



Periinfarct rewiring supports recovery after primary motor cortex stroke

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Abstract

After stroke restricted to the primary motor cortex (M1), it is uncertain whether network reorganization associated with recovery involves the periinfarct or more remote regions. We studied 16 patients with focal M1 stroke and hand paresis. Motor function and resting-state MRI functional connectivity (FC) were assessed at three time points: acute (<10 days), early subacute (3 weeks), and late subacute (3 months). FC correlates of recovery were investigated at three spatial scales, (i) ipsilesional non-infarcted M1, (ii) core motor network (M1, premotor cortex (PMC), supplementary motor area (SMA), and primary somatosensory cortex), and (iii) extended motor network including all regions structurally connected to the upper limb representation of M1. Hand dexterity was impaired only in the acute phase ($P = 0.036$). At a small spatial scale, clinical recovery was more frequently associated with connections involving ipsilesional non-infarcted M1 (Odds Ratio = 6.29; $P = 0.036$). At a larger scale, recovery correlated with increased FC strength in the core network compared to the extended motor network ($\rho = 0.71$; $P = 0.006$). These results suggest that FC changes associated with motor improvement involve the perilesional M1 and do not extend beyond the core motor network. Core motor regions, and more specifically ipsilesional non-infarcted M1, could hence become primary targets for restorative therapies.

Keywords

Functional connectivity, network, primary motor cortex, recovery, stroke

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Introduction

The severity of paresis after stroke is mainly determined by the localization and extent of the lesion.¹ In contrast, the neural correlates of motor recovery are less well defined. Reorganization in brain networks is increasingly identified as a surrogate of clinical recovery.^{2,3} However, whether this process differently affects local perilesional tissue⁴ and distant cortical areas³ remains largely unknown, limiting the development of efficient restorative therapies.

After stroke limited to the primary motor cortex (M1), the clinical relevance of connectivity changes from and to the perilesional tissue has not been determined in humans. In non-human primates with M1 lesion, new transcallosal and intrahemispheric axons reinnervate the adjacent M1 during recovery.^{5–7} In rodents, improved motor function is related to restoration of interhemispheric functional connectivity (FC)

involving the peri-infarct.⁸ In humans, difficulties to recruit patients with reproducible focal cortical lesions make it challenging to establish the clinical relevance of connection changes with the peri-infarct. Human and non-human primate studies reporting selective M1 lesions are limited to small case series.^{9–11}

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Beyond the peri-infarct, limited knowledge exists on how stroke restricted to M1 affects the core motor network that includes M1, the premotor cortex (PMC), the supplementary motor area (SMA), and the primary somatosensory cortex (S1). In non-human primates, such lesions trigger new connections, between ipsilesional M1 and contralesional PMC, and between M1 and S1 in the lesioned hemisphere.⁶ Following subcortical strokes in humans, motor recovery is consistently associated with restoration of connections between ipsilesional M1 and contralesional core motor areas including M1,^{12,13} suggesting a pivotal role of interhemispheric connections.¹⁴ The heterogeneity of lesion size and location is however a usual limitation of human studies, especially with cortical involvement. It is therefore unclear whether connectivity changes in the core motor network of patients with cortical lesions restricted to M1 are clinically relevant.

At a larger scale, how brain areas beyond the core motor network contribute to recovery after M1 stroke has not been established in human nor in animal studies. Stroke-induced motor deficits are more explained by lesion location than large-scale changes in functional networks.^{1,15} Furthermore, computational simulation of M1 “lesions” results in connectivity changes of limited spatial extent.¹⁶ Conflicting evidence exist regarding the impact of strokes beyond the core motor network, in patients with heterogeneous lesions.¹⁷ So far, no studies have specifically compared the functional relevance of FC changes within and outside the core motor network, in patients with stroke restricted to M1.

We investigated the FC correlates of motor recovery in a unique population of patients with strokes limited to M1. The following hypotheses were tested:

- (i) Restoration of function correlates with increased FC involving the ipsilesional non-infarcted M1.
- (ii) Lesions of M1 affect the core motor network rather than larger-scale networks.

We performed detailed motor examinations and assessed resting-state MRI FC at three time points within 3 months of stroke. We used a fine-grained parcellation of motor areas to evaluate FC changes at different scales, from individual connections within the core motor network to global changes within and outside the core motor network.

Material and methods

We prospectively included 16 consecutive stroke patients with a lesion restricted to M1 and contralateral hand paresis, among 1656 stroke patients admitted in our Stroke Center during the study period. All patients

were right-handed (10 males; age 72.9 ± 11.9 y; Figure 1, Supplementary Table 1, Supplementary Figure I). Exclusion criteria were significant carotid or intracranial artery stenosis (>50%), history of psychiatric disease, concomitant psychotropic medications, clinical or radiological evidence of previous stroke, relevant white matter disease (Fazekas score > 2). All patients underwent standard physical therapy. Detailed motor function and imaging data were obtained at three time points (TP) during recovery: acute (TP1; <10 days after stroke), early subacute (TP2; 3 weeks), and late subacute stage (TP3; 3 months).¹⁸ In three patients, one MRI scanning session was not performed due to technical issues (N=2) and patient refusal (N=1). Therefore, correlations between MRI data and between clinical and MRI data over time (TP1 vs TP2 and TP2 and TP3) were based on the analysis of 14 pairs. For control purposes, the same behavioural and imaging measures were acquired at one time point in 16 right-handed healthy subjects matched for age, gender, and cardiovascular risk factors (10 males; 70.3 ± 9.7 y). The study was conducted in accordance with the Helsinki declaration and was approved by the local ethics committee (Commission cantonale d'éthique de la recherche de Genève). Written informed consent was obtained from each participant.

Behavioural measures

We assessed hand motor function using measures of dexterity (nine-hole pegboard task), isometric grip strength (JAMAR dynamometer, Asimow Engineering Co., Los Angeles, CA), the Fugl-Meyer and NIH stroke scales (see Supplementary Table 1). A two-point discrimination test was performed on the index fingers to rule out sensory deficits. For dexterity and grip strength, performance of the paretic hand was normalized by performance of the unaffected hand, leading to a laterality ratio (i.e., paretic/unaffected hand performance). Thus, the laterality ratio is >1 when dexterity of one hand is impaired and tends towards 1 when the paretic hand improves (and the opposite for grip strength). Due to data non-normality (Kolmogorov-Smirnov test), we used Wilcoxon tests to assess recovery of motor hand function over time.

Imaging acquisition

All images were obtained on a 3T MRI (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany; 64-channel head-coil) on the same day as behavioural testing. Resting state functional images were acquired with a gradient EPI sequence (TE/TR = 30/1200 ms, voxel size = 3 mm

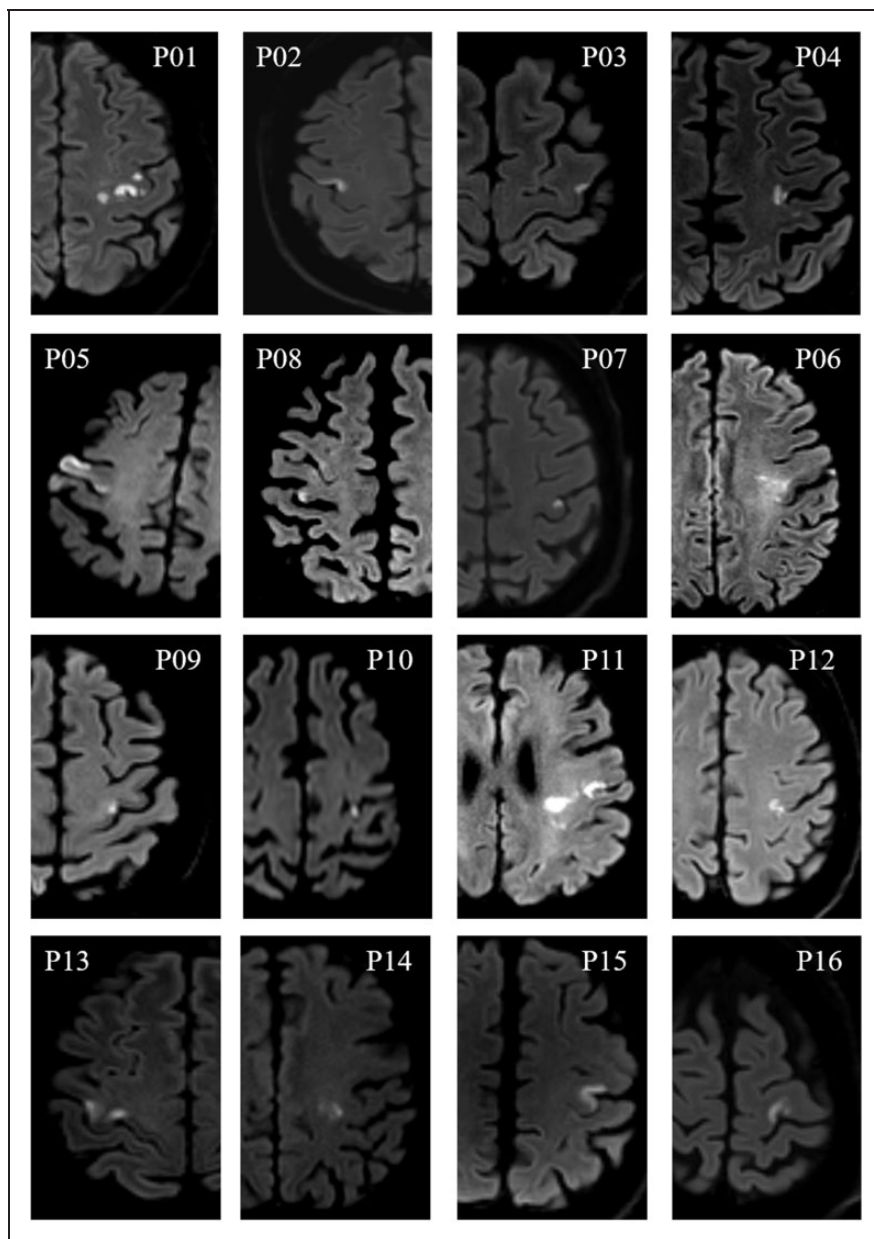


Figure 1. Lesions in the primary motor cortex (axial DWI, radiological convention).

isotropic, 400 volumes). Wakefulness was monitored using eye-tracking. Respiratory movements were recorded using a transducer at the level of maximum respiratory expansion (BioPac Inc, Santa Barbara, USA). T1 anatomical scans were collected using an MPRAGE sequence (TE/TR = 2.27/2300 ms, voxel size = 1.0 mm³ isotropic). T2-weighted (TE/TR = 108/6090 ms, voxel size = 0.4 × 0.4 × 4.0 mm) and DWI (TE/TR = 52/4300 ms, voxel size = 1.4 × 1.4 × 4.0 mm) sequences were acquired for lesion mapping. Brain MRI angiography (TOF) and precerebral Doppler ultrasound were performed to rule out intracranial or precerebral stenosis.

Delineation of the infarct

Each infarct was delineated on T2 images (with help from DWI images) by experienced stroke neurologists/neuroscientists (MVA, EC, ED). We used MRICron for outlining and estimating lesion volumes (<https://people.cas.sc.edu/rorden/index.html>).

Data analysis

Overall strategy. In patients with similar M1 lesions, we investigated the FC correlates of hand motor recovery at three time points within three months of stroke. Two approaches were considered. In the first, small scale

approach, we studied the correlation between recovery and FC changes in individual connections of the core motor network, focusing on the ipsilesional non-infarcted M1. In the second approach, we compared the global impact of stroke on the core and on a larger scale motor network using the measure of global connectivity strength. To that purpose, we identified relevant connections using Network-Based Statistics (NBS). Regions of interest (ROIs) were defined within the Brainnetome atlas,¹⁹ which subdivides M1 into five subregions consistent with the motor homunculus, including the upper limb area (A4ul). Moreover, this cross-validated connectivity-based atlas provides a structural connectome for all subregions referenced in this atlas.

Functional connectivity pre-processing. Anatomical and functional data were preprocessed using SPM12 (www.fil.ion.ucl.ac.uk/spm) and in-house MATLAB scripts.²⁰ Functional images were realigned for each subject. T1 anatomical images were co-registered to the mean image of the functional data and segmented into grey matter, white matter, and cerebrospinal fluid (CSF) tissue maps. The Brainnetome atlas was then mapped onto the native grey matter map and co-registered to the functional images. The following regressors were introduced (i) the six motion parameters, (ii) the average CSF signal, and (iii) respiratory fluctuations using RETROICOR.²¹ Time-courses were filtered in 4 frequency subbands using a wavelet transform. Analyses were centered on the frequency range $0.03 < f < 0.06$ Hz.²² We computed pairwise Pearson correlation coefficients between the 246 regions of the Brainnetome atlas¹⁹ and then obtained connectivity matrices for each subject, including the infarcted area. Finally, we flipped left and right hemisphere ROIs in patients with right lesions (N=4) to ensure consistency of lesion side across subjects.²³ There was no difference in motion across time points²⁴ (Friedman test; $\chi^2(2)=0.462$, $P=0.794$).

Anatomical definition of ROIs. We explored three distinct networks as follows: The *core motor network* comprised canonical sensorimotor cortical regions, namely, M1, PMC, SMA, and S1 (corresponding to a total of 28 regions in the Brainnetome atlas; full list in Supplementary Table 2); The *extended motor network* was defined based on the connectogram provided with the Brainnetome atlas,¹⁹ and included 106 ROIs structurally connected to A4ul (upper limb region of M1; see full list in Supplementary Table 2). We chose A4ul as the seed region for the definition of the extended motor network because (1) all patients presented with isolated hand paresis and (2) the M1 upper limb region was consistently damaged in our patients. The core

motor network was part of the extended motor network. Finally, the *non-core motor network* included all ROIs from the extended motor network that were not part of the core motor network.

Small-scale analysis: FC correlates of clinical recovery within the core motor network. We determined, for each connection within the core motor network, the correlation between FC changes and changes in motor dexterity across time as follows: Raw correlation coefficients were first extracted from the 28 ROIs, approximately Gaussianized using Fisher R-to-Z transform, and normalized by total strength (sum of edge weights). The final quantity of interest was the difference in Gaussianized, normalized FC between two consecutive time points. Correlations between temporal changes in individual connection values ($27 \times 28 / 2 = 378$ edges) and changes in hand dexterity were computed using Spearman correlation. The significance of each correlation was assessed using Storey's positive false discovery rate (pFDR) multiple comparison correction technique to account for the large number of edges. For each edge, we also calculated the median of the temporal FC changes across subjects (median delta FC) to show the trend of connectivity changes. Spearman correlation, uncorrected P -values, pFDR corrected P -values, and median delta FC are reported in Table 1. Finally, we tested whether top correlations between FC change and dexterity changes (those with $P < 0.01$ uncorrected) involved more frequently the ipsilesional M1 than expected by chance, using Fisher's exact test ($\alpha = 0.05$).

Large-scale analysis: Clinical relevance of global changes in FC over time. We first identified connected components (linked edges) showing the greatest FC increase (respectively decrease) over time by applying the NBS toolbox²⁵ to the extended motor network ($(106 \times 105) / 2 = 5565$ edges). In NBS, each paired t -statistic (between time point pairs) had to reach a value $|T| > 2.5$ for the connection to be retained for the next step of the analysis (equivalent $P < 0.01$). Then, supra-threshold connections were systematically searched for any interconnected components to derive networks of FC increase (or decrease) among the 106 ROIs. The null distribution of the connected component size was derived using a non-parametric permutation approach (5000 permutations). Finally, community structure in significant NBS networks was identified using the Louvain method, implemented in the Brain Connectivity Toolbox.²⁶ For ease of description, the 106 ROI of the extended motor network were labeled according to 15 regions (Supplementary Table 2).

We then computed the total strength (sum of edge weights) among edges showing increased (respectively

Table 1. Correlations between changes in FC and changes in hand dexterity (%) from TP1 (<10 days) to TP2 (3 weeks).

	Node 1	Node 2	rho	P value (uncorrected)	P value (pFDR)	Median delta FC
1	i A4tl	c A6dl	0.837	0.0003	0.0229	0.0189
2	i A6cvl	c A6dl	0.793	0.0012	0.0476	0.0435
3	i A6cvl	c A6cvl	0.741	0.0035	0.0973	-0.0699
4	i A4tl	c A6m	0.736	0.0038	0.0790	0.0931
5	i A4ll	c A4tl	0.732	0.0041	0.0683	0.1699
6	i A4tl	c A4hf	0.697	0.0073	0.1013	-0.1699
7	i A6dl	c_A4ul	-0.688	0.0084	0.0991	-0.0113
8	i A4t	i A6cvl	0.679	0.0095	0.0987	0.0149

Spearman correlations (rho) ($P < 0.01$ uncorrected) are displayed, as well as corresponding P values, and pFDR-corrected P values. Median delta FC is the cross-subject median of FC changes. A4 = M1 area; ll: lower limb; ul: upper limb; t: trunk; hf: head face; tl: tongue larynx; A6: area 6; dl: dorsolateral; m: medial (SMA); cdl: caudal dorsolateral; cvl: caudal ventrolateral; vl A1/2/3: Primary sensory cortex; tru: trunk; A2: area 2.

decreased) FC over time in the core and non-core motor networks, and assessed their correlations with changes in motor performance using Spearman coefficients. To evaluate whether the core motor was more engaged in clinical recovery than the non-core network, the clinical relevance of FC changes was further evaluated using the *strength fraction*,²⁷ defined here as the total strength ratio between the core and non-core motor network. BrainNet viewer²⁸ was used for data visualization.

Results

Motor behaviour

Hand dexterity (Nine hole peg test) significantly improved in patients from TP1 to TP2 (median laterality ratio at TP1: 1.18 (IQR = 1.06–1.71) and at TP2: 1.03 (IQR = 0.94–1.27); Wilcoxon test, $P = 0.01$) but not between TP2 and TP3 ($P = 1$; Figure 2). There was no change in grip strength (JAMAR dynamometer) between TP1 and TP2 ($P = 0.41$), nor between TP2 and TP3 ($P = 0.06$; Figure 2). Compared to controls, hand dexterity was significantly impaired at TP1 in stroke patients (median laterality ratio in controls = 1.06 (IQR = 0.98–1.1); Mann-Whitney test, $P = 0.036$), but not at TP2 ($P = 0.98$), nor at TP3 ($P = 0.42$). Grip strength was not different from controls at any time point (TP1: $P = 0.14$; TP2: $P = 0.21$; TP3: $P = 0.38$).

Motor deficit and lesion volume

Median lesion volume was 0.57 cm^3 (IQR = 0.38–1.6). Lesion volume correlated with loss of dexterity (Spearman rho = 0.67, $P = 0.005$), but not with recovery of motor function (dexterity from TP1 to TP2: $P = 0.47$).

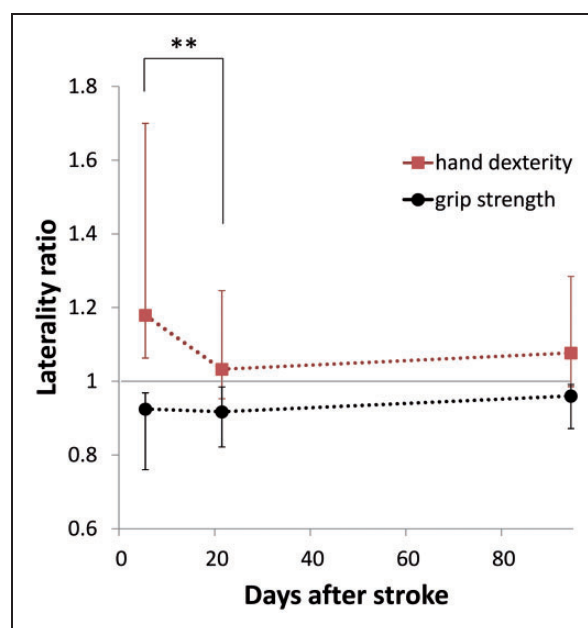


Figure 2. Evolution of motor performance over time. Laterality ratios of hand performance (medians) for hand dexterity (paretic/unaffected performance, in red) and grip strength (unaffected/paretic performance for illustration, in black) at three time points (acute: 3 days; early subacute: 3 weeks; late subacute: 3 months). Vertical bars represent 25–75th percentiles. $**P = 0.01$.

Changes in functional networks and recovery

Small-scale analysis: FC correlates of clinical recovery within the core motor network. Table 1 shows correlations between FC changes of individual connections and clinical recovery. 2 connections had significant correlations after multiple comparisons corrections (pFDR < 0.05: iA4tl -cA6dl rho = 0.837; pFDR = 0.023 and iA6cvl -cA6dl; rho = 0.793; pFDR = 0.048) (Table 1, Figure 3 and Supplementary Figure II). 8 connections had weaker, non-significant correlations ($P < 0.01$ uncorrected). Within these, the ipsilesional A4ul (infarcted region) was not involved in any of these correlations.

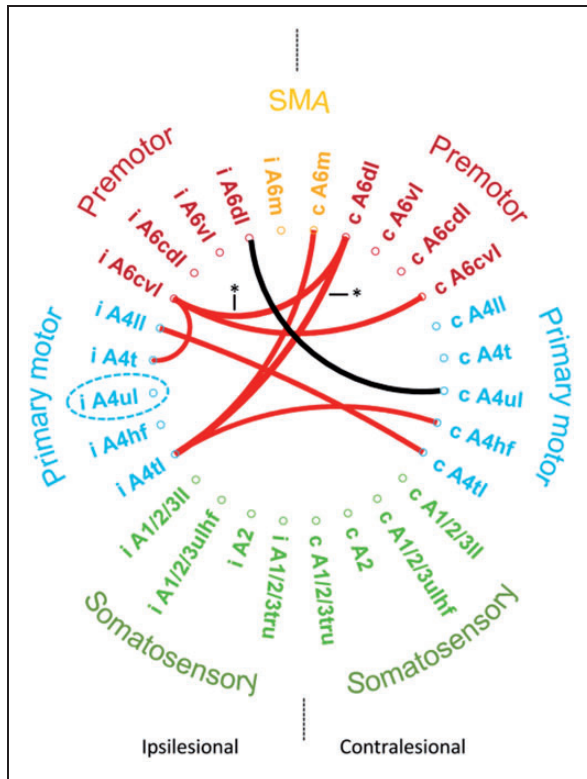


Figure 3. Correlation between changes in dexterity and Functional Connectivity (FC) changes in the core motor network from TP1 (< 10 days) to TP2 (3 weeks). Correlations between % change in hand dexterity and FC changes in the core motor system ($P < 0.01$ uncorrected). Each node represents a component of the core motor network (SMA, premotor, primary motor and somatosensory cortices). Primary motor cortex nodes (A4) are topographically represented, in agreement with their spatial organization on the motor homunculus. Significant correlations after correction for multiple comparison ($pFDR < 0.05$) are indicated (*). Positive correlations are represented in red and negative in black. Line widths are proportional to the rho correlation values (see Table 1 for detailed values). The dashed circle highlights the lesion site in M1, corresponding to the A4ul (upper limb) node. i = ipsilesional hemisphere, c = contralateral hemisphere. A4 = M1 area; ll: lower limb; ul: upper limb; t: trunk; hf: head face; tl: tongue larynx; A6: area 6; dl: dorsolateral; m: medial (SMA); cdl: caudal dorsolateral; cvl: caudal ventrolateral; vl A1/2/3: Primary sensory cortex; tru: trunk; A2: area 2.

By contrast the other nodes of the ipsilesional (non-infarcted) M1 were involved in 5 out of 8 connections (including 5/7 positive correlations and 0/1 negative correlation). The proportion of connections involving the ipsilesional M1 was significantly higher than connections between other regions of the core motor network (odds ratio (OR)=6.29; $P = 0.036$). The median FC change was positive in 6/8 correlations (most patients showed increase in connectivity) and negative in 2/8.

Large-scale analysis: Clinical relevance of global changes in FC over time. We analyzed changes in connectivity at a larger spatial scale using three distinct motor networks. The extended motor network included all 106 ROIs structurally connected to A4ul.¹⁹ The core motor network was part of the extended motor network and included M1, PMC, SMA, and S1 (28 ROIs). Finally, the non-core network contained the 78 ROIs included in the extended but not in the core motor network.

TP1 to TP2. From TP1 to TP2, NBS identified a network of 50 edges of increased FC in the extended motor network ($P_{FWER} = 0.042$; Figure 4(a); Supplementary Table 3). 26% of these edges were ipsilesional, 12% contralateral, and 62% interhemispheric. More edges were located in the core motor network than in the non-core network (OR = 2.60; $P = 0.02$). Similarly, more edges were identified within the core network than between the core and non-core networks (OR = 2.68; $P = 0.04$). No correlation was observed between motor performance and total strength in the core ($\rho = 0.32$, $P = 0.26$) or non-core networks ($\rho = 0.09$, $P = 0.76$) taken separately. However, improvement in hand dexterity was significantly associated with an increase in strength fraction (ratio of connectivity strengths between core and non-core motor areas; $\rho = 0.71$, $P = 0.006$; Figure 4(b)), suggesting a stronger engagement of the core motor network in clinical recovery. We then searched for communities within the NBS network, in order to distinguish clusters of regions which would be more frequently interconnected (Figure 5(c)). We found that the main community contained areas that largely matched the clinically relevant connections identified previously in the a priori defined core motor network (ipsilesional and contralateral M1, contralateral SMA, and contralateral S1).

We further evaluated patterns of decreased connectivity from TP1 to TP2. NBS identified a network of decreased FC composed of 71 edges within the extended motor network ($P_{FWER} = 0.002$; Supplementary Figure IIIA; Supplementary Table 4). 31% of these edges were ipsilesional, 17% were contralateral, and 52% interhemispheric. There was no significant difference in the percentage of edges encompassed within the core motor network, the non-core network or between both networks (core vs. non-core OR: 2.53, $P = 0.053$; core vs. edges connecting core and non-core nodes OR: 0.75, $P = 0.7$). There was no correlation between changes in hand dexterity and strength fraction ($\rho = -0.11$; $P = 0.70$). We further identified four communities within this NBS network (Supplementary Table 4B). No community included both M1 regions concomitantly. (Supplementary Figure IIIA).

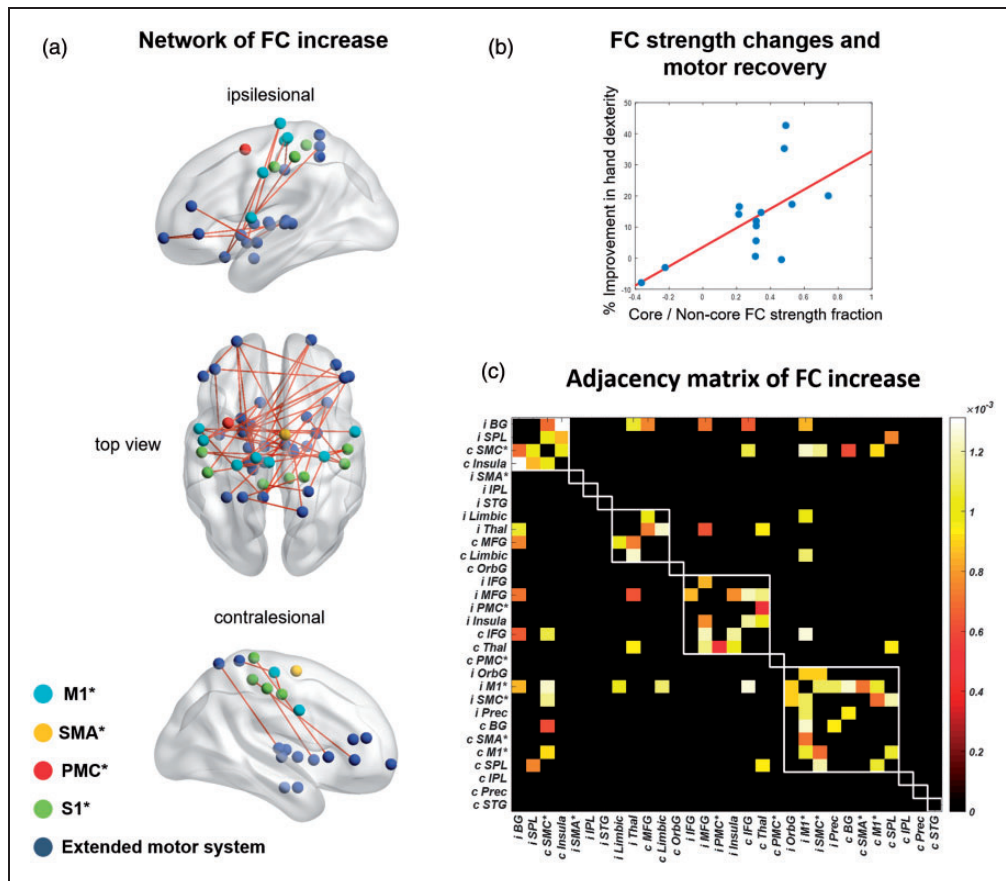


Figure 4. Global increases in Functional Connectivity (FC) between TP1 (<10 days) and TP2 (3 weeks). (a) Network of FC increase (NBS network; $T > 2.5$) between the acute and the early subacute stages (colour-coded node types). (b) The ratio of FC strength between the core and non-core networks correlates significantly with recovery of hand dexterity ($\rho = 0.71$, $P = 0.006$). (c) Adjacency matrix showing the mean differences in connectivity weight according to connection type between the two time points. The white squares outline regions being more often interconnected, i.e., communities. *Areas of the core motor network. M1 = Primary motor area, PMC = Premotor cortex, SMA = Supplementary Motor Area, S1 = Primary somatosensory cortex; see full list of nodes in Supplementary Table 2.

TP2 to TP3. NBS identified 94 edges forming a network of increased FC within the extended motor network ($P_{\text{FWER}} = 0.004$; Figure 5(a); Supplementary Table 3). 31% of these edges were ipsilesional, 13% were contralesional, and 56% interhemispheric. The proportion of edges was similar within the core network, the non-core network, and between both networks (core vs. non-core OR: 0.63, $P = 0.5$; core vs. edges connecting core and non-core nodes OR: 0.57, $P = 0.4$). In addition, there was no correlation between changes in hand dexterity and strength fraction ($\rho = -0.23$; $P = 0.42$). We further identified four communities within this NBS network (Figure 5(b)). No community included both M1 regions concomitantly. From TP2 to TP3, NBS identified 126 edges forming a network of decreased FC within the extended motor network ($P_{\text{FWER}} = 0.0004$; Supplementary Figure IVA; Supplementary Table 3A). 33% of these edges were ipsilesional, 29% were contralesional, and 63%

interhemispheric. There were significantly more edges with decreased connectivity from TP2 to TP3 within the core network than within the non-core network (OR: 6.84, $P < 0.001$). Similarly, more edges were identified within the core network than between the core and non-core networks (OR: 7.84, $P < 0.001$). However, there was no correlation between changes in hand dexterity and strength fraction ($\rho = -0.23$; $P = 0.42$). We further identified 3 communities within this NBS network, one of which included most regions defining the core motor network (ipsilesional and contralesional M1, contralesional SMA, and contralesional S1) (Supplementary Figure IVB).

Discussion

In our cohort of patients with isolated M1 stroke and associated hand paresis, we demonstrated that (i) hand dexterity was impaired in contrast to grip strength, (ii)

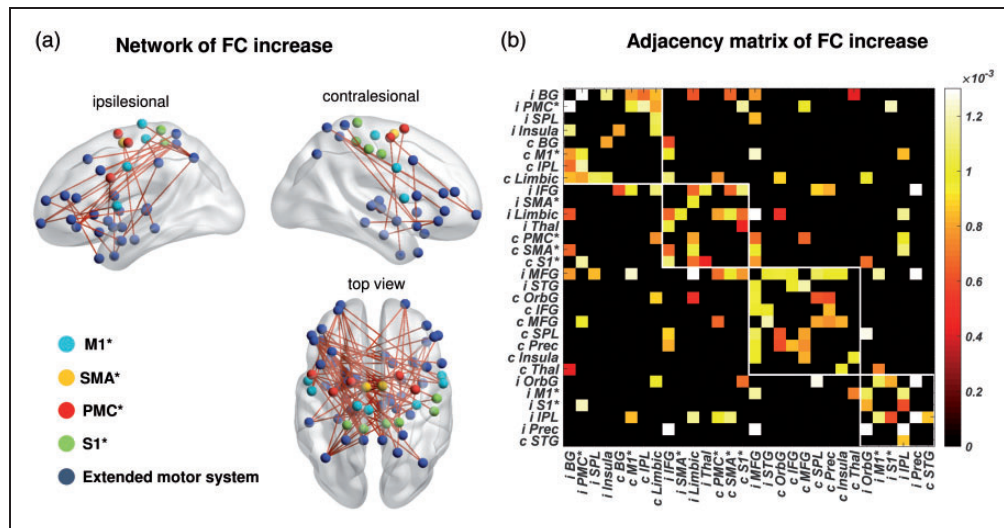


Figure 5. Global increases in Functional Connectivity (FC) between TP2 (3 weeks) and TP3 (3 months). (a) Network of FC increase (NBS network; $T > 2.5$) between the early subacute and late subacute stages (colour-coded node types). (b) Adjacency matrix showing the mean differences in connectivity weight according to connection type between the two time points. The white squares outline regions being more often interconnected, i.e., communities. *Areas of the core motor network. M1 = Primary motor area, PMC = Premotor cortex, SMA = Supplementary Motor Area, S1 = Primary somatosensory cortex; see full list of nodes in Supplementary Table 2.

functional recovery related to reorganization of FC in the core motor system (M1, PMC, SMA, and S1), mobilizing specific connections involving the non-infarcted part of M1, and (iii) restoration of motor performance was more strongly related to FC increase within the core motor network than beyond the core network.

Recovery of hand dexterity

Hand dexterity, assessed with the 9-hole peg test, was significantly affected in contrast to grip strength. Because strokes commonly affect cortical and subcortical regions, it is challenging to determine whether cortical strokes are more likely associated with impairment of grip strength or dexterity. Previous studies showed that loss of hand dexterity was associated with a cortical involvement,²⁹ as previously reported in 4 patients with a lesion limited to M1⁹ and in rodent studies.³⁰ Alteration of finger movements following isolated M1 lesions was also observed in non-human primates tested with precision-grip.³¹ In that study and despite loss of dexterity, the primates remained able to walk, climb, or jump with ease. In our patients, we found that lesion volume correlated with the severity of initial loss of function but not with recovery. Complete normalization of hand dexterity was observed within 3 weeks after stroke (TP2) with standard rehabilitation therapy. Several studies have reported incomplete long-term recovery of hand function following lesions of the M1

hand representation in the adult monkey.^{10,31} Whereas our patients recovered 9-hole peg test performances comparable to controls, we cannot exclude that the use of other tests to assess skilled movements and strength (e.g. finger pinch) may have detected persistent changes in motor performance.

Role of the non-infarcted M1 in the recovery of hand dexterity

Recovery of function was associated with changes in FC between specific nodes of the core motor network. Because all patients suffered from hand paresis, we considered that the upper limb subregion was consistently infarcted. In non-human primates, focal damage of M1 triggers functional remapping to the adjacent M1, more specifically in the territory formerly occupied by the elbow and shoulder.¹⁰ In stroke patients with good recovery, a shift of hand-related brain activation to the rim of the infarct is described,^{32,33} such as a dorsal displacement of hand representation during movement of the paretic hand in patients with M1 strokes.⁹ Our data highlight the role of M1 areas adjacent to the infarcted M1, for motor recovery. It is still unknown whether this process reflects unmasking of pre-existing, but mostly silent, connections involving non-infarcted regions, or axonal sprouting towards these perilesional regions. Increased coupling between ipsilesional M1 and contralateral dorsolateral PMC appeared clinically relevant in our study, as previously

described in patients with subcortical motor strokes.^{36,37} In our study, better recovery was also associated with increased connectivity between ipsilesional and contralesional M1 areas. These results are consistent with previous studies including subcortical and cortical stroke patients, reporting a correlation between motor impairment and altered connections between homotopic M1.^{34,35} The importance of interhemispheric connections has also been reported between the ipsilesional M1 and contralesional prefrontal cortex and SMA.²³ As a whole, our results emphasize the clinical relevance of functional reorganization between nodes of the core motor network, in which ipsilesional non-infarcted M1 may play a significant role. Our findings may orient restorative therapies to target non-infarcted ipsilesional M1, for instance by modulating its excitability.³⁸

Assessment of the clinical relevance of global changes in FC over time

Applying NBS to the extended motor network, we found a large-scale network of increased FC between TP1 (<10 days) and TP2 (3 weeks). This network included connections within and outside the core motor network. Improvement of motor function between TP1 and TP2 was specifically associated with an increased strength fraction between core and non-core areas. This suggests that better recovery is observed when the core motor network is more strongly engaged, compared to non-core regions that also have associative and integrative functions. The association between loss of function and global network strength has been studied in other neurological diseases. In brain tumor patients, motor recovery was related to an increased mean FC strength in the core motor network.³⁹ In our cohort, a relative FC increase within the core motor network may reflect a greater demand within the main nodes of the motor network during recovery. At later time-points (early to late subacute stages), despite stability of motor function, we observed a significant decrease in FC mainly in the core motor network as compared to the non-core network. The clinical significance of these findings is uncertain. Early after stroke, decreased connectivity has been described in the motor network especially between homologous regions. Normalisation of initially decreased interhemispheric FC has been associated with clinical recovery.¹² However, persistence of reduced connectivity has been shown beyond the motor network, within subcortical regions associated with effort and cognitive processing.¹³ The clinical impact of decreasing FC following stroke has only rarely been assessed. One longitudinal study showed that patients had increased connectivity between

lesioned M1 and cerebellum, thalamus, middle frontal gyrus posterior parietal cortex at onset, compared to healthy subjects. These relative increases in connectivity were not consistently observed in later time points, indicating a probable decrease in FC with time for these connections.²³ Increases and decreases of FC that are not correlated with motor recovery may reflect adaptive mechanisms that develop after restoration of function and/or changes in non-motor functions. The increase and decrease FC that are not correlated with motor recovery may reflect adaptive mechanisms that develop after restoration of function and/or changes in non-motor functions.

There are several limitations to this study. First, this study is limited to 16 consecutive cases. However, patients presenting with a lesion restricted to M1 are rare. Our patients were prospectively recruited among 1656 patients admitted to our stroke unit during the study period. Further, our study includes a larger number of patients with lesion restricted to M1 compared to previous reports. Additionally, patients were scanned at three time points, giving us the opportunity to study the clinical relevance of connectivity changes over time. Secondly, and despite our best efforts, there is still some heterogeneity in lesion size and localisation, including some involvement of surrounding white matter. Even following experimental lesions in rodent and non-human primate studies, resulting damage is not strictly limited to M1. Third, we restricted our definition of the core motor network to the SMA, PMC, M1 and S1. However, other cortical and subcortical brain regions may be considered as part of the motor network. For instance, we did not include the cerebellum nor the intraparietal sulcus that have shown to play a role in motor recovery. Previous studies have indeed demonstrated that, in well-recovered patients, effective connectivity was enhanced between M1 and the intraparietal sulcus.^{40,41} Finally, we limited our study to three months after stroke and cannot determine further changes in FC. However, we observed complete restoration of function at three weeks already. Other data, in more severe stroke patients, suggest that most of recovery occurs within three months after stroke.⁴²

In conclusion, we demonstrated, based on a unique population of stroke patients with a lesion restricted to M1, the clinical relevance of functional changes in connectivity at different spatial scales during recovery. Our results highlight the importance of the non-infarcted M1 and the core motor network for recovery, as opposed to larger-scale networks. Our findings may orient restorative therapies, to specifically modulate non-infarcted M1 connectivity.

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Declaration of conflicting interests

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Authors' contributions

MVA: study design, data analysis, data interpretation, drafting manuscript. ED: study design, data acquisition, data interpretation, manuscript revision. AB: study design, data acquisition, manuscript revision. AK: study concept and design, data interpretation, manuscript revision. JR: data analysis, data interpretation, manuscript revision. EC: study concept and design, data analysis, data interpretation, drafting manuscript.

Supplementary material

Supplemental material for this article is available at <http://jcbfm.sagepub.com/content/by/supplemental-data>.

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