

Longitudinal changes in the inferior cerebellar peduncle and lower limb motor recovery following subcortical infarction

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Abstract

Background

The cerebellum receives afferent signals from spinocerebellar pathways regulating lower limb movements. However, the longitudinal changes in the spinocerebellar pathway in the early stage of unilateral supratentorial stroke and their potential clinical significance have received little attention.

Methods

Diffusion tensor imaging and Fugl-Meyer assessment of lower limb were performed 1, 4, and 12 weeks after onset in 33 patients with acute subcortical infarction involving the supratentorial areas, and in 33 normal subjects. We evaluated group differences in diffusion metrics in the bilateral inferior cerebellar peduncle (ICP) and analyzed the correlation between ICP diffusion metrics and changes to the Fugl-Meyer scores of the affected lower limb within 12 weeks after stroke.

Results

Significantly decreased fractional anisotropy and increased mean diffusivity were found in the contralesional ICP at week 12 post stroke relative to controls (all $P < 0.01$) and those at week 1 (all $P < 0.05$). There were significant fractional anisotropy decreases in the ipsilesional ICP at week 4 ($P = 0.008$) and week 12 ($P = 0.004$) relative to controls. Both fractional anisotropy ($r_s = 0.374$, $P = 0.038$) and mean diffusivity ($r_s = -0.499$, $P = 0.004$) changes in the contralesional ICP correlated with changes in Fugl-Meyer scores of the affected lower limbs in all patients.

Conclusion

Bilateral ICP degeneration occur in the early phase of supratentorial stroke and contralesional ICP degeneration may hinder recovery of the affected lower limb. ICP could serve as a potential therapeutic target for improving lower limb function after supratentorial stroke.

Background

The cerebellum receives afferent signals from both the sensorimotor cortex and the muscles regulating limb movements via the cortico-ponto-cerebellar and spinocerebellar pathway, respectively [1, 2]. The cortico-ponto-cerebellar tract transfers efferent motor signals from the sensorimotor cortex to the contralateral cerebellum via the middle cerebellar peduncle [1]. The spinocerebellar tract, especially the dorsal spinocerebellar tract (DSCT), mainly conveys somatosensory information from the spindles and Golgi tendon organs of the ipsilateral trunk and limb muscles, and enters the cerebellum via the inferior cerebellar peduncle (ICP) [3]. Secondary degeneration in the contralesional middle cerebellar peduncle after supratentorial stroke has been widely reported in diffusion tensor imaging (DTI) studies, associated with the severity of hemiplegic limb function after stroke, and proposed as a crucial mechanism of

crossed cerebellar diaschisis [4, 5]. However, the pattern of ICP changes after supratentorial stroke and its relationship with post-stroke changes of motor function have been rarely reported.

Recently, Kim et al. [6] found a secondary degeneration characterized by reduced fractional anisotropy (FA) and elevated mean diffusivity (MD) in the contralesional ICP in 23 patients with subacute middle cerebral artery (MCA) stroke, a change associated with patients' ambulatory and lower limb function. They believed that insufficient peripheral proprioceptive stimulation to the cerebellum due to lower limb weakness may result in secondary changes in the spinocerebellar pathway, but they could not fully determine whether FA reduction in the contralesional ICP was affected by hemiplegic muscles, a hypofunctional cerebellum, or both due to the retrospective and cross-sectional design of their study. Therefore, longitudinal studies are necessary to clarify the possible mechanism of contralesional ICP degeneration after supratentorial ischemic stroke. In addition, Li et al. [7] reported that structural reorganization of the ipsilesional ICP can be induced via repetitive transcranial magnetic stimulation of the ipsilesional primary motor cortex in patients with acute subcortical infarction involving MCA territory, suggesting a possible direct connection between the ICP and the ipsilateral primary motor cortex. Studies with probabilistic fiber tracking further confirmed that, in addition to a 100% connectivity between the ICP and the anterior lobe of the cerebellum, especially lobules IV–V, the ICP also had a high connectivity with ipsilateral sensory-motor related cerebral cortices [8]. Nevertheless, whether supratentorial stroke lesions can also cause secondary damage in the ipsilesional ICP due to a connectivity disruption between the ICP and sensory-motor cortices remain unclear.

In this study, we hypothesized that secondary degeneration may occur in the bilateral ICP in the early phase of supratentorial ischemic stroke, but the mechanisms underlying bilateral ICP degeneration may be different. Insufficient peripheral proprioceptive stimulation due to lower limb weakness may lead to the degeneration of the contralesional ICP after supratentorial stroke, but secondary damage in the ipsilesional ICP may be attributed to Wallerian degeneration, a well-known phenomenon defined as anterograde degeneration of a nerve tract distal to an ischemic injury [9-11]. Further, contralesional ICP degeneration may hamper the recovery of motor function of the affected lower limb. In order to test our hypothesis, DTI combined with amplitude of low-frequency fluctuation (ALFF), an index used to investigate brain function in healthy subjects [12] and patients with neurological disorders [13, 14], were used to assess the microstructural integrity of the ICP and functional changes of the anterior lobe of the cerebellum (lobules IV-VI), respectively, during a 12-week follow-up after acute subcortical infarction involving supratentorial regions. We also analyzed the correlation between changes to these indices and improvements in motor function of the affected lower limb.

Material And Methods

Participants

This research was approved by the First Affiliated Hospital of Sun Yat-Sen University ethics committee. Written informed consents were gained from each participant. We applied the following inclusion criteria:

(1) a first unilateral supratentorial subcortical infarct (<7 days) (Fig. 1); (2) no intra-cranial or extra-cranial artery occlusion on magnetic resonance angiography confirmed by either ultrasound or magnetic resonance angiography; (3) baseline scores of < 34 on the lower limb (LL) component of the Fugl–Meyer (FM-LL); (4) age 18-75 years; and (5) patients receiving routine rehabilitation therapies, as reported earlier [15-18].¹²¹³¹⁴ Exclusion criteria were: (1) medical implants contraindicated for cerebral magnetic resonance imaging (MRI); (2) additional neurological diseases other than stroke; (3) traumatic brain injury or psychiatric disease or alcohol abuse; (4) any revascularization therapy; (5) presence of aphasia or apraxia, or use of any medications likely to affect motor examinations during the follow-up period. We also recruited age- and gender-matched healthy controls.

Experimental design

Each patient underwent three MRI acquisitions: within the first week (week 1; < 7 days), the fourth week (week 4; 28 ± 4 days), and the 12th week (week 12; 84 ± 4 days) [15-18]. Neurological and FM-LL assessments were performed before MRI examination at each time point. Controls, however, were examined only once.

Behavioral assessments

The National Institutes of Health Stroke Scale was used to assess initial neurological deficits. FM-LL scale was administered to evaluate LL motor deficits at 1-week, 4-weeks, and 12-weeks after stroke.

Image acquisition

MRI was performed using a 3 T MRI system (Tim Trio; Siemens, Erlangen, Germany). High resolution ($1 \times 1 \times 1 \text{ mm}^3$) 3D T1-weighted images were acquired using MPRAGE with repetition time (TR) = 2,530 ms, echo time (TE) = 3.45 ms, inversion time = 1,100 ms, flip angle = 7° , field of view = $256 \times 256 \text{ mm}^2$, 192 slices. DTI data were gained using a single-shot echo-planar imaging sequence with TR = 7,000 ms, TE = 91 ms, flip angle = 90° , matrix = 128×128 , voxel size = $2 \times 2 \times 3 \text{ mm}^3$, axial slices = 50, field of view = $256 \times 256 \text{ mm}^2$, non-collinear directions = 64, $b = 1,000 \text{ s/mm}^2$. Resting-state functional images were collected using an echo-planar imaging sequence with TR = 2,000 ms, TE = 30 ms, flip angle = 90° , field of view = $220 \times 220 \text{ mm}^2$, voxel size = $3.44 \times 3.44 \times 3 \text{ mm}^3$, averages = 1, axial slices = 33.

DTI and resting-state functional data preprocessing

DTI data preprocessing were performed using the Pipeline for Analyzing Brain Diffusion Images toolkit (PANDA, <http://www.nitrc.org/projects/panda/>) [19] and FSL (<http://fsl.fmrib.ox.ac.uk/fsl>) [20]. The detailed preprocessing procedures can be obtained from our previous research [15, 17, 18]. The functional MRI images were preprocessed using Data Processing & Analysis for Brain Imaging (DPABI; <http://rfmri.org/DPABI>), which is based on Resting-state Data Analysis Toolkit (REST; <http://www.restfmri.net>) and Statistical Parametric Mapping (SPM12; <http://www.fil.ion.ucl.ac.uk/spm>). Briefly, preprocessing procedures included the first ten volumes' removal, slice timing and motion

correction, the transformation from individual space to Montreal Neurological Institute space, spatial smoothing with a Gaussian kernel of $4 \times 4 \times 4 \text{ mm}^3$, and band-pass filtering (0.01-0.08 Hz). Participant data were excluded if they met the head motion criteria, which included head motion $> 2 \text{ mm}$ translation or a 2° rotation in any direction. For the ALFF calculation, the time courses were first converted to the frequency domain using fast Fourier transform. The square root of the power spectrum was then computed and averaged across 0.01-0.08 Hz at each voxel. This averaged square root was considered as the ALFF [12-14]. To reduce the global effects of variability across subjects, the ALFF of each voxel was divided by the global mean ALFF value obtained for each participant.

Regions of interest (ROIs) analysis

For ROI analysis, we selected the bilateral ICP and the anterior lobe of the cerebellum (lobules IV-VI). The bilateral ICP was extracted from the Johns Hopkins University white matter tractography atlas (JHU-ICBM-DTI-81-WMPM-90p) [21] and the bilateral anterior lobe of the cerebellum from the Automated Anatomical Labeling atlas. Averaged FA and MD values for each ICP were obtained for each subject using the corresponding normalized diffusion metric maps. The mean ALFF values of each anterior lobe of the cerebellum were acquired for each participant using the individual ALFF maps.

Statistical analysis

Categorical variables were compared using the Pearson χ^2 or Fisher exact tests (when the expected number was ≤ 5). Age was compared between the patient group and the control group using the independent t test after normality testing by the Shapiro-Wilk test. In the patient group, FM-LL scores obtained at multiple time points were compared using the paired-samples Wilcoxon signed-rank test. Analyses of variance with repeated measures were employed to compare absolute values within ROIs between time points, and a *post hoc* analysis was conducted based on the Bonferroni correction for multiple testing. A Spearman's partial correlation analysis was used to determine correlations between changes in FM-LL scores and changes in ICP diffusion parameter values when adjusting for age and gender as covariates, which was defined as the difference between FM-LL scores or diffusion parameter values at baseline and 12 weeks. All tests were 2-sided and $P < 0.05$ was considered significant. The FA and MD values of the ICP and the ALFF values of the anterior lobe of the cerebellum at each time point were compared with those of controls by independent t -test with a corrected P value threshold (corrected $P_{\text{threshold}} = 0.05/3$). All analyses were conducted using SPSS 16.0 for Windows (SPSS, Chicago, IL, USA).

Results

Subject characteristics and behavioral assessment

In total, 33 patients (14 women and 19 men, mean age: 53.4 years) and 33 healthy controls (14 women and 19 men, mean age: 53.7 years) were included in the study. The demographic and clinical characteristics of the groups are detailed in Table 1 and supplementary Table I. No significant differences in age, sex, and vascular risk factors except for hypertension were found between groups. In the patient

group, both FM-LL scores at the week 4 and week 12 were significantly higher than those at week 1 (all $P < 0.001$ [Cohen's $d = 3.859$]), while the FM-LL scores at the week 12 were significantly higher than those at week 4 ($P < 0.001$, $d = 3.441$).

Dynamic changes in DTI-derived metrics and ALFF after stroke

The results of the comparison of the DTI-derived metrics and ALFF are shown in Fig. 2. Significantly decreased FA and increased MD were found in the contralesional ICP at week 12 post stroke compared with controls (FA, $P = 0.003$, $d = 0.753$; MD, $P = 0.008$, $d = 0.692$) and with values recorded at week 1 (FA, $P = 0.035$, $d = 0.543$; MD, $P = 0.025$, $d = 0.584$). There were significant FA decreases but not MD increases in the ipsilesional ICP at week 4 ($P = 0.008$, $d = 0.674$) and week 12 ($P = 0.004$, $d = 0.729$) relative to controls, but no significant differences in the FA and MD of the ipsilesional ICP between time points. The results of ALFF analysis revealed that compared with the control group, the patient group exhibited significant decreases in the mean ALFF values of the contralesional anterior lobe of the cerebellum from week 4 ($P < 0.0001$, $d = 1.108$) to week 12 ($P = 0.004$, $d = 0.74$) after stroke, but such changes were not found in the ipsilesional anterior lobe of the cerebellum. The mean ALFF values of the bilateral anterior lobe of the cerebellum did not significantly differ between time points.

Correlational analyses between motor assessments and DTI-derived metrics

As shown in Fig. 3, Spearman's partial correlation analysis revealed that both FA ($r_s = 0.374$, $P = 0.038$) and MD ($r_s = -0.499$, $P = 0.004$) changes in the contralesional ICP correlated with changes in FM-LL scores across patients when adjusting for age and gender as covariates.

Discussion

In this study, we found that patients with acute subcortical infarction involving the supratentorial areas exhibited significantly decreased FA in the bilateral ICP and reduced ALFF in the contralesional anterior lobe of the cerebellum post-stroke. The FA and MD changes in the contralesional ICP found within a 12-week follow-up period correlated with FM-LL score changes of the affected limb across patients. These findings supported our hypothesis that (1) secondary degeneration occurred in the bilateral ICP in the early phase of supratentorial ischemic stroke, and (2) the contralesional ICP degeneration hampered recovery of motor function of the affected lower limb.

Significant FA decreases and MD increases at 12-weeks after stroke were detected in the contralesional ICP, indicating that a secondary degeneration of the contralesional ICP far from the stroke lesion, progressively deteriorating with time, can be clearly and quantitatively detected by DTI and. Our finding of decreased FA and increased MD in the contralesional ICP seems inconsistent with the structural changes in this area in subacute supratentorial stroke patients. Kim et al. [6] found a marked FA reduction and MD increase in the contralesional ICP at 27 days after stroke in the patient group compared with the control group. This discrepancy in results may be due to experimental design differences. Since in their study only patients with modified Rankin Scale score ≥ 3 were recruited, while in the present study, patients

with less severe deficits in lower limb function were also included and, therefore, our results can be readily generalized to a wider patient population with supratentorial stroke. We found that changes in both FA and MD in the contralesional ICP significantly correlated with changes in FM-LL scores during a 12-week follow-up period, suggesting that the contralesional ICP degeneration hampered the recovery of motor function of the affected lower limb after stroke. The integrity of the corticospinal tract (CST) has been correlated with lower limb function using the FM assessment of the lower extremities [22]. However, recent studies have indicated that CST integrity, as evaluated by the CST lesion load, was only weakly associated with lower limb function [23, 24] and did not accurately predict a proportional recovery of the lower extremities after stroke [25]. Therefore, the lower limb motor recovery following stroke is insufficiently explained by the integrity of the CST alone. Based on the findings of previous studies, our result that lower limb motor function was also associated with ICP integrity is noteworthy.

Kim et al. [6] considered that insufficient peripheral proprioceptive stimulation to the cerebellum from a weak lower limb may result in secondary degeneration in the contralesional spinocerebellar pathway, but they could not fully determine whether FA reduction in the contralesional ICP was affected by hemiplegic muscles, a hypofunctional cerebellum, or both due to the retrospective and cross-sectional design of their study. We found that ALFF in the contralesional anterior lobe of the cerebellum reduced sharply at week 4 but increased somewhat at week 12 after onset. Therefore, we believed it impossible for ICP degeneration to contribute to reduced cerebellar function because ICP degeneration occurred after cerebellar function declined. Insufficient peripheral proprioceptive stimulation due to lower limb weakness may lead to a hypofunctional cerebellum and the degeneration of the contralesional ICP after supratentorial stroke, but whether a hypofunctional cerebellum also contributes to the degeneration in the contralesional ICP after supratentorial stroke need to be verified by future studies.

In the present study, patients also exhibited a degeneration characterized by reduced FA in the ipsilesional ICP in the early phase of supratentorial ischemic stroke. The mechanisms of secondary degeneration in the ipsilesional ICP should be different from those in the contralesional ICP because the motor function of the ipsilesional lower limb is not affected. Studies with probabilistic fiber tracking confirmed that the ICP was not only connected to the anterior lobe of the cerebellum, but also with ipsilateral sensory-motor related cerebral cortices. In the present study, we also found that the patients exhibited a disruption of the ipsilesional connectivity between the ICP and cerebral cortices due to the ischemic lesion in the acute stage of stroke using DTI-based deterministic fibre tracking algorithm (see supplementary Fig. I). Therefore, we believe that the disruption of structural integrity in the ipsilesional ICP may be attributed to Wallerian degeneration, a well-known phenomenon defined as anterograde degeneration of a nerve tract distal to an ischemic injury [9-11].

A major limitation of this study is that the ICP selected in our study contains multiple fiber tracts connected to the cerebellum, and so the FA and MD of the ICP are not specific to the DSCT, mainly because of its small size and the difficulty to differentiate from adjacent tracts due to the limited resolution of the DTI sequence. Future studies should be conducted focusing on the pattern of changes of individual tracts such as DCST following supratentorial stroke, which may refine our findings. In

addition, although the ICP also includes the cuneocerebellar tract, that conveys somatosensory signals from the ipsilateral upper limb muscle to the cerebellum, the role of ICP degeneration in the functional upper limb affectation after supratentorial stroke remains unknown because of a lack of neuroimaging basis for the clinic-anatomic association between upper limb function and ICP integrity. Finally, the relatively small sample size of our study is another limitation.

Conclusions

Our results provide evidence that secondary degeneration occurs in the bilateral ICP following an acute subcortical infarct involving supratentorial areas, and that contralesional ICP degeneration hinders motor recovery of the affected lower limb, but the mechanisms of bilateral ICP degeneration may be different. The findings of this study will improve our understanding of the mechanisms underlying the action of neuromodulation techniques including peripheral nerve and cerebellar stimulation and raise the possibility that the ICP could serve as a potential therapeutic target for improving lower limb function after stroke.

Abbreviations

ALFF, amplitude of low-frequency fluctuation, CST, corticospinal tract; DSCT: dorsal spinocerebellar tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; FM-LL, lower limb component of the Fugl–Meyer; ICP: inferior cerebellar peduncle; LL, lower limb; MCA, middle cerebral artery; MD, mean diffusivity; MRI, magnetic resonance imaging; TE, echo time; TR, repetition time.

Declarations

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Authors' contributions

Author contributions included conception and study design (GL, JSZ), acquisition of data (GL, CD, KQP, SQT and CMX), statistical analysis (GL, YMG, and CD), interpretation of results (GL, SHX and YMG), drafting the manuscript work (GL and YMG) or revising it critically for important intellectual content (all authors) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (all authors).

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Availability of data and materials

The datasets in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consents were gained from each participant and the research was approved by the First Affiliated Hospital of Sun Yat-Sen University ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kim Y, Im S, Kim SH, Park GY. Laterality of cerebellar afferent and efferent pathways in a healthy right-handed population: a diffusion tensor imaging study. *J Neurosci Res.* 2019;97:582-96.
2. Grimaldi G, Manto M. Topography of cerebellar deficits in humans. *Cerebellum* 2012;11:336-51.
3. Mann MD. Axons of dorsal spinocerebellar tract which respond to activity in cutaneous receptors. *J Neurophysiol.* 1971;34:1035-50.
4. Pantano P, Baron JC, Samson Y, Bousser MG, Derouesne C, Comar D. Crossed cerebellar diaschisis. Further studies. *Brain* 1986;109:677-94.
5. Kim Y, Kim SH, Kim JS, Hong BY. Modification of cerebellar afferent pathway in the subacute phase of stroke. *J Stroke Cerebrovasc Dis.* 2018;27:2445-52.
6. Kim JS, Kim SH, Lim SH, Im S, Hong BY, Oh J, et al. Degeneration of the inferior cerebellar peduncle after middle cerebral artery stroke: another perspective on crossed cerebellar diaschisis. *Stroke.* 2019;50:2700-7.
7. Li J, Zuo Z, Zhang X, Shao X, Lu J, Xue R, et al. Excitatory repetitive transcranial magnetic stimulation induces contralesional cortico-cerebellar pathways after acute ischemic stroke: a preliminary DTI Study. *Front Behav Neurosci.* 2018;12:160.

8. Habas C, Cabanis EA. Anatomical parcellation of the brainstem and cerebellar white matter: a preliminary probabilistic tractography study at 3 T. *Neuroradiology*. 2007;49:849-63.
9. Liang Z, Zeng J, Zhang C, Liu S, Ling X, Wang F, et al. Progression of pathological changes in the middle cerebellar peduncle by diffusion tensor imaging correlates with lesser motor gains after pontine infarction. *Neurorehabil Neural Repair*. 2009;23:692-8.
10. Liang Z, Zeng J, Zhang C, Liu S, Ling X, Xu A, et al. Longitudinal investigations on the anterograde and retrograde degeneration in the pyramidal tract following pontine infarction with diffusion tensor imaging. *Cerebrovasc Dis*. 2008;25:209-16.
11. Liang Z, Zeng J, Liu S, Ling X, Xu A, Yu J, et al. A prospective study of secondary degeneration following subcortical infarction using diffusion tensor im J *Neurol Neurosurg Psychiatry*. 2007;78:581-6.
12. Yang H, Long XY, Yang Y, Yan H, Zhu CZ, Zhou XP, et al. Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. *Neuroimage*. 2007;36:144-52.
13. Zhang J, Meng L, Qin W, Liu N, Shi FD, Yu C. Structural damage and functional reorganization in ipsilesional M1 in well-recovered patients with subcortical stroke. *Stroke*. 2014;45:788-93.
14. Zhang Z, Lu G, Zhong Y, Tan Q, Chen H, Liao W, et al. fMRI study of mesial temporal lobe epilepsy using amplitude of low-frequency fluctuation analysis. *Hum Brain Mapp*. 2010;31:1851-61.
15. Liu G, Dang C, Chen X, Xing S, Dani K, Xie C, et al. Structural remodeling of white matter in the contralesional hemisphere is correlated with early motor recovery in patients with subcortical infarction. *Restor Neurol Neurosci*. 2015;33:309-19.
16. Liu G, Dang C, Peng K, Xie C, Chen H, Xing S, et al. Increased spontaneous neuronal activity in structurally damaged cortex is correlated with early motor recovery in patients with subcortical infarction. *Eur J Neurol*. 2015;22:1540-7.
17. Liu G, Tan S, Dang C, Peng K, Xie C, Xing S, et al. Motor recovery prediction with clinical assessment and local diffusion homogeneity after acute subcortical infarction. *Stroke*. 2017;48:2121-8.
18. Liu G, Peng K, Dang C, Tan S, Chen H, Xie C, et al. Axial diffusivity changes in the motor pathway above stroke foci and functional recovery after subcortical infarction. *Restor Neurol Neurosci*. 2018;36:173-82.
19. Cui Z, Zhong S, Xu P, He Y, Gong G. PANDA: a pipeline toolbox for analyzing brain diffusion images. *Front Hum Neurosci*. 2013;7:42.
20. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. *FSL*. 2012;62:782-90.
21. Mori S, Wakana S, Van Zijl PCM, Nagee-Poetscher L. *MRI Atlas of Human White Matter*. London: Elsevier Science; 2005.
22. Jayaram G, Stagg CJ, Esser P, Kischka U, Stinear J, Johansen-Berg H. Relationships between functional and structural corticospinal tract integrity and walking post stroke. *Clin Neurophysiol* 2012;123:2422-8.

23. Jones PS, Pomeroy VM, Wang J, Schlaug G, Tulasi Marrapu S, Geva S, et al. Does stroke location predict walk speed response to gait rehabilitation? *Hum Brain Mapp.* 2016;37:689-703.
24. Dawes H, Enzinger C, Johansen-Berg H, Bogdanovic M, Guy C, Collett J, et al. Walking performance and its recovery in chronic stroke in relation to extent of lesion overlap with the descending motor tract. *Exp Brain Res.*2008; 186:325-33.
25. Smith MC, Byblow WD, Barber PA, Stinear CM. Proportional recovery from lower limb motor impairment after stroke. *Stroke.* 2017;48:1400-3.

Tables

Table 1 Demographic and clinical characteristics of the groups

	Patients group (n=33)	Control group (n=33)
Age, years (Mean ± SD)	53.4 ± 1.81	53.7 ± 2.32
Women, n (%)	14 (42.4)	14 (42.4)
Hypertension, n (%)	19 (57.6)	11 (33.3)*
Diabetes mellitus, n (%)	11 (33.3)	7 (21.2)
Hypercholesterolemia, n (%)	7 (21.2)	5 (15.2)
Tobacco users, n (%)	4 (12.1)	4 (12.1)
Lesion in left hemisphere, n (%)	17 (51.5)	
Median lesion volume (range; mL)	5.9 (0.9-28.5)	
Median NIHSS at week 1 (range)	9 (2-18)	
Median FM-LL at week 1 (range)	9 (00-33)	
Median FM-LL at week 4 (range)	27 (00-34) [†]	
Median FM-LL at week 12 (range)	32 (11-34) ^{†#}	

Empty cells indicate no assessment. FM-LL indicates Fugl-Meyer score of lower limb; NIHSS, National Institutes of Health Stroke Scale. * $P < 0.05$, compared with the patient group. [†] $P < 0.001$, compared with week 1; [#] $P < 0.001$, compared with week 4.

Figures

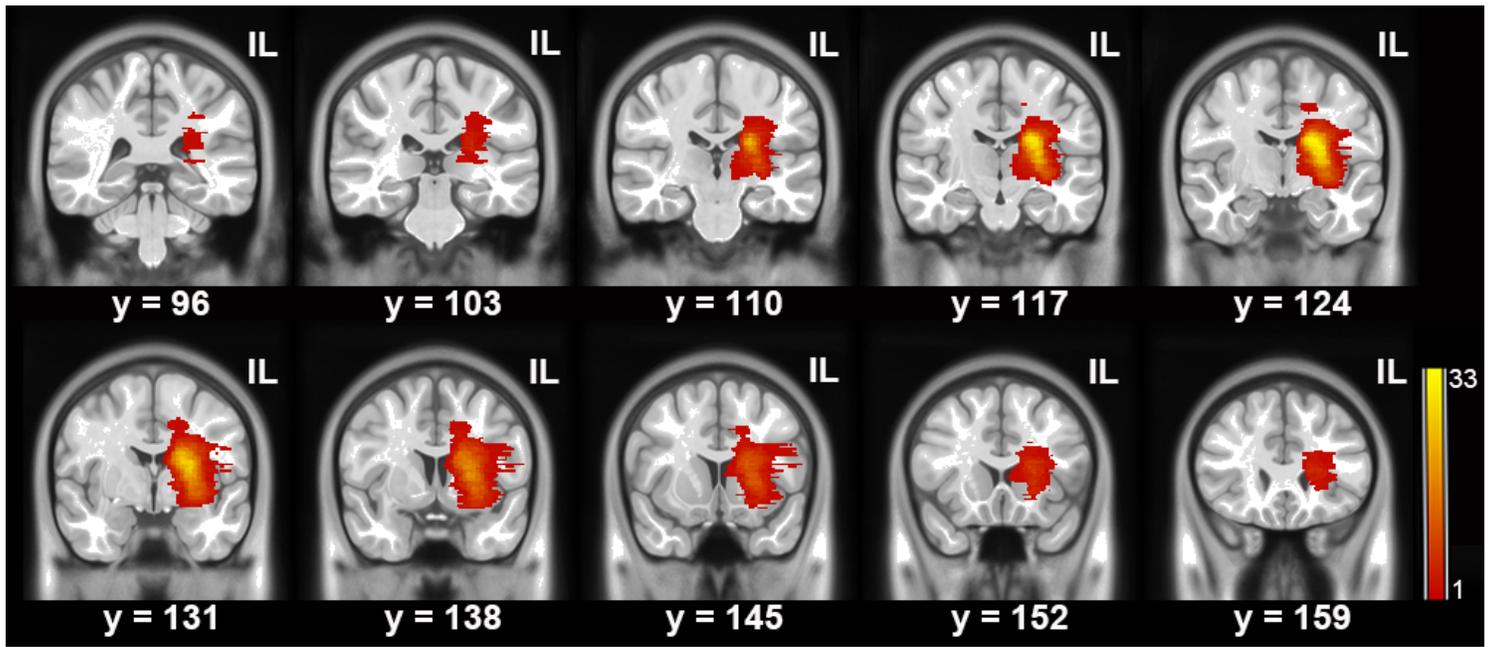


Figure 1

Lesion maps of the patients. All lesions are aligned to the same hemisphere for visualization. Colors represent the number of patients with a lesion at the given location. IL = ipsilesional side.

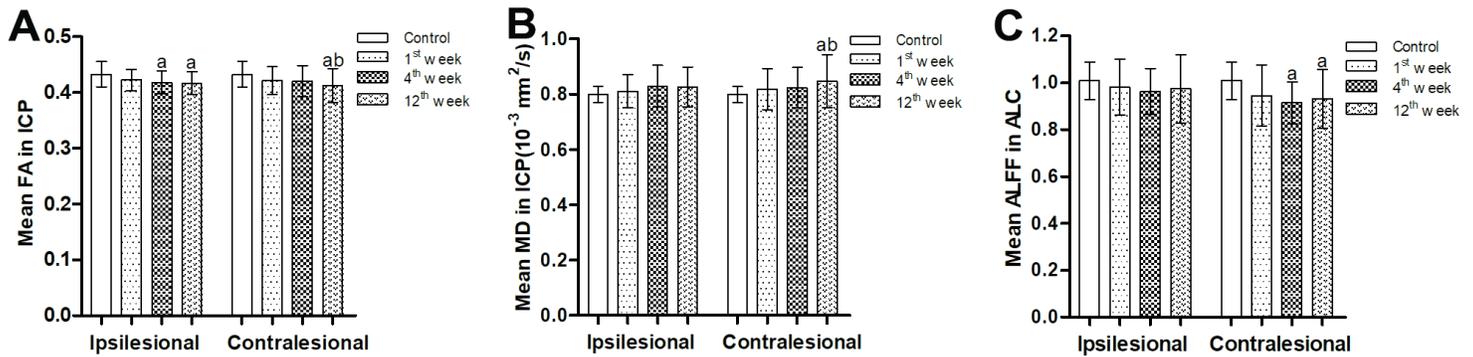


Figure 2

The diffusion parameters and ALLF values differences between groups. Bar charts represent the mean FA (A) values and MD (B) values of ICP and the mean ALFF (C) values of the ALC in patients at different time points after stroke and controls. The error bars represent the standard deviation of the mean. ALC, anterior lobe of cerebellum; ALFF, amplitude of low-frequency fluctuation; FA, fractional anisotropy; ICP, inferior cerebellar peduncle; MD, mean diffusivity. aP < 0.05, compared with the controls, bP < 0.05, compared with the first week.

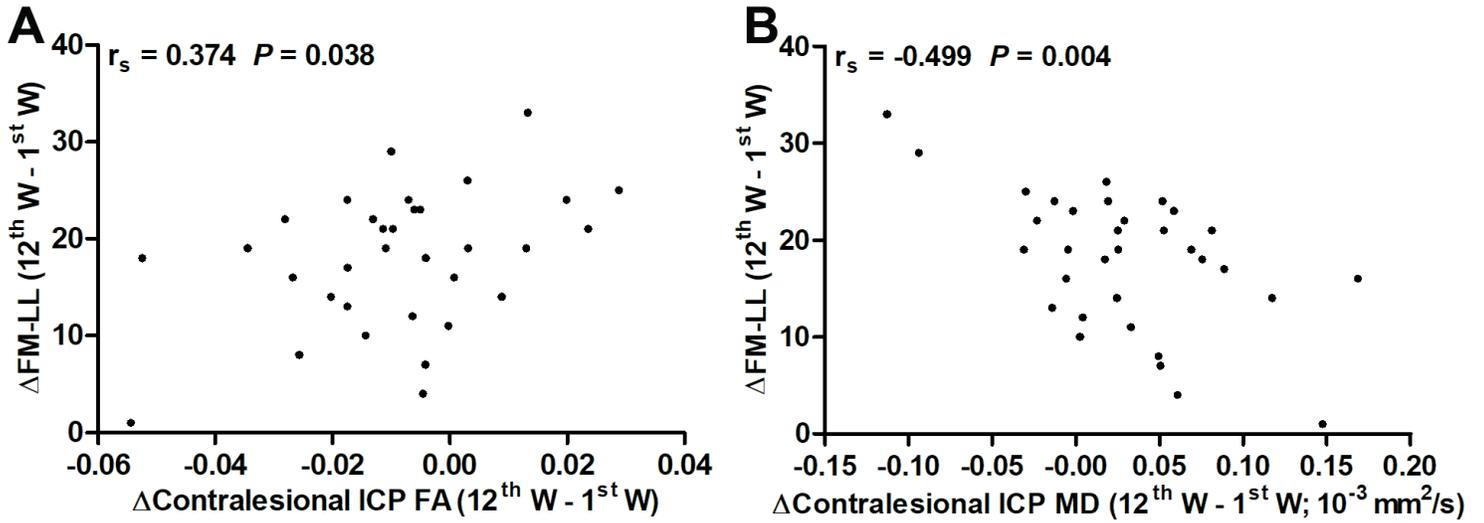


Figure 3

Spearman correlation maps. Spearman correlation plots for change in FM-LL scores (y-axis), as well as the change in FA (A) and MD (B) values of ICP (x-axis). Δ FM-LL scores or FA and MD of the contralesional ICP are values measured at week 12 after deducting values measured at week 1. FA, fractional anisotropy; FM-LL, Fugl-Meyer score of lower limb; ICP, inferior cerebellar peduncle; MD, mean diffusivity; W, week. r_s = Spearman correlation coefficient.

Supplementary Files

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