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RESEARCH

Resting-State Cortico-Cerebellar Connectivity Correlates with Post-Stroke Motor Recovery - A Prospective Functional MRI Study

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Abstract
Cerebellar functional and structural connectivity are likely related to motor function after stroke. Less is known about motor recovery, which is defined as a gain of function between two time points, and about the involvement of the cerebellum. Fifteen patients who were hospitalized between 2018 and 2020 for a first cerebral ischemic event with persistent upper limb deficits were assessed by resting-state functional MRI (rsfMRI) and clinical motor score measurements at 3, 9 and 15 weeks after stroke. Age- and sex-matched healthy subjects ($n=15$) were assessed once. The objectives were (1) to study whether the level of connectivity between the contralesional cerebellum (lobules IV-V-VI and lobule VIII) and the ipsilesional motor regions on rsfMRI is predictive of motor recovery and (2) to compare these connectivities with those of healthy subjects. Upper limb motor recovery was positively correlated with functional connectivity between contralesional cerebellar lobule VIII and the ipsilesional supplementary motor area (SMA). The greater the connectivity between these regions, the better the motor recovery. In patients, the corticocerebellar network between lobule IV-V-VI and the ipsilesional M1 and SMA showed weaker synchronization at rest than in healthy subjects. Cortico-cortical connectivity was not associated with recovery. Resting-state functional connectivity, including contralesional cerebellar lobule VIII, could be a tool for studying and predicting recovery in stroke patients. Our study highlights the role of the cerebellum in motor recovery after stroke, enabling us to consider new therapeutic targets in neuromodulation.

Keywords Cerebellum · Neuronal plasticity · Functional MRI · Stroke · Motor recovery

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Introduction

Motor deficits are the most frequent impairment after stroke, with 50–80% of patients presenting with hemiparesis of the upper limb at the acute stage of stroke and approximately 40% at the chronic stage [1]. This proportion decreases with recovery, driven by structural and functional plasticity mechanisms, which underlie this process [2]. Indeed, reorganization of surviving central nervous system elements supports behavioral recovery, for example, through re-organization of cortical representational maps, or changes in activity of association cortices (either by synapse strengthening or loss of inhibitory inputs) or activity-dependent use of alternative pathways. Among the brain regions involved in motor recovery, the cerebellum is of particular interest. The cerebellum is well known to be involved in movement execution (especially visually-guided movements), motor adaptation and learning in healthy subjects [3, 4]. The beneficial role of the cerebellum in stroke has been demonstrated for many years. First, the resolution of cerebellar diaschisis, which was described as an hypometabolism and hypoperfusion in the cerebellum by loss of excitation from the motor cortex, observed in the acute phase was associated with good motor outcomes [5]. Subsequently, a more recent publication using diffusion tensor imaging and tractography demonstrated that cortico-ponto-cerebellar and dentato-thalamo-cortical tracts, the afferent and efferent pathways of the cerebellum to/from motor areas, may be associated with residual motor function of the upper limb, independent of corticospinal tract damage [6]. Third, evidence from functional imaging studies has significantly improved the understanding of changes in cerebellar activity and their relevance to upper limb function recovery after stroke [7]. However, in terms of functional connectivity (FC), i.e., interactions between two brain regions, including the cerebellum, the results are less consistent: decreases and increases in cortico-cerebellar interactions have been described over time. Functional connectivity refers to the temporal coherence in activation patterns of anatomically separated brain regions. Decrease in FC values (i.e. less coherence between signals of 2 regions) could be the reflection of direct or indirect damage of structural pathways and increased FC values may correspond to compensatory mechanisms [8]. To date, studies on cerebellar functional connectivity are still scarce [9–14].

By employing resting-state functional imaging methods, which eliminate the need for motor tasks and thereby mitigate variability in task success-related findings, researchers have identified favorable associations between motor function and the strength of connectivity between the primary motor cortex (M1) and the cerebellum [11, 15]. Nonetheless, the majority of these investigations lacked longitudinal designs, and patients were assessed using deficiency scores such as the Medical Research Council scale, which inadequately evaluates upper limb functional activity. Activity limitation scores such as the Action Research Arm Test (ARAT) are now recommended according to the International Classification of Functioning, Disability, and Health.

Following these observations, our aim was to conduct a longitudinal study investigating cerebello-cortical functional connectivity to characterize its alterations and determine whether and which connectivity between the cerebellum and motor regions may be predictive of motor recovery after stroke. We hypothesized that cerebello-cortical connectivity will be dysfunctional, as previous reports showed reduced functional or effective connectivities between the cerebellum and the sensorimotor cortex including the supplementary motor area and the parietal cortex. Furthermore, we thought that functional connectivities-behaviour correlations would concern the cerebello-primary motor cortex loop [11] and more specifically lobule VIII of the cerebellum as a recent rsfMRI study indicated that lobule VIII is more involved in goal-directed motor tasks [16] and may play a more significant role in adaptive visuomotor tasks or motor learning.

Methods

Participants

The patient cohort was a single-center longitudinal cohort enrolled from the stroke unit and the neurorehabilitation department of La Pitié-Salpêtrière Hospital. The goal was to study potential magnetic resonance imaging (MRI) biomarkers to predict motor recovery (ClinicalTrials.gov Identifier: NCT03739892).

Sixteen patients who met the following criteria were included in this analysis: (i) had experienced their first cerebral infarction, (ii) had persistent upper limb motor deficits, (iii) were capable of undergoing a task-oriented rehabilitation program, (iv) were aged between 18 and 90 years, (v) had no contraindications for MRI, and (vi) had no medical conditions that would compromise follow-up. Subsequently, one participant was excluded due to a failure (MRI coil dysfunction) in the first MRI data acquisition ($n = 15$).

Patients participated in a standardized 6-week rehabilitation program. This rehabilitation program consisted of daily sessions of physical therapy and occupational therapy. Furthermore, they received daily individualized upper limb rehabilitation using an augmented-reality device to increase the rehabilitation dose.

Each patient was assessed at three distinct time points: (i) V1: upon admission to rehabilitation, within three weeks of the stroke event; (ii) V2: at the end of the 6-week

standardized rehabilitation program; and (iii) V3: six weeks after V2, roughly three months following the stroke. Each visit included an evaluation of upper limb motor function and a multimodal MRI including both structural and functional sequences. Upper limb function was evaluated by the Action Research Arm Test. This score consists of 19 items assessing the ability to manipulate various objects with standardized tools. Scores range from 0 to 57 and are linked to functional abilities measuring activity limitations. Given that gaining 1 ARAT point at a score of 20 is not equivalent to gaining 1 point at a score of 50, we developed a derived score that reflects the ratio between the actual degree of recovery and the maximum expected recovery. We defined the "effective recovery rate" (ERR) as the ratio between the real recovery (ARAT score between V3 or V2 and V1) and the theoretical maximal recovery, which is the difference between the maximum ARAT score (i.e., 57) and the ARAT score at V1 ((Tx-T1)/(57-T1)). Based on the ERR at V3, we defined two groups of patients: (1) a group of patients with good recovery where the effective recovery rate at V3 was $>70\%$ and (2) a group of patients with poor recovery. The rate of 70% was chosen based on the proportional recovery rule, which states that most survivors recover a fixed proportion ($\approx 70\%$) of lost function after stroke [17].

Healthy control subjects were matched 1:1 for both age and sex from a cohort acquired in EPFL (Ecole Polytechnique Fedérale de Lausanne, Pr Hummel) with the same MRI scan and sequences. Healthy controls were included in this study based on (i) age ≥ 18 years, (ii) right-handedness, (iii) no use of psychoactive medication drugs or alcohol abuse, (iv) no contraindications for MRI, and (v) no neurological or psychiatric conditions.

Healthy subjects were evaluated once following the same MRI protocol and employing identical procedures.

This study adhered to established ethical guidelines and received approval from the local ethics committee (CPP Sud Méditerranée III for patients, the Cantonal Ethics Committee of Vaud, Switzerland for healthy subjects). Written informed consent was obtained from each participant or his or her legal representative/family member.

Image Acquisition and Analysis

MRI Parameters

MRI data were acquired using a SIEMENS MAGNETOM Prisma 3T MR scanner with a 64-channel head coil. Head movements were restricted with foam pads. Patients were instructed to stay motionless, with their eyes closed and awake.

The protocol included a T1 MPRAGE (Magnetization Prepared Rapid Gradient Echo) anatomical sequence (isotropic voxel of 1 mm, a repetition time (TR) of 2.3 s, a echo time (TE) of 0.9 ms and a flip angle of 8°), a fluid attenuation inversion recovery (FLAIR) TSE (Turbo Spin Echo) sequence (isotropic voxel of 1 mm, TR of 5 s, TE of 1.8 ms and a flip angle of 120°), and diffusion with multiband echo planar imaging (EPI) (isotropic voxel of 1.64 mm, a TR of 4.9 s, a TE of 77 ms, a multiband factor of 2, and a 7/8 partial Fourier transform). 7 b = 0 s/mm2 volumes and 5 different shells: 46, 29, 16, 7, and 3 directions for b-values of 3,000, 2,000, 1,000, 700, and 300 s/mm2, respectively). Resting-state functional MR images were acquired eyes opened using EPI with the following parameters: TR of 1 s, TE of 32 ms, an isotropic voxel size of 2 mm, 420 volumes, sequence duration of 7 min.

Preprocessing

Functional MRI Gray matter, white matter, and CSF (cerebrospinal fluid) were first segmented on T1 volumes using CAT12 from SPM12.

The functional images were processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) following standard proc edures. The functional images were realigned to the mean volume of the sequence to correct for head movements. The functional images with posterior-anterior phase encoding were used to correct susceptibility distortions in the functional images using FSL's TOPUP [16]. The corrected volumes were normalized in the Montreal Neurological Institute (MNI) space by coregistering them onto T1 and then applying the deformation field from the anatomical images. Images were flipped if the infarct was left-sided, although all patients had stroke lesions in the right hemisphere. Finally, the functional images were smoothed using an isotropic 8-mm full width at half-maximum Gaussian kernel and bandpass filtered between 0.01 and 0.08 Hz to remove noise.

Diffusion Imaging The data were first denoised, and Gibbs artifacts were removed with MRtrix3 software [18]. The b = 0 volumes were then extracted and combined with the opposite phase direction volumes to perform EPI distortion correction with the TOPUP tool from FSL (5.0) [19]. We then corrected the motion and eddy current distortion data with the eddy tool from FSL [20]. Fractional anisotropy (FA) maps were generated using the diffusion tensor model. For each tract of interest (corticospinal tract[CST], dentatothalamocortical tract [DTCT]), template tracts were obtained from healthy whole-brain tractography using MRtrix3

(details in [21]). We then extracted density-weighted FA values from the affected and unaffected fasciculi.

Image Processing

Network Definition We first defined an a priori network based on 12 regions of interest (ROIs) using current data regarding structural and functional interactions for which involvement in motor recovery and motor learning has been demonstrated or suggested [22–26]. We selected 5 cortical ROIs in each hemisphere, including the primary motor cortex (M1), ventral and dorsal premotor cortex (PMv and PMd), supplementary motor area (SMA), and the inferior parietal cortex (Par). We also selected two cerebellar motor regions known for motor representation [27, 28], one composed of lobules IV, V, and VI (Ce456) and a second consisting of lobule VIII (Ce8). For connections, we then hypothesized a priori that all cortical ipilateral regions were connected to each other, as well as all homotypic regions. From the potentially 66 ROI-to-ROI connections, we ultimately selected a network of 27 connections that we deemed relevant for the study of motor recovery, as described in the introduction (Fig. 1, see supplementary material for justification of our ROIs and connections).

The ipsilesional cerebellum was excluded, as a review of other resting-state fMRI studies on motor recovery revealed that no significant correlations were reported with this cerebellar region [11].

Cortical motor regions of interest were selected from the Human Motor Area Template [29], and cerebellar motor regions were defined with the AAL template [30]. We carried out systematically a visual check to ensure the coincidence of the ROIs with patient's anatomy.

Statistical Analysis

All variables were tested using the Shapiro–Wilk normality test. As normality was not achieved for all variables, we used nonparametric tests for the statistical analysis. The descriptive statistics are presented as the median and interquartile range (IQR). Missing data ($n=3$ patients) concerning V3 for rsfMRI functional connectivity (FC) values and the ARAT were imputed with the last known visit (V2) to perform the whole analysis (including the longitudinal analysis) with 15 patients. Other missing data were not imputed.

Comparisons of the proportions were performed using the chi-square test. The Mann–Whitney U test and Wilcoxon rank sum test were used for between-group and longitudinal comparisons, respectively.

Using the Conn-Toolbox extension of SPM12, correlations between averaged BOLD time courses for the different ROIs were computed and converted into Z scores using Fisher transformation. We then performed a correlation analysis between functional ROI-to-ROI connectivity and motor recovery based on the ERR at V3, as well as between-group (good vs. poor) comparisons. We also performed a correlation analysis with the ARAT score at V1 to investigate whether the correlations with the ERR at V3 reflected the ARAT score at V1. To further analyze whether the functional connectivity was related to structural bundle damage, we computed Spearman's rank correlation coefficients between the cerebello-cortical network FC values and the damage to the CST and DTCT tracts.

We then compared the functional connectivity values between healthy subjects and patients (and subgroups) using Mann–Whitney U tests.

All tests were corrected for multiple comparisons using the false discovery rate (FDR).

Finally, we performed a longitudinal analysis on connectivity values in the whole cohort and patient subgroups using the Friedman test for the factor session (V1, V2, V3). Post-hoc Conover tests were performed for comparisons between time points.

Analysis was performed using JASP (version 0.18.1, Netherland, 2023). A corrected p value of <0.05 was considered to indicate statistical significance.

Results

Participants

Fifteen patients (10 men, 66.7%) were analyzed. The descriptive characteristics are summarized in Table 1. The lesion locations were as follows: subcortical ($n=9$, 60.0%), cortical ($n=4$, 26.7%) and cortico-subcortical ($n=2$, 13.3%). Only one patient's lesion overlapped with the ROIs (SMA-i for patient #19). The lesion probability map is presented in Fig. 2, and the highest incidence (the voxels most likely infarcted) was located in the internal capsule. All lesions (100% of the patients ($n=15$)) overlapped with the CST.

Patients improved significantly on the ARAT (F(3,15): 19.473; $p<0.001$, $p<0.001$ for V1-V2 and $p<0.001$ for V2-V3). The effective recovery rate was 58% at V2 (IQR: 35–78) and 67% at V3 (IQR 54–83). Individual data are presented in supplementary Table 1.

Fifteen healthy subjects were matched 1–1 for sex (10 men, 66%, $p=1.00$) and age (median: 64 (IQR 59.5-70.75) years, $p=1.00$).

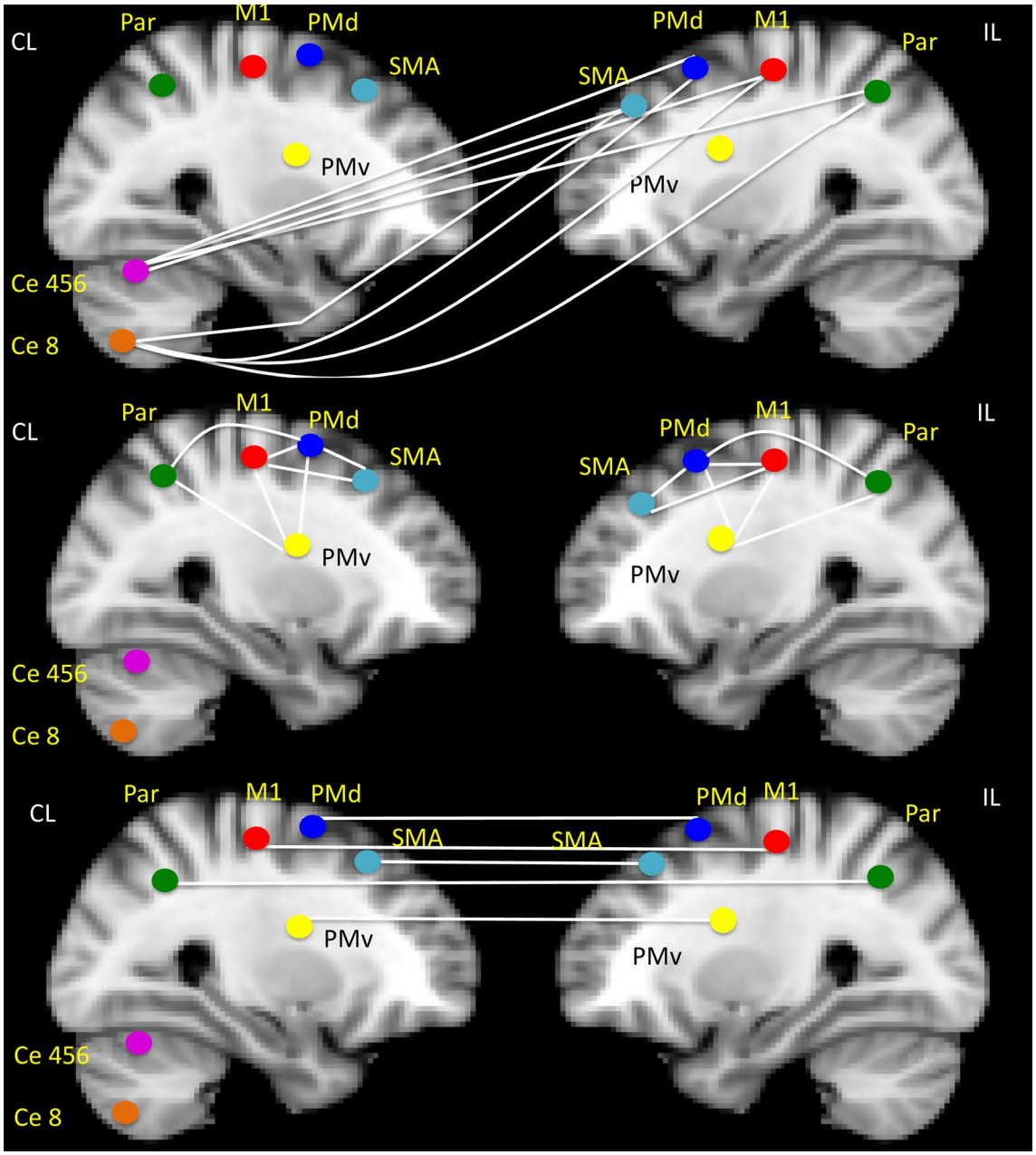

Fig. 1 Definition of the cerebello-cortical network. **First row**: Cerebellocortical connections. Connections between the contralesional cerebellum (Ce 456 and Ce8) and the ipsilesional cortical areas ($n=8$): the SMA, PMd, M1 and Par. **Second row**: Intrahemispheric connections between the ipsilesional cortical areas ($n=7$) and between the contralesional cortical areas ($n=7$). **Third row**: Interhemispheric connections between the homotopic regions ($n=5$). SMA: Supplementary Motor Area, PM: premotor area (d: dorsal, v: ventral), M1: primary Motor cortex, Ce 456: lobules IV, V and VI of the cerebellum, Ce 8: lobule VIII of the cerebellum, Par: inferior parietal lobule. CL: contralesional; IL: ipsilesional

Correlation Between Functional Connectivity Levels and Upper Limb Motor Function

The ERR at V3 at the end of rehabilitation was positively correlated with functional connectivity between the contralesional cerebellar lobule VIII (Ce8-c) and the ipsilesional primary motor cortex (M1-i) (rho = 0.674; 95% CI: 0.247–0.882; $p_{unc}=0.006$), the ipsilesional dorsal premotor cortex (PMd-i) (rho = 0.520; 95% CI: 0.011–0.815; $p_{unc}=0.047$), and the ipsilesional supplementary motor area (SMA-i) (rho = 0.803; 95% CI: 0.493–0.932; $p_{unc}<0.001$) (Fig. 3). Only the Ce8-c/SMA-i connectivity remained significant after FDR-correction ($p_{corr}=0.027$). The greater the functional connectivity between these two regions was, the greater the motor recovery of the upper limb at V3. An

Table 1 Patients characteristics

	All ($n=15$)	Poor recoverers group ($n=8$)	Good recoverers group ($n=7$)	p-value
Age (years)	64.0 (59.5, 70.5)	68.0 (61.7, 75.7)	62.0 (59.0, 65.0)	0.183
Sex ratio (M/F, %)	10 (66.7%)	5 (62.5%)	5 (71.4%)	>0.999
Side (n,%) Left	5 (33.3%)	3 (37.5%)	2 (28.6%)	>0.999
Time poststroke V1 (days)	22.0 (13.5, 33.0)	22.5 (15.2, 35.5)	20.0 (13.5, 32.0)	0.602
Time poststroke V2 (days)	63.0 (58.2, 77.0)	61.0 (56.0, 69.5)	69.0 (59.0, 78.5)	0.406
Time poststroke V3 (days)	111.5 (102.5, 123.7)	107.0 (103.5, 132.0)	120.0 (101.0, 121.0)	0.808
ARAT V1	31.0 (14.5, 42.0)	20.0 (5.7, 37.5)	35.0 (29.5, 42.0)	0.247
ARAT V2	47.5 (38.2, 54.7)	38.0 (31.5, 48.0)	54.0 (47.5, 55.0)	0.062
ARAT V3	53.0 (37.5, 55.0)	37.5 (35.0, 45.2)	53.0 (53.0, 56.0)	0.031
ERR % (V2)	0.58 (0.35, 0.78)	0.40 (0.13, 0.53)	0.81 (0.68, 0.85)	0.008
ERR % (V3)	0.67 (0.54, 0.83)	0.54 (0.39, 0.60)	0.85 (0.78, 0.97)	0.001
CST FA ratio (affected/unaffected hemisphere)	0.91 (0.86, 0.93)	0.90 (0.84, 0.96)	0.91 (0.87, 0.92)	0.643
DTCT FA ratio (affected/unaffected hemisphere)	0.92 (0.91–0.94)	0.96 (0.93, 0.97)	0.91 (0.91, 0.92)	0.298

Values are the median and interquartile range (IQR). Abbreviations: ARAT: Action Research Arm Test, ERR: Effective Recovery Rate, FA: fractional anisotropy, CST: Corticospinal Tract, DTCT: Dentato-thalamo-cortical Tract

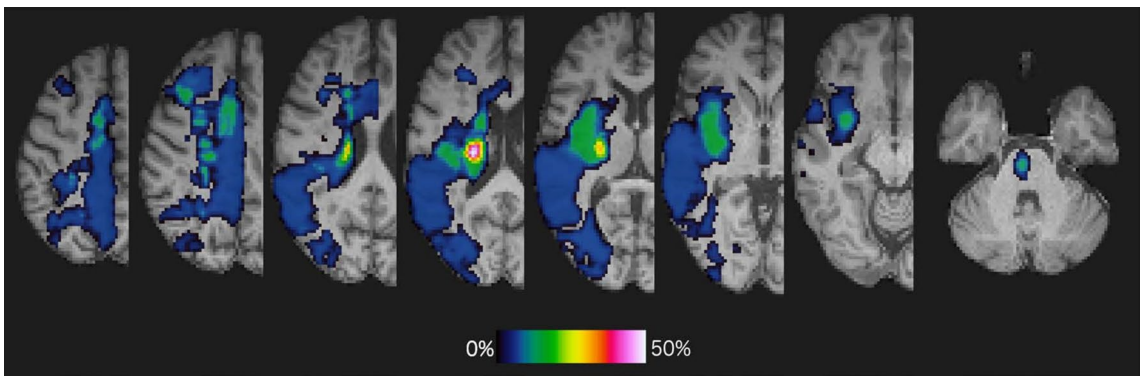

Fig. 2 Lesion probability maps for the whole cohort overlaid on a T1 template. The color bar reflects the percentage of patients for which the voxel was lesioned by the infarct

additional analysis (without a priori on ROIs) using connectivity maps with contralesional lobule VIII as a seed identified the same correlations with the ERR at V3: M1, SMA PMd and even parietal cortices (see supplementary Fig. 1).

Cerebellocortical connectivity did not correlate with initial severity, as determined by the ARAT at V1.

When comparing the group with good vs. poor recoverers at V1 (Table 2), patients who had good recovery tended to have stronger functional connectivity values within the same pair of regions—Ce8c/M1-i ($U=10.000$; p_{unc}: 0.040 $p_{corr}=0.27$), Ce8c/PMd-i ($U=10.000$; p_{unc}: 0.040 $p_{corr}=0.27$) and Ce8-c/SMA-i ($U=5.000$; p_{unc}: 0.006 $p_{corr}=0.162$). However, these differences were no longer significant after FDR correction for multiple comparisons.

There was no statistically significant correlation between cortico-cortical connectivity and the ERR at V3. We found no significant correlation between cortico-cerebellar connectivity and the white matter bundles analyzed (CST, DTCT).

Comparison of Functional Connectivity Between Patients and Healthy Subjects

The functional connectivity values for patients and healthy subjects are shown in Table 3. Comparisons are illustrated in Fig. 4 and supplementary Tables 2–4.

At V1, the functional connectivity between contralesional cerebellar lobules IV, V and VI (Ce456-c) and the ipsilesional M1 as well as the ipsilesional supplementary motor area was significantly weaker in patients than in healthy subjects (Ce456-c/M1-i: $U=182.000$; $p_{unc}=0.003$, $p_{corr}=0.036$); Ce456-c/SMA-i: $U=190.000$ $p_{unc}<0.001$ $p_{corr}=0.027$). The

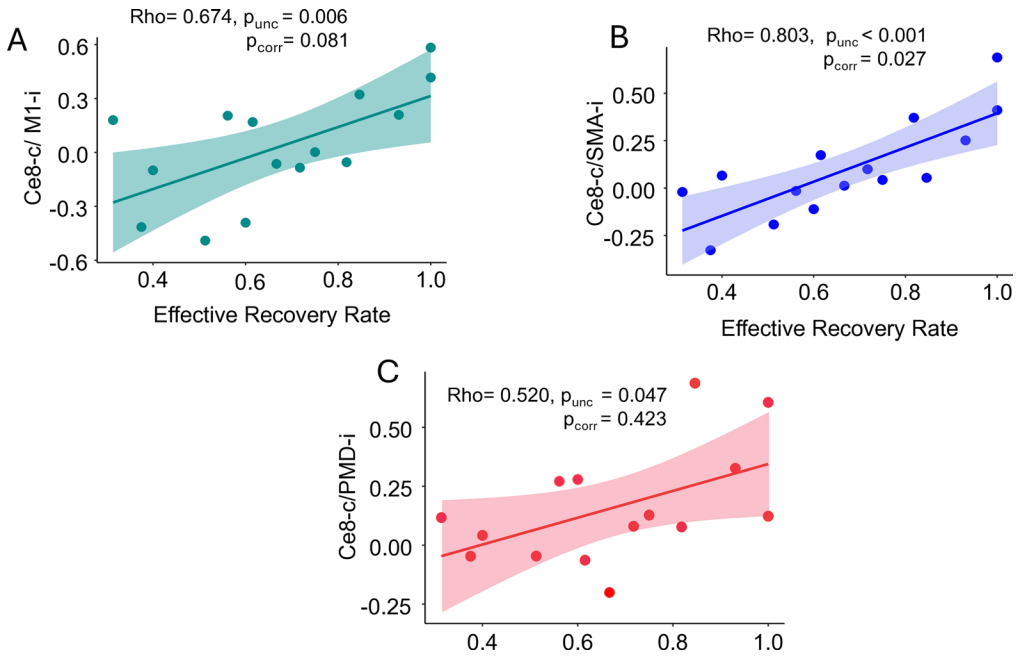

Fig. 3 Correlation between functional connectivity at V1 and effective motor recovery at V3. **(A)** Ce8-c/M1-i vs. effective recovery, **(B)** Ce8-c/SMA-i vs. effective recovery, **(C)** Ce8-c/PMd-i vs. effective recovery. Uncorrected and FDR-corrected p values are given for each correlation

functional connectivity between the contralesional cerebellar lobule VIII (Ce8-c) and the dorsal premotor cortex was also significantly weaker in patients than in healthy subjects (Ce8-c/PMd-i: U = 181.000 p_{unc}=0.004 p_{corr}=0.036).

Ce456-c/M1-i and Ce456c/SMA-i remained diminished when comparing the healthy subjects to the patients' functional connectivity at V2 and V3 (at V2: p_{corr}=0.099 and p_{corr}=0.027, respectively; at V3: p_{corr}=0.013 and p_{corr}=0.014, respectively). However, the Ce8-c/PMd-i normalized with no further significant difference at V2 and V3 (p_{corr}=0.18 at V2, p_{corr}= 0.06 at V3).

These changes were driven by the poor recovery group who had weaker functional connectivity than healthy subjects between the following ROIs: Ce456-c/M1-i (p_{corr} =0.03), Ce456-c/SMA-i (p_{corr} =0.009), Ce8-c/PMd-i (p_{corr} =0.009) and Ce8-c/SMA-i (p_{corr} = 0.009) at V1. All these functional connectivity values remained weaker at V2 and V3, except for the Ce8-c/SMA-i at V3 (p_{corr} =0.18). (see Supplementary Tables 5–7).

No differences between the good recovery group and the healthy control group were found (see Supplementary Tables 8–10).

Longitudinal Analysis of Functional Connectivity in Patients

The only functional connectivity that changed over time was the functional connectivity between the contralesional M1 and the PMd. There was a decrease over time between V1 and V3 ($\chi 2_{Friedman}$ = 12.5; p_{unc} = 0.02). This decrease was no longer significant after FDR correction (p_{corr} = 0.054). (see Supplementary Table 11)

No significant longitudinal changes were detected in the poor or good recovery groups (see Supplementary Tables 12–13).

Discussion

In this study, we demonstrated that only cerebello-cortical interactions from lobule VIII of the cerebellum were associated with good motor recovery after stroke in a prospective cohort in the subacute phase. Additionally, we found that these interactions, especially those from the anterior cerebellum (lobules IV-V-VI), were decreased compared to those of healthy subjects at V1 and remained abnormal over time. Finally, there were no longitudinal alterations observed within the cortico-cortical network, and these connectivities did not correlate with motor recovery in the upper limb.

The cerebello-Cortical Network and Poststroke Motor Recovery

We found that (1) the ipsilesional cortico-cerebellar functional connectivity from lobule VIII and not lobule VI correlated positively with recovery and that (2) the functional connectivity of the ipsilesional cortical areas and between hemispheres did not correlate with motor recovery.

Table 2 Functional connectivity (FC) values in poor and good recovery groups

	Poor recovery group	Good recovery group
Cortico-cerebellar FC		
Ce456-c / M1-i	0.001 (-0.192-0.143)	0.120 (0.047–0.247)
Ce456-c-/ PMd-i	0.181 (-0.004-0.250)	0.340 (0.114–0.406)
Ce456-c-/ SMA-i	0.023 (-0.184-0.063)	0.042 (-0.044-0.301)
Ce456-c-/ Par-i	0.146 (-0.165-0.204)	0.056 (-0.107-0.132)
Ce8-c / M1-i	-0.082 (-0.397-0.172)	0.209 (-0.027-0.369)
Ce8-c/ PMd-i	-0.002 (-0.051-0.155)	0.128 (0.102–0.466)
Ce8-c/ SMA-i	-0.018 (-0.131-0.026)	0.252 (0.077–0.391)
Ce8-c/ Par-i	0.132 (-0.009-0.212)	0.080 (-0.059-0.340)
Intrahemispheric cortical FC		
M1-i / PMd-i	0.318 (0.146–0.359)	0.559 (0.359–0.646)
M1-i / PMv-i	0.484 (0.116–0.587)	0.671 (0.441–0.780)
M1-i / SMA-i	0.560 (0.326–0.739)	0.827 (0.725–1.164)
PMd-i / PMv-i	0.535 (0.505–0.690)	0.551 (0.507–0.595)
PMd-i / SMA-i	0.345 (0.233–0.434)	0.432 (0.382–0.675)
PMd-i / Par-i	0.442 (0.387–0.481)	0.338 (0.302–0.409)
PMv-i-/ Par-i	0.307 (0.216–0.515)	0.448 (0.323–0.515)
M1-c / PMd-c	0.330 (0.138–0.650)	0.481 (0.286–0.713)
M1-c / PMv-c	0.348 (0.201–0.453)	0.273 (0.244–0.612)
M1-c / SMA-c	0.704 (0.644–0.764)	0.956 (0.827–1.151)
PMd-c / PMv-c	0.719 (0.550–0.810)	0.533 (0.417–0.739)
PMd-c / SMA-c	0.331 (0.272–0.415)	0.424 (0.400-0.599)
PMd-c/ Par-c	0.531 (0.451–0.640)	0.539 (0.458–0.614)
PMv-c-/ Par-c	0.735 (0.470–0.877)	0.653 (0.548–0.669)
Inter-hemispheric FC		
M1-i /M1-c	0.945 (0.615–1.173)	1.215 (0.901–1.412)
PMd-i /PMd-c	0.534 (0.375–0.761)	0.600 (0.526–0.792)
PMv-i /PMv-c	0.676 (0.577–0.784)	0.774 (0.629–0.810)
SMA-i /SMA-c	0.838 (0.539–1.046)	1.169 (0.941–1.305)
Par-i /Par-c	0.566 (0.518–0.670)	0.648 (0.606–0.756)

Values are the median ± interquartile range (IQR)

Abbreviations: FC: Functional Connectivity, -i: ipsilesional, -c: contralesional, Ce456: cerebellar lobule IV-V-VI, Ce8: cerebellar lobule VIII, M1: Primary motor cortex, PMd: Dorsal pre-motor cortex, PMv: Ventral Pre-motor cortex, SMA: Supplementary Motor Area, Par: Inferior Parietal cortex

As early as 1952, a cortical stimulation study in animals described two distinct sensorimotor body representations in the cerebellum [31], one in lobules IV, V and VI and the other in lobule VIII. Functional connectivity studies sometimes dichotomized these regions into the superior cerebellum (lobules IV, V and VI) and anteroinferior cerebellum (lobule VIII) [11, 32]. O'Reilly et al. (2010) described the involvement of cerebellar lobules V, VI, and VIII in a sensorimotor resting-state network integrating the prefrontal, premotor, primary motor, and posterior parietal cortex [26]. Guell et al. (2018) proposed a two-axis functional organization of the cerebellum, from primary to transmodal tasks and from task-unfocused to task-focused tasks [28]. They showed that the contribution of the second motor representation (lobule VIII) involved in more associative, task-focused processes was different from that of the first motor representation (lobules IV-V-VI) involved in pure motor processes. Thus, our observations suggest that the level of this task-oriented activity, when stronger, is correlated with a better motor outcome. This finding holds even more because the motor assessment method chosen in our study is an activity limitation score (ARAT) rather than a pure deficiency score.

The importance of the connection between the cerebellum and some of the ipsilesional cortical regions of the motor system in motor recovery could be anticipated, especially M1.

However, the role of the connectivity between lobule VIII and SMA in motor recovery was less described ([11] using rsfMRI [10], using task based fMRI). Activations of the SMA have been associated with good motor outcomes according to task-based fMRI [33]. The SMA plays a role in initiating and executing movement and participates in the planning of essential motor sequences during recovery [34]. It is worthy to highlight that it was the initial « configuration » i.e. the FC between Ce8-c/SMA-i at V1 that predicted motor recovery but that this FC did not change over time. As stated by Branscheidt et al. (2022) in a study of 19 patients using fMRI, changes in FC are not necessarily associated with motor recovery and could be relative [35].

A second finding is that, in contrast to these cortico-cerebellar connectivities, functional connectivity between the ipsilesional cortical areas or between hemispheres did not correlate with recovery. These findings are in line with a recent study that found no correlation between cortico-cortical connectivity at rest and motor recovery and that found no poststroke cortico-cortical connectivity changes over time despite substantial behavioral recovery [35].

Cerebello-Cortical Network Organization in Stroke Patients

Previous studies have consistently shown reduced activity in both ipsilateral cortical motor regions (M1, SMA) and contralateral cerebellar lobules (V and VI) in affected patients compared to healthy subjects [32, 36]. However, these decreased functional connectivities are not associated with poor motor recovery and might be relative. The decrease in cortical activity may partly explain the difference in cortico-cerebellar functional correlation between our subjects and control subjects. Furthermore, the fact that significantly different connectivities were exclusively cortico-cerebellar could be explained by the predominantly subcortical localization of the lesions ($n=9$, 60%). Indeed, most cortico-cortical connections are mediated by superficial fibers, known as "U fibers," which are spared by lesions in the majority of patients. It is possible that the disconnection effect, both structural and functional, was less significant for these

Table 3 Functional connectivity (FC) values in patients and healthy subjects * means a FDR-corrected p value < 0.05 for the comparison of healthy subjects vs. patients

	Healthy subjects	Patients (V1)	Patients (V2)	Patients (V3)
Cortico-cerebellar FC				
Ce456-c / M1-i	0.314 (0.212–0.493)	0.110 (-0.088-0.208)*	0.132 (-0.031-0.235)	0.017 (-0.141-0.119)*
Ce456-c-/ PMd-i	0.324 (0.125–0.496)	0.228 (0.034–0.359)	0.201 (-0.052-0.296)	0.073 (-0.026-0.313)
Ce456-c-/ SMA-i	0.327 (0.168–0.533)	0.037 (-0.128-0.181)*	0.052 (-0.022-0.184)*	0.019 (-0.190-0.103)*
Ce456-c-/ Par-i	0.028 (-0.061-0.148)	0.099 (-0.170-0.186)	-0.037 (-0.129-0.061)	-0.013 (-0.073-0.188)
Ce8-c / M1-i	0.114 (0.038–0.218)	0.002 (-0.092-0.207)	0.084 (0.004–0.224)	0.042 (-0.090-0.168)
Ce8-c/ PMd-i	0.353 (0.227–0.514)	0.117 (-0.002-0.275)*	0.189 (-0.024-0.259)	0.154 (-0.017-0.289)
Ce8-c/ SMA-i	0.211 (0.108–0.465)	0.054 (-0.018-0.213)	0.100 (-0.002-0.208)	0.122 (-0.179-0.286)
Ce8-c/ Par-i	0.098 (-0.028-0.251)	0.120 (-0.024-0.289)	0.010 (-0.051-0.056)	0.030 (-0.045-0.181)
Intrahemispheric cortical FC				
M1-i / PMd-i	0.382 (0.333–0.446)	0.342 (0.188–0.582)	0.319 (0.159–0.418)	0.354 (0.098–0.493)
M1-i / PMv-i	0.470 (0.359–0.572)	0.529 (0.237–0.684)	0.388 (0.287–0.643)	0.363 (0.157–0.617)
M1-i / SMA-i	0.773 (0.620–0.888)	0.725 (0.391–0.904)	0.725 (0.592–1.019)	0.728 (0.427–1.018)
PMd-i / PMv-i	0.803 (0.497–0.913)	0.543 (0.507–0.646)	0.572 (0.502–0.677)	0.540 (0.415–0.699)
PMd-i / SMA-i	0.480 (0.430–0.585)	0.431 (0.309–0.492)	0.438 (0.249–0.604)	0.464 (0.220–0.607)
PMd-i / Par-i	0.465 (0.315–0.745)	0.405 (0.324–0.457)	0.284 (0.078–0.485)	0.376 (0.095–0.562)
PMv-i-/ Par-i	0.331 (0.217–0.415)	0.360 (0.249–0.525)	0.360 (0.188–0.535)	0.372 (0.208–0.424)
M1-c / PMd-c	0.393 (0.222–0.483)	0.443 (0.209–0.705)	0.257 (0.128–0.520)	0.257 (0.071–0.392)
M1-c / PMv-c	0.423 (0.348–0.496)	0.316 (0.237–0.462)	0.316 (0.277–0.552)	0.176 (0.083–0.471)
M1-c / SMA-c	0.881 (0.579-1,000)	0.773 (0.704–0.976)	0.719 (0.627–0.965)	0.830 (0.538–1.006)
PMd-c / PMv-c	0.786 (0.586–0.861)	0.700 (0.460–0.756)	0.436 (0.359–0.717)	0.593 (0.470–0.772)
PMd-c / SMA-c	0.362 (0.291–0.516)	0.399 (0.306–0.513)	0.389 (0.300-0.564)	0.414 (0.321–0.553)
PMd-c/ Par-c	0.646 (0.529–0.887)	0.539 (0.452–0.638)	0.410 (0.283–0.644)	0.398 (0.240–0.743)
PMv-c-/ Par-c	0.685 (0.524–0.848)	0.657 (0.492–0.742)	0.587 (0.449–0.624)	0.592 (0.416–0.743)
Inter-hemispheric FC				
M1-i /M1-c	0.896 (0.737–1.121)	1.005 (0.733–1.363)	1.107 (0.708–1.313)	1.154 (0.848-1.400)
PMd-i /PMd-c	0.725 (0.484–0.795)	0.600 (0.438–0.827)	0.516 (0.464–0.647)	0.567 (0.463–0.688)
PMv-i /PMv-c	0.530 (0.344–0.743)	0.686 (0.564–0.810)	0.633 (0.521–0.777)	0.633 (0.465–0.813)
SMA-i /SMA-c	1.081 (1.009–1.299)	1.006 (0.659–1.221)	0.981 (0.788–1.180)	1.030 (0.824–1.123)
Par-i /Par-c	0.625 (0.530–0.734)	0.628 (0.535–0.727)	0.558 (0.486–0.632)	0.585 (0.525–0.781)

Values are the median ± interquartile range (IQR), * report FDR corrected significance

Abbreviations: FC: Functional Connectivity, -i: ipsilesional, -c: contralesional, Ce456: cerebellar lobule IV-V-VI, Ce8: cerebellar lobule VIII, M1: Primary motor cortex, PMd: Dorsal pre-motor cortex, PMv: Ventral Pre-motor cortex, SMA: Supplementary Motor Area, Par: Inferior Parietal cortex

connections. However, the limited size of our sample did not allow us to carry out additional subgroup analyses to confirm this hypothesis. Although this explanation seems plausible, it was surprising not to find only one difference in cortico-cortical interactions (interhemispheric connectivities between M1-IHI especially), considering the literature [11, 37, 38]. There may have three explanations for this lack of difference in IHI between patients and controls in our functional connectome. First, stroke location highly impacts the decrease in IHI in patients. This IHI imbalance model may not be present for stroke lesions that do not involve a structural damage to transcallosal fibers [39, 40]. As stated in the results, the majority of our patients had subcortical stroke and only two patients had lesions that could potentially damage transcallosal fibers at the level of the frontal lobe. Second, the condition in which IHI is studied is crucial. Meaningful abnormalities in interhemispheric inhibition would be better detected when active movements of a paretic limb were performed rather than at rest [41].

Third, the lack of results concerning cortico-cortical connectivity could be due to a lack of power due to the small sample size in the present study.

Strengths, Limitations and Perspectives

Our study had some limitations that need to be addressed. First, the main limitation of our study is the small number of patients ($n = 15$), which explains the lack of power of some analyses. Due to the small sample size, positive results can be considered, but negative results are more contentious to interpret, given the robustness and stringency of the FDR correction. However, our sample size is in the range of that of previously published fMRI longitudinal cohorts [11,

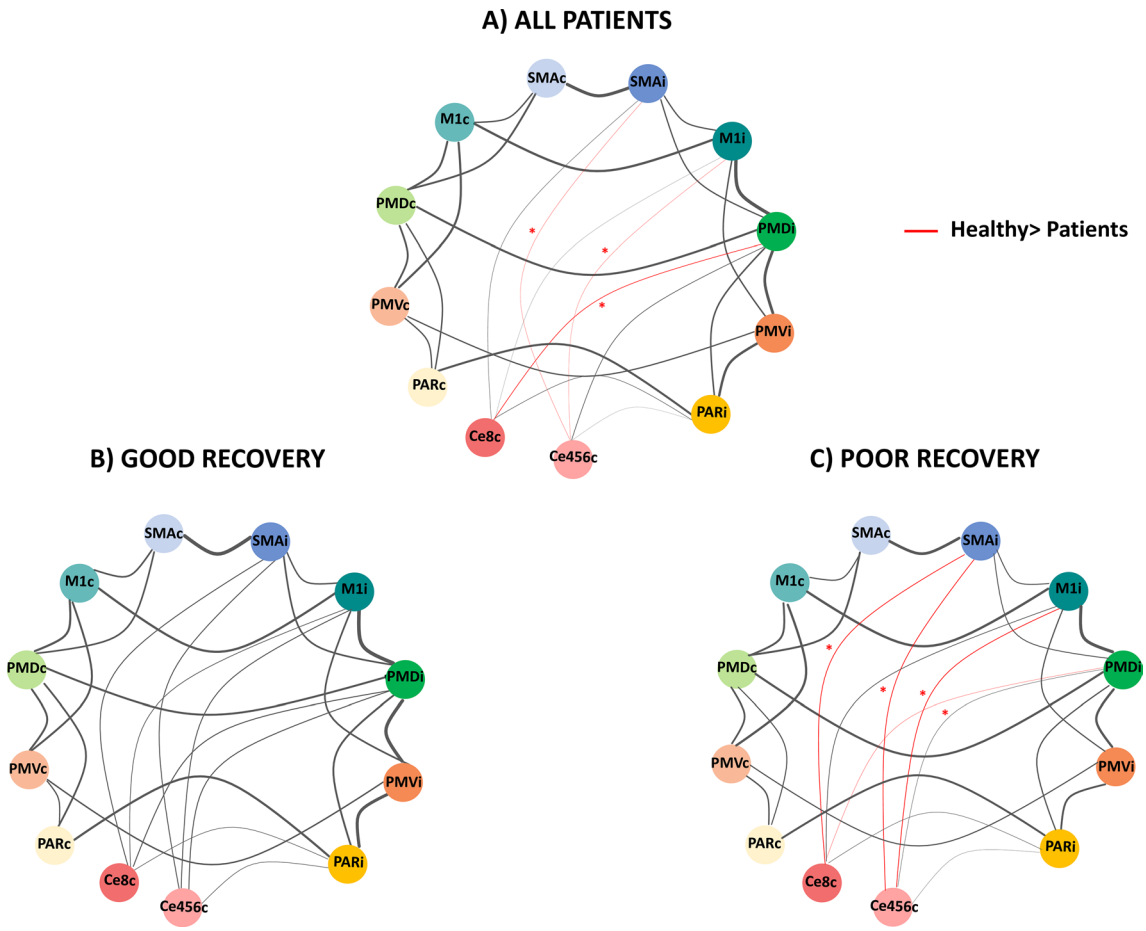

Fig. 4 Comparison of functional connectivity values between patients at V1 and healthy subjects for (**A**) all patients, (**B**) patients with good recovery, and (**C**) patients with poor recovery The red lines correspond to the connections that are weaker in stroke patients than in healthy controls. The mark * corresponds to a significant FDR corrected p-value. The black lines represent the connections that were not different between the two groups. The width of the lines corresponds to the strength of the connectivity

12]. Using the resting state for the functional connectome is both a limit and a strength. This is a limitation, as the signal is lower than that in task-based fMRI studies and less robust. However, on the other hand, resting-state fMRI could be performed in all patients, even those with more severe symptoms, contrary to task-based fMRI. Our cohort is not biased in favor of mild to minor deficits. Then, further studies are needed because the generalisability of our study could be questioned since the results are valid for our population, severe enough to go to a rehabilitation center and with a high prevalence of subcortical lesions.

A strength of our study is that we matched our patients with the healthy subjects in a 1:1 ratio. Second, motor recovery was defined by an activity limitation score (ARAT) rather than a pure deficiency score according to the Internal Classification of Functioning, Disability and Health, (such as the Fugl Meyer score), which is close to the activity of daily living tasks.

It is noteworthy that much attention has recently been given to noninvasive brain stimulation protocols targeting the cerebellum. Indeed, as in our study, the cerebellum and lobule VIII in particular have dense functional connections to cortical areas of the motor network. Cerebellar stimulation could be utilized to modulate these connected neocortical areas and their respective functional networks affected by supratentorial stroke via nonimpaired cerebellar entry. Successful results have already been published, and our study reinforced the physiopathological basis of this approach.

Conclusion

Our study suggested that the level of functional connectivity of the cortico-cerebellar network at rest could serve as a relevant biomarker for assessing and predicting motor recovery after stroke. Motor recovery in the subacute phase was correlated exclusively with the intensity of functional connectivity of contralesional cerebellar lobule VIII with the ipsilesional supplementary motor area (SMA). Our results

must be generalized with caution due to our small sample size and requires further validation. In addition, by extending our knowledge of the mechanisms underlying motor recovery, our results could also serve as a rationale for the therapeutic application of noninvasive brain stimulation, targeting noninjured regions and promoting coupled stimulation of the cerebellum and motor (or premotor) cortices in particular.

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Data Availability Data are available upon reasonable request to the corresponding author.

Declarations

Ethical Approval The study protocol was approved by the institutional ethics committee and conducted in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from each participant or his or her legal representative/family member.

Competing Interests The authors declare no competing interests.

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