/brain.2011.0008>
- 834 Frost, S. B., Barbay, S., Friel, K. M., Plautz, E. J., & Nudo, R. J. (2003). Reorganization of
835 remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery.
836 *Journal of Neurophysiology*, 89(6), 3205–3214. <http://doi.org/10.1152/jn.01143.2002>
- 837 Fugl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S., & Steglind, S. (1975). The post-stroke
838 hemiplegic patient. 1. a method for evaluation of physical performance. *Scandinavian*
839 *Journal of Rehabilitation Medicine*, 7(1), 13–31.
- 840 Golestani, A.-M., & Goodyear, B. G. (2011). A resting-state connectivity metric independent of
841 temporal signal-to-noise ratio and signal amplitude. *Brain Connectivity*, 1(2), 159–167.
842 <http://doi.org/10.1089/brain.2011.0003>
- 843 Golestani, A.-M., Tymchuk, S., Demchuk, A., Goodyear, B. G., VISION-2 Study Group. (2013).
844 Longitudinal evaluation of resting-state fMRI after acute stroke with hemiparesis.
845 *Neurorehabilitation and Neural Repair*, 27(2), 153–163.
846 <http://doi.org/10.1177/1545968312457827>
- 847 Grefkes, C., & Ward, N. S. (2014). Cortical reorganization after stroke: how much and how
848 functional? *The Neuroscientist: a Review Journal Bringing Neurobiology, Neurology and*
849 *Psychiatry*, 20(1), 56–70. <http://doi.org/10.1177/1073858413491147>
- 850 He, H., & Liu, T. T. (2012). A geometric view of global signal confounds in resting-state
851 functional MRI. *NeuroImage*.
- 852 Ioannidis, J. P. A., Greenland, S., Hlatky, M. A., Khoury, M. J., Macleod, M. R., Moher, D., et
853 al. (2014). Increasing value and reducing waste in research design, conduct, and analysis.

Cortical reorganization after stroke

- 854 Lancet (London, England), 383(9912), 166–175. <http://doi.org/10.1016/S0140->
855 [6736\(13\)62227-8](http://doi.org/10.1016/S0140-6736(13)62227-8)
- 856 Kerr, N. L. (1998). HARKing: hypothesizing after the results are known. *Personality and Social*
857 *Psychology Review: an Official Journal of the Society for Personality and Social*
858 *Psychology, Inc*, 2(3), 196–217. http://doi.org/10.1207/s15327957pspr0203_4
- 859 Krakauer, J. W. (2004). Functional imaging of motor recovery after stroke: remaining
860 challenges. *Current Neurology and Neuroscience Reports*, 4(1), 42–46.
- 861 Krakauer, J. W. (2007). Avoiding performance and task confounds: multimodal investigation of
862 brain reorganization after stroke rehabilitation. *Experimental Neurology*, 204(2), 491–495.
863 <http://doi.org/10.1016/j.expneurol.2006.12.026>
- 864 Krakauer, J. W., & Carmichael, S. T. (2017). *Broken Movement*. MIT Press.
- 865 Lee, J. K. (2004). Nogo Receptor Antagonism Promotes Stroke Recovery by Enhancing Axonal
866 Plasticity. *Journal of Neuroscience*, 24(27), 6209–6217.
867 <http://doi.org/10.1523/JNEUROSCI.1643-04.2004>
- 868 Lee, J., Lee, A., Kim, H., Chang, W. H., & Kim, Y.-H. (2018). Differences in motor network
869 dynamics during recovery between supra- and infra-tentorial ischemic strokes. *Human Brain*
870 *Mapping*, 39(12), 4976–4986. <http://doi.org/10.1002/hbm.24338>
- 871 Li, S., Nie, E. H., Yin, Y., Benowitz, L. I., Tung, S., Vinters, H. V., et al. (2015). GDF10 is a
872 signal for axonal sprouting and functional recovery after stroke. *Nature Neuroscience*,
873 18(12), 1737–1745. <http://doi.org/10.1038/nn.4146>
- 874 Lin, L. Y., Ramsey, L., Metcalf, N. V., Rengachary, J., Shulman, G. L., Shimony, J. S., &
875 Corbetta, M. (2018). Stronger prediction of motor recovery and outcome post-stroke by
876 cortico-spinal tract integrity than functional connectivity. *PloS One*, 13(8), e0202504.
877 <http://doi.org/10.1371/journal.pone.0202504>
- 878 Liu, Y., & Rouiller, E. M. (1999). Mechanisms of recovery of dexterity following unilateral
879 lesion of the sensorimotor cortex in adult monkeys. *Experimental Brain Research*.
880 *Experimentelle Hirnforschung. Expérimentation Cérébrale*, 128(1-2), 149–159.
- 881 Macleod, M. R., Michie, S., Roberts, I., Dirnagl, U., Chalmers, I., Ioannidis, J. P. A., et al.
882 (2014). Biomedical research: increasing value, reducing waste. *Lancet* (London, England),
883 383(9912), 101–104. [http://doi.org/10.1016/S0140-6736\(13\)62329-6](http://doi.org/10.1016/S0140-6736(13)62329-6)
- 884 Mawase, F., Bar-Haim, S., & Shmuelof, L. (2017). Formation of Long-Term Locomotor
885 Memories Is Associated with Functional Connectivity Changes in the Cerebellar-Thalamic-
886 Cortical Network. *The Journal of Neuroscience: the Official Journal of the Society for*
887 *Neuroscience*, 37(2), 349–361. <http://doi.org/10.1523/JNEUROSCI.2733-16.2017>
- 888 Miyai, I., Suzuki, T., Kang, J., Kubota, K., & Volpe, B. T. (1999). Middle cerebral artery stroke
889 that includes the premotor cortex reduces mobility outcome. *Stroke*, 30(7), 1380–1383.
- 890 Miyai, I., Yagura, H., Oda, I., Konishi, I., Eda, H., Suzuki, T., & Kubota, K. (2002). Premotor
891 cortex is involved in restoration of gait in stroke. *Annals of Neurology*, 52(2), 188–194.
892 <http://doi.org/10.1002/ana.10274>
- 893 Moxon, K. A., Oliviero, A., Aguilar, J., & Foffani, G. (2014). Cortical reorganization after spinal
894 cord injury: always for good? *Neuroscience*, 283, 78–94.
895 <http://doi.org/10.1016/j.neuroscience.2014.06.056>
- 896 Munafò, M. R., Nosek, B. A., Bishop, D. V. M., Button, K. S., Chambers, C. D., Percie du Sert,
897 N., et al. (2017). A manifesto for reproducible science. *Nature Human Behaviour*, 1(1),
898 0021. <http://doi.org/10.1038/s41562-016-0021>
- 899 Napieralski, J. A., Butler, A. K., & Chesselet, M. F. (1996). Anatomical and functional evidence

- 900 for lesion-specific sprouting of corticostriatal input in the adult rat. *The Journal of*
901 *Comparative Neurology*, 373(4), 484–497. [http://doi.org/10.1002/\(SICI\)1096-](http://doi.org/10.1002/(SICI)1096-9861(19960930)373:4<484::AID-CNE2>3.0.CO;2-Y)
902 9861(19960930)373:4<484::AID-CNE2>3.0.CO;2-Y
- 903 Nijboer, T. C. W., Buma, F. E., Winters, C., Vansteensel, M. J., Kwakkel, G., Ramsey, N. F., &
904 Raemaekers, M. (2017). No changes in functional connectivity during motor recovery
905 beyond 5 weeks after stroke; A longitudinal resting-state fMRI study. *PloS One*, 12(6),
906 e0178017. <http://doi.org/10.1371/journal.pone.0178017>
- 907 Nosek, B. A., Alter, G., Banks, G. C., Borsboom, D., Bowman, S. D., Breckler, S. J., et al.
908 (2015). SCIENTIFIC STANDARDS. Promoting an open research culture. *Science* (New
909 York, N.Y.), 348(6242), 1422–1425. <http://doi.org/10.1126/science.aab2374>
- 910 Nudo, R. J. (2006). Mechanisms for recovery of motor function following cortical damage.
911 *Current Opinion in Neurobiology*, 16(6), 638–644.
912 <http://doi.org/10.1016/j.conb.2006.10.004>
- 913 Nuzzo, R. (2015, October 8). How scientists fool themselves - and how they can stop. *Nature*,
914 pp. 182–185. <http://doi.org/10.1038/526182a>
- 915 Overman, J. J., Clarkson, A. N., Wanner, I. B., Overman, W. T., Eckstein, I., Maguire, J. L., et
916 al. (2012). A role for ephrin-A5 in axonal sprouting, recovery, and activity-dependent
917 plasticity after stroke. *Proceedings of the National Academy of Sciences of the United States*
918 *of America*, 109(33), E2230–9. <http://doi.org/10.1073/pnas.1204386109>
- 919 Park, C.-H., Chang, W. H., Ohn, S. H., Kim, S. T., Bang, O. Y., Pascual-Leone, A., & Kim, Y.-
920 H. (2011). Longitudinal changes of resting-state functional connectivity during motor
921 recovery after stroke. *Stroke; a Journal of Cerebral Circulation*, 42(5), 1357–1362.
922 <http://doi.org/10.1161/STROKEAHA.110.596155>
- 923 Picard, N., & Strick, P. L. (1996). Motor Areas of the Medial Wall: A Review of Their Location
924 and Functional Activation. *Cerebral Cortex* (New York, NY), 6(3), 342–353.
925 <http://doi.org/10.1093/cercor/6.3.342>
- 926 Radlinska, B., Ghinani, S., Leppert, I. R., Minuk, J., Pike, G. B., & Thiel, A. (2010). Diffusion
927 tensor imaging, permanent pyramidal tract damage, and outcome in subcortical stroke.
928 *Neurology*, 75(12), 1048–1054. <http://doi.org/10.1212/WNL.0b013e3181f39aa0>
- 929 Rehme, A. K., Eickhoff, S. B., Rottschy, C., Fink, G. R., & Grefkes, C. (2012). Activation
930 likelihood estimation meta-analysis of motor-related neural activity after stroke.
931 *NeuroImage*, 59(3), 2771–2782. <http://doi.org/10.1016/j.neuroimage.2011.10.023>
- 932 Salimi-Khorshidi, G., Douaud, G., Beckmann, C. F., Glasser, M. F., Griffanti, L., & Smith, S. M.
933 (2014). Automatic denoising of functional MRI data: combining independent component
934 analysis and hierarchical fusion of classifiers. *NeuroImage*, 90, 449–468.
935 <http://doi.org/10.1016/j.neuroimage.2013.11.046>
- 936 Shimazu, H., Maier, M. A., Cerri, G., Kirkwood, P. A., & Lemon, R. N. (2004). Macaque ventral
937 premotor cortex exerts powerful facilitation of motor cortex outputs to upper limb
938 motoneurons. *The Journal of Neuroscience: the Official Journal of the Society for*
939 *Neuroscience*, 24(5), 1200–1211. <http://doi.org/10.1523/JNEUROSCI.4731-03.2004>
- 940 Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-
941 Berg, H., et al. (2004). Advances in functional and structural MR image analysis and
942 implementation as FSL. *NeuroImage*, 23 Suppl 1, S208–19.
943 <http://doi.org/10.1016/j.neuroimage.2004.07.051>
- 944 Starkey, M. L., Bleul, C., Zörner, B., Lindau, N. T., Mueggler, T., Rudin, M., & Schwab, M. E.
945 (2012). Back seat driving: hindlimb corticospinal neurons assume forelimb control following

Cortical reorganization after stroke

- 946 ischaemic stroke. *Brain : a Journal of Neurology*, 135(Pt 11), 3265–3281.
947 <http://doi.org/10.1093/brain/aws270>
- 948 Thiel, A., & Vahdat, S. (2015). Structural and resting-state brain connectivity of motor networks
949 after stroke. *Stroke; a Journal of Cerebral Circulation*, 46(1), 296–301.
950 <http://doi.org/10.1161/STROKEAHA.114.006307>
- 951 Vahdat, S., Darainy, M., Milner, T. E., & Ostry, D. J. (2011). Functionally specific changes in
952 resting-state sensorimotor networks after motor learning. *The Journal of Neuroscience: the*
953 *Official Journal of the Society for Neuroscience*, 31(47), 16907–16915.
954 <http://doi.org/10.1523/JNEUROSCI.2737-11.2011>
- 955 van Meer, M. P. A., van der Marel, K., Otte, W. M., Berkelbach van der Sprenkel, J. W., &
956 Dijkhuizen, R. M. (2010). Correspondence between altered functional and structural
957 connectivity in the contralesional sensorimotor cortex after unilateral stroke in rats: a
958 combined resting-state functional MRI and manganese-enhanced MRI study. *Journal of*
959 *Cerebral Blood Flow and Metabolism: Official Journal of the International Society of*
960 *Cerebral Blood Flow and Metabolism*, 30(10), 1707–1711.
961 <http://doi.org/10.1038/jcbfm.2010.124>
- 962 van den Heuvel, M. P., Mandl, R. C. W., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally
963 linked resting-state networks reflect the underlying structural connectivity architecture of the
964 human brain. *Human Brain Mapping*, 30(10), 3127–3141. <http://doi.org/10.1002/hbm.20737>
- 965 Wahl, A. S., Omlor, W., Rubio, J. C., Chen, J. L., Zheng, H., Schroter, A., et al. (2014).
966 Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat
967 corticospinal tract after stroke. *Science (New York, N.Y.)*, 344(6189), 1250–1255.
968 <http://doi.org/10.1126/science.1253050>
- 969 Wang, C., Qin, W., Zhang, J., Tian, T., Li, Y., Meng, L., et al. (2014). Altered functional
970 organization within and between resting-state networks in chronic subcortical infarction.
971 *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International*
972 *Society of Cerebral Blood Flow and Metabolism*, 34(4), 597–605.
973 <http://doi.org/10.1038/jcbfm.2013.238>
- 974 Warraich, Z., & Kleim, J. A. (2010). Neural plasticity: the biological substrate for
975 neurorehabilitation. *PM & R : the Journal of Injury, Function, and Rehabilitation*, 2(12 Suppl
976 2), S208–19. <http://doi.org/10.1016/j.pmrj.2010.10.016>
- 977 Weissenbacher, A., Kasess, C., Gerstl, F., Lanzenberger, R., Moser, E., & Windischberger, C.
978 (2009). Correlations and anticorrelations in resting-state functional connectivity MRI: A
979 quantitative comparison of preprocessing strategies. *NeuroImage*, 47(4), 1408–1416.
980 <http://doi.org/10.1016/j.neuroimage.2009.05.005>
- 981 Wittenberg, G. F. (2010). Experience, cortical remapping, and recovery in brain disease.
982 *Neurobiology of Disease*, 37(2), 252–258. <http://doi.org/10.1016/j.nbd.2009.09.007>
- 983 Xu, J., Ejaz, N., Hertler, B., Branscheidt, M., Widmer, M., Faria, A. V., et al. (2017). Separable
984 systems for recovery of finger strength and control after stroke. *Journal of Neurophysiology*,
985 *jn.00123.2017*. <http://doi.org/10.1152/jn.00123.2017>
- 986 Yousry, T. (1997). Localization of the motor hand area to a knob on the precentral gyrus. A new
987 landmark. *Brain: a Journal of Neurology*, 120(1), 141–157.
988 <http://doi.org/10.1093/brain/120.1.141>
- 989 Yozbatiran, N., Der-Yeghiaian, L., & Cramer, S. C. (2008). A Standardized Approach to
990 Performing the Action Research Arm Test. *Neurorehabilitation and Neural Repair*, 22(1),
991 78–90. <http://doi.org/10.1177/1545968307305353>

- 992 Zaaami, B., Edgley, S. A., Soteropoulos, D. S., & Baker, S. N. (2012). Changes in descending
993 motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain: a*
994 *Journal of Neurology*.
- 995 Zarahn, E., Alon, L., Ryan, S. L., Lazar, R. M., Vry, M. S., Weiller, C., et al. (2011). Prediction
996 of Motor Recovery Using Initial Impairment and fMRI 48 h Poststroke. *Cerebral Cortex*
997 *(New York, NY)*, 21(12), 2712–2721. <http://doi.org/10.1093/cercor/bhr047>
- 998 Zuo, X.-N., & Xing, X.-X. (2014). Test-retest reliabilities of resting-state FMRI measurements in
999 human brain functional connectomics: A systems neuroscience perspective. *Neuroscience &*
1000 *Biobehavioral Reviews*, 45, 100–118. <http://doi.org/10.1016/j.neubiorev.2014.05.009>
1001
1002