



White matter tract disruption is associated with ipsilateral hand impairment in subacute stroke: a diffusion MRI study

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Abstract

Purpose The ipsilateral hand (ILH) is impaired after unilateral stroke, but the underlying mechanisms remain unresolved. Based on the degeneracy theory of network connectivity that many connectivity patterns are functionally equivalent, we hypothesized that ILH impairment would result from the summation of microstructural white matter (WM) disruption in the motor network, with a task-related profile. We aimed to determine the WM disruption patterns associated with ILH impairment.

Methods This was a cross-sectional analysis of patients in the ISIS-HERMES Study with ILH and diffusion-MRI data collected 1 month post-stroke. Patients performed three tasks, the Purdue Pegboard Test (PPT), handgrip strength, and movement time. Fractional anisotropy (FA) derived from diffusion MRI was measured in 33 WM regions. We used linear regression models controlling for age, sex, and education to determine WM regions associated with ILH impairment.

Results PPT was impaired in 42%, grip in 59%, and movement time in 24% of 29 included patients (mean age, 51.9 ± 10.5 years; 21 men). PPT was predicted by ipsilesional corticospinal tract (i-CST) ($B = 17.95$; $p = 0.002$) and superior longitudinal Fasciculus (i-SLF) ($B = 20.52$; $p = 0.008$); handgrip by i-CST ($B = 109.58$; $p = 0.016$) and contralesional anterior corona radiata ($B = 42.69$; $p = 0.039$); and movement time by the corpus callosum ($B = -1810.03$; $p = 0.003$) i-SLF ($B = -917.45$; $p = 0.015$), contralesional pons-CST ($B = 1744.31$; $p = 0.016$), and i-corticoreticulospinal pathway ($B = -380.54$; $p = 0.037$).

Conclusion ILH impairment was associated with WM disruption to a combination of ipsilateral and contralesional tracts with a pattern influenced by task-related processes, supporting the degeneracy theory. We propose to integrate ILH assessment in rehabilitation programs and treatment interventions such as neuromodulation.

Keywords Less-affected hand · Ipsilateral pyramidal tract · Contralesional hemisphere · Sensorimotor systems · Structural Connectivity

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Glossary

FA	fraction of Anisotropy (diffusion MRI measure of white matter integrity)
FMS	Fugl-Meyer Score (Total score ranging 0 to 226, upper limb motor score subscore 0-66, sensory score 0-24 and coordination score 0-6)
JHU atlas	Johns Hopkins University atlas based on the MNI-ICBM labels 2-mm template
ILH	Ipsilateral Hand
MST	Movement Screening Test = movement time
NIHSS	National Institute of Health Stroke Scale (neurological severity)
PPT	Purdue Pegboard Test

RBANS	Repeatable Battery for the Assessment of Neuropsychological Status (global assessment of cognitive functions with a mean of 100 in healthy participants)
SD	Standard deviation

White matter tracts and Regions of Interest (ROIs)

ACR	Anterior Corona Radiata
ALIC	Anterior Limb of Internal Capsule
body-CC	body or middle segment of the Corpus Callosum (CC3 and CC4)
CST	Corticospinal tract
SCR	Superior Corona Radiata
PLIC	Posterior Limb of Internal Capsule
CP	Cerebral Peduncle
CRP	Cortico Reticulospinal Pathway
genu-CC	genu of the Corpus Callosum
ICP	inferior cerebellar peduncle
MCP	middle cerebellar peduncle
SCP	superior cerebellar peduncle
SLF	superior longitudinal fasciculus
i	ipsilesional
c	contralesional

Introduction

Hand movements represent a specific and essential function in humans required for everyday life activities. Following stroke, loss of hand functionality is one of the main factors affecting disability and remains a major target of rehabilitation interventions [1, 2]. Parallel to sensorimotor deficits of the paretic hand contralateral to the lesion, the ipsilateral hand (ILH) may show sensorimotor deficits for a large variety of sensorimotor tasks from the acute to chronic periods of stroke [3–8]. ILH impairment is frequent in subacute stroke [8] and may compound functional disability since patients require both hands to perform daily life activities [9].

Although several mechanisms have been postulated to account for post-stroke ILH deficits, no consensus has been reached and many aspects remain unresolved [10]. Anatomically, ILH impairment may result from ipsilateral descending motor pathways (i.e., fibers emerging from the damaged hemisphere and descending in the spinal cord without decussating), transcallosal fibers interacting with the undamaged hemisphere, and altered sensorimotor information through fibers crossing in the brainstem such as cerebellar peduncles. Accordingly, a first theory implicates the “uncrossed” ipsilateral corticospinal tract (CST) [11], as 3–15% of the corticospinal fibers descend in the ipsilateral spinal lateral funiculus without decussating in the medullary pyramids [12, 13] (Fig. 1). ILH impairment may also relate to the

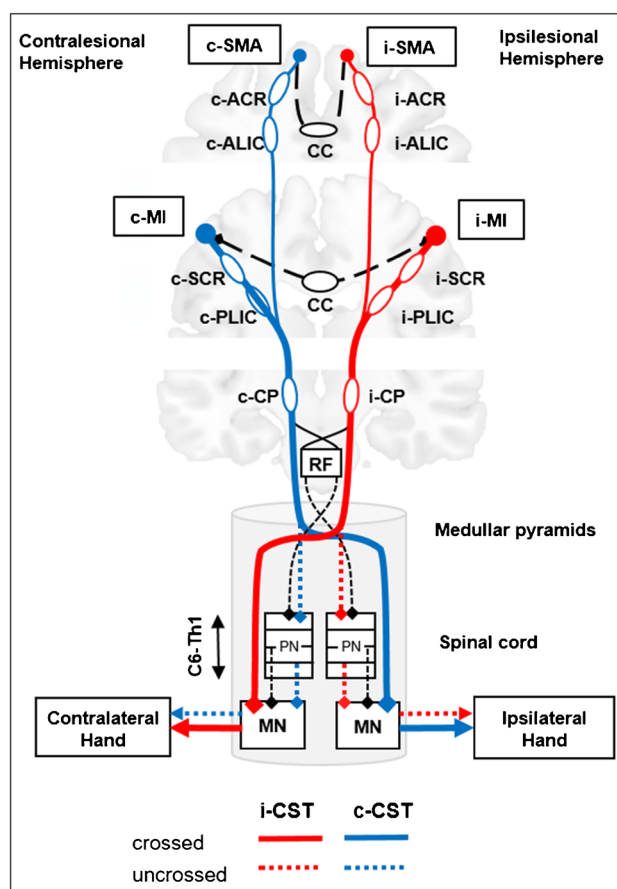


Fig. 1 Schematic representation of crossed and uncrossed fibers of the corticospinal tract (CST). ACR and ALIC fibers emerging from the SMA and PMC and SCR-PLIC fibers emerging from PMC and MI merge in the CP to form the CST, which continue in the pons and medulla. Then, the CST is divided into 2 parts. (1) Crossed CST (solid red and blue lines): most CST fibers decussate in the medullary pyramids to descend in the contralateral spinal cord and terminate in the contralateral anterior spinal horn to distal extremity muscles (direct cortico-motoneurons). (2) Uncrossed CST (dotted red and blue lines): a small proportion of the CST descends in the ipsilateral spinal lateral funiculus without decussating and terminates bilaterally in the ventromedial intermediate zone to propriospinal neurons. In addition, information is shared between the ipsilesional and contralesional hemispheres through transcallosal fibers (CC, dashed dark lines), before travelling through the CST. *Abbreviations:* CST=corticospinal tract, SCR=superior corona radiata; PLIC=posterior limb of internal capsule, CP=cerebral peduncle. Other ROIs are ACR=anterior corona radiata; ALIC=anterior limb of internal capsule; CC=corpus callosum; RF=reticular formation; PN=propriospinal neurons; MN= motoneurons; i=ipsilesional; and c=contralesional tracts

cerebellar peduncles via the fronto-cerebellar loops and the corticoreticulospinal pathway (CRP) that has bilateral spinal outputs. Another theory relies on bilateral parietal hemispheric control of unilateral movements [6, 10, 14, 15]. The lateralization of motor control has been recently revisited to enhance the role of the contralesional hemisphere, based on increased contralesional activity in the sensorimotor network

[16–18], and bilateral motor control supported by the posterior parietal cortex [19]. ILH impairment may also relate to interhemispheric transcallosal disconnections [20] as the corpus callosum (CC) coordinates motor function through the balance of excitatory and inhibitory interhemispheric interactions [14]. Finally, the impact of neuropsychological deficits such as apraxia and neglect has also been reported as a factor of ILH impairment [21–23].

Such a large variety of mechanisms can be put in perspective with the theory about degeneracy of the connectivity in neural networks [24] proposing that many patterns of neural architecture are functionally equivalent. Indeed, the connectivity pattern for a specified task arises during development in part by a process involving exuberant extension of neuronal processes that compete for targets. In this view, degenerate mechanisms would allow for sensorimotor plasticity and behavioral adaptation [25].

Based on the degeneracy theory, we hypothesized that ILH impairment would result from the summation of several disruptions to the sensorimotor network, with a pattern determined by the motor and visuomotor processes engaged in the ILH tasks. Since diffusion MRI provides reliable measures of white matter microstructure such as fractional anisotropy (FA) reflecting the neural changes related to the stroke lesion and its remote effects [26–30], we aimed to determine microstructure white matter (WM) disruption patterns associated with ILH impairment. WM disruption was assessed with FA measures in the motor WM network and ILH with three behavioral tasks engaging distinct motor and visuomotor processes. To this extent, we performed a cross-sectional analysis of patients in the ISIS-HERMES Study [31] with concomitant ILH and FA measures collected 1 month post-stroke.

Materials and methods

Participants

Patients

We enrolled 31 patients in the randomized controlled stem cell trial (ISIS-HERMES) at the stroke unit of the hospital from October 2010 to 2014 (ClinicalTrials.gov NCT00875654) [31]. In this study, we used the clinical, behavioral, and MRI data collected 1 month post-stroke, corresponding to the baseline visit performed before cell therapy administration. Patients received standard medical care including thrombolysis and thrombectomy when indicated. The ISIS-HERMES study was approved by the Institutional Review Board (CPP: 07-CHUG-25). Written informed consent was obtained from all patients before they participated in the study. The main inclusion criteria were

age 18–70 years, first-ever unilateral infarct in the internal carotid artery territory, moderate to severe neurological deficit defined as a NIH stroke scale (NIHSS) [32] score ≥ 7 , and the ability to follow a rehabilitation program. In addition to the inclusion–exclusion criteria listed in Table S1, we excluded patients with apraxia, or neglect diagnosed with an extinction NIHSS subscore > 1 .

Healthy participants

In addition, we included 31 healthy participants matched for age (± 5 years) and sex to the patients. Exclusion criteria are listed in Table S1.

Demographic and clinical measures

Age, sex, education level, handedness [33], height, weight, and stroke risk factors were collected. Of note, all participants were right-handed. Neurological severity was assessed using NIHSS and sensorimotor deficit using the Fugl-Meyer Score (FMS) [34], with upper limb motor, sensory, and coordination subscores (Table 1). A global cognitive assessment was performed with the Mini-Mental State Exam and the RBANS, exploring five domains (spatial, attention/executive, immediate and delayed memory, language) [35]. Assessments were performed by a stroke neurologist (NIHSS, neuropsychologists (RBANS, behavioral measures), and physiotherapists (FMS).

Behavioral measures

We explored ILH impairment using three behavioral tests. The Purdue Pegboard Test (PPT) (Lafayette Instrument Company, Indiana) [36] was performed as described in <http://www.equipement-ergotherapie.com/8-dexterité-manipulation.html>, as a standardized quantitative test requiring motor (for grasping) and visuomotor (for reaching) components. The hand dynamometer (Lafayette Instrument Company, Indiana; <https://www.prohealthcareproducts.com/100-kg-220lb-hand-grip-dynamometer-lafayette-instruments/>) is a validated test to measure handgrip force (Grip). The Motor Screening Task (MST) measures movement time to assess sensorimotor deficits in CANTAB (<https://www.cambridgecognition.com/cantab/cognitive-tests/attention/motor-screening-task-mot/>). Raw scores were converted to percentiles to adjust for age and sex using published norms [37] and CANTAB norms. Scores below the 5th percentile were considered as impaired. The frequency of ILH impairment was also assessed in [patients](#) without cognitive deficit, defined as RBANS > 40 .

Table 1 Patients' clinical and behavioral data ($n = 29$)

Variables	Mean	SD	Median	Percentile 25	Percentile 75
Age (years)	52.14	9.84	53.00	59.00	46.50
Education (years)	10.90	3.53	10.00	14.00	8.00
Lesion volume (ml)	102.66	63.99	97.00	141.50	49.50
Barthel Index	44.48	32.39	45.00	12.50	72.50
NIHSS	13.90	4.72	12.00	17.50	11.00
FMS total score/226	136.86	38.97	130.00	166.50	106.00
FMS motor score /66	36.45	27.91	31.00	52.00	15.00
FMS sensory score /24	11.31	7.92	14.00	17.00	0
FMS hand coordination /6	0.93	1.98	0	0	0
MMSE	25.15	6.20	27.00	29.00	24.50
Paretic PPT performance	1.25	3.23	0	0	0
Paretic Grip performance	3.79	9.79	0	0	0
Paretic MST (s)	634	284	441	942	423
ILH PPT performance	10.84	4.41	12.00	14.33	9.17
ILH Grip performance	23.90	12.34	21.66	34.83	16.50
ILH MST (s)	561	223	502	593	409

See glossary for abbreviations

MRI data acquisition

The MRI protocol included structural and diffusion sequences. All participants were scanned on a 3 T Philips magnet (Achieva 3.0 TTX; Philips, the Netherlands) with a 32-channel head coil. High-resolution (1 mm^3) sagittal 3D-T1-weighted (TR 9.9 ms, TE 4.6 ms, flip angle 8° , TI 920 ms, inter shot time 1792 ms) and fluid-attenuated inversion recovery (FLAIR) images (TR 8 s, TE 342 ms) were acquired. Diffusion-weighted images were acquired using single-shot echo-planar imaging (EPI) sequence (TR 11 ms, TE 72 ms, FOV 240 mm, slice thickness 2.0 mm, 70 axial slices, SENSE factor 2, fold-over direction anteroposterior, fat shift direction P, fat suppression, and voxel size $1.67 \times 1.67 \times 2 \text{ mm}$). We acquired 60 noncollinear directions with a b value of 1000 s/mm^2 and 10 directions with a b value of 0 s/mm^2 that were averaged to give 1 average direction.

MRI data analysis

Structural images were used to manually delineate lesion masks and compute lesion volumes using MRICron (<https://www.nitrc.org/projects/mricron>). Diffusion-weighted images were processed with the *Diffusionist* toolkit derived from FSL software, as previously described [38]. Each DWI image was visually checked and removed if corrupted. Then, after correction of eddy-current distortions, the diffusion tensor was estimated.

We used FA to assess WM disruptions. Voxel-wise FA images were constructed from the resulting tensors. Linear and nonlinear registration transformations were applied to

the FSL FA template in the MNI-152 space by incorporating the knowledge of each brain lesion using manually delineated lesion masks [39]. FA was estimated only in the template's skeleton and outside the lesion mask. We estimated average FA values with atlas-based regions of interest (ROI) approach using the human brain WM JHU atlas [40]. As FA values vary along the CST tract, we selected the JHU atlas that includes 4 ROIs for the CST. FA was estimated in a set of 33 ROIs listed in Table 2 and represented in Fig. S1. *Diffusionist* toolkit and related documentation can be found at <http://mri-diffusionist.com/>.

Statistical analysis

ILH impairment was explored using descriptive statistics. First, we explored the relationship between behavioral tasks (PPT, handgrip, and MST percentiles) and clinical scores using Spearman correlations. As both ILH scores and FA measures showed a normal distribution, we tested the linear associations between ROI-derived FA and ILH raw scores using partial Pearson's correlations controlling for education, age, and sex, with 95% confidence intervals obtained with bootstrapping based on 1000 samples. In addition, FA values were compared between stroke patients and healthy participants using a t -test with bootstrapping based on 1000 samples to provide robust 95% confidence intervals.

We used linear regression models to determine the WM ROIs and thus the tracts associated with ILH impairment. The effects of ROIs, lesion side, volume, BMI, height, and weight were tested and included in the model only if significant. All models were adjusted for the effects of education, age, and sex. The best model was determined with

Table 2 Partial correlations between ILH tasks and JHU tracts controlling for education, age, and sex, with bootstrapping based on 1000 samples

Tracts	PPT				Grip				MST			
	r	p	95% CI		r	p	95% CI		r	p	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
Vol tot	-0.38	0.058	-0.76	0.08	-0.34	0.093	-0.68	0.06	0.44	0.025	0.17	0.69
Corticospinal tract (CST)												
i-Pons	0.30	0.137	-0.14	0.64	0.30	0.141	-0.08	0.60	-0.18	0.387	-0.53	0.28
c-Pons	0.05	0.814	-0.47	0.41	0.12	0.564	-0.48	0.48	0.05	0.820	-0.20	0.38
i-CP	0.48	0.014	0.10	0.79	0.51	0.008	0.19	0.75	-0.26	0.192	-0.62	0.11
c-CP	0.42	0.031	0.03	0.71	0.44	0.024	0.08	0.68	-0.29	0.149	-0.68	0.06
i-PLIC	0.57	0.002	0.32	0.80	0.40	0.044	0.09	0.69	-0.32	0.108	-0.66	0.04
c-PLIC	0.16	0.423	-0.22	0.54	0.09	0.662	-0.28	0.49	-0.02	0.913	-0.44	0.28
i-SCR	0.41	0.038	-0.02	0.70	0.37	0.061	-0.06	0.68	-0.27	0.175	-0.60	0.21
c-SCR	0.20	0.337	-0.16	0.49	0.08	0.691	-0.36	0.52	-0.11	0.601	-0.42	0.22
Hemispheric tracts												
i-ACR	0.50	0.009	0.16	0.77	0.42	0.034	0.08	0.73	-0.50	0.009	-0.73	-0.22
c-ACR	0.54	0.005	0.27	0.76	0.59	0.002	0.23	0.78	-0.56	0.003	-0.77	-0.25
i-ALIC	0.42	0.032	0.04	0.72	0.22	0.271	-0.14	0.54	-0.18	0.368	-0.54	0.25
c-ALIC	0.48	0.012	0.16	0.74	0.44	0.024	0.11	0.72	-0.43	0.029	-0.71	-0.08
i-SLF	0.54	0.005	0.15	0.79	0.39	0.049	-0.04	0.78	-0.57	0.002	-0.80	-0.26
c-SLF	0.49	0.011	0.05	0.79	0.52	0.007	0.24	0.77	-0.49	0.010	-0.73	-0.16
i-PCR	0.63	0.001	0.26	0.83	0.61	0.001	0.33	0.81	-0.40	0.046	-0.63	-0.14
c-PCR	0.44	0.026	0.04	0.70	0.50	0.010	0.14	0.75	-0.52	0.007	-0.77	-0.16
Commissural tracts (corpus callosum)												
Genu	0.62	0.001	0.33	0.85	0.61	0.001	0.31	0.79	-0.61	0.001	-0.83	-0.36
Body	0.42	0.032	0.08	0.70	0.46	0.017	0.06	0.72	-0.31	0.118	-0.58	0.01
Splenium	0.54	0.004	0.18	0.77	0.60	0.001	0.21	0.86	-0.47	0.015	-0.69	-0.17
Cerebellar peduncles												
i-SCP	0.31	0.119	-0.08	0.64	0.38	0.053	-0.01	0.64	-0.23	0.263	-0.52	0.09
c-SCP	0.47	0.016	0.12	0.73	0.45	0.020	0.11	0.68	-0.32	0.113	-0.62	0.01
i-ICP	0.35	0.077	-0.09	0.67	0.41	0.038	0.06	0.64	-0.34	0.093	-0.59	-0.09
c-ICP	0.17	0.405	-0.29	0.64	0.18	0.374	-0.20	0.55	-0.20	0.319	-0.57	0.15
i-MCP	0.11	0.587	-0.30	0.46	0.20	0.335	-0.32	0.55	-0.05	0.798	-0.31	0.24
c-MCP	0.26	0.205	-0.16	0.58	0.16	0.436	-0.24	0.50	-0.10	0.615	-0.47	0.33
Cortico Reticulospinal Pathway (CRP)												
i-Pons-CRP	0.34	0.092	0.11	0.59	0.31	0.130	0.03	0.64	-0.35	0.084	-0.67	0.06
i-CP-CRP	0.24	0.244	-0.08	0.52	0.24	0.242	-0.05	0.56	-0.25	0.216	-0.59	0.19
i-PLIC-CRP	0.30	0.143	-0.07	0.61	0.20	0.326	-0.16	0.56	-0.32	0.109	-0.64	0.06
i-CR-CRP	0.02	0.922	-0.33	0.31	0.07	0.747	-0.31	0.41	-0.22	0.271	-0.55	0.06
c-Pons-CRP	0.06	0.783	-0.35	0.38	0.08	0.696	-0.30	0.48	-0.03	0.900	-0.43	0.37
c-CP-CRP	0.07	0.733	-0.28	0.48	0.14	0.510	-0.24	0.50	-0.04	0.848	-0.47	0.37
c-PLIC-CRP	-0.05	0.829	-0.42	0.37	0.10	0.632	-0.27	0.48	-0.02	0.910	-0.29	0.22
c-CR-CRP	-0.02	0.925	-0.35	0.37	-0.13	0.515	-0.45	0.20	0.08	0.717	-0.21	0.33

Abbreviations: *r* indicates Pearson correlation coefficient; *p* significance (2-tailed); *95% CI* 95% confidence interval. Tracts: ipsilesional (i-) and contralesional (c-). ROIs: *SCR* superior corona radiata; *PLIC* posterior limb of the internal capsule; *CP* cerebral peduncle; *PCR* posterior corona radiata; *SCP* superior, *MCP* middle, and *ICP* inferior cerebellar peduncles; *SLF* superior longitudinal fasciculus, *CC* genu body and splenium of the corpus callosum, *ACR* anterior corona radiata, *ALIC* anterior limb of the internal capsular

the statistical significance of the factors with the *F*-test ($p < 0.05$), model fit estimated with Durbin-Watson test and distribution of residuals, and model accuracy assessed with

adjusted R^2 . Internal validation was performed with bootstrapping based on 1000 samples. Statistical data analyses were performed using SPSS 23.0.

Results

Twenty-nine patients (21 males, 10 right lesions, all right-handed) completed clinical, behavioral, and MRI assessments at 1 month post-stroke (Fig. S2). We also included 29 age- and sex-matched healthy participants (21 males, mean age 51.1 ± 12.2 years, all right-handed). Clinical data are presented in Table 1. Lesion overlap (Fig. 2) highlights that the middle cerebral artery territory was infarcted in all patients.

ILH assessment

Behavioral measures are presented in Table 1. ILH was impaired in 12 patients for PPT (41.4%, 95% CI = 24.1–62.1), 17 for grip (58.6%, 95% CI = 41.4–75.9) and 7 for MST (24.1%, 95% CI = 10.3–41.4). In the subgroup of 24 patients without cognitive deficit, rates were not significantly different from the whole group, with PPT impaired in 10 patients (41.7%, 95% CI = 21.7–62.5), grip in 16 patients (66.7%, 95% CI = 47.6–86.4), and MST in 7 patients (29.2%, 95% CI = 10.0–47.6).

Factors associated with ILH impairment

PPT, Grip, and MST significantly correlated with clinical but cognitive scores (Table S2). ILH correlated with the paretic hand for PPT, with a trend for grip and MST (Table S3). There was no significant effect of lesion side on ILH performances. FA values were significantly lower in the patients than in the healthy participants for all ROIs but the contralesional pons-CST, PLIC-CST, and PLIC-CRT, and bilateral SCR-CRT (Table S4).

Table 2 reports ILH and FA correlations. PPT correlated with the ipsilesional (i-) CST (CP-, PLIC, and SCR ROIs), contralesional (c-) CP-CST, bilateral SLF, ALIC, ACR, and PCR, CC, and c-SCP. Grip correlated with the same ROIs but i-SCR and i-ALIC, and with i-ICP. MST correlated with bilateral SLF, ACR, PCR, c-ALIC, CC genu and splenium, and lesion volume.

Linear regression models are presented in Table 3. PPT was predicted by ipsilesional PLIC-CST ($B = 17.95$; $p = 0.002$) and SLF ($B = 20.52$; $p = 0.008$) with no significant effect of education, age, and sex; $r^2 = 0.696$, indicating good model accuracy. Handgrip strength was predicted by ipsilesional CP-CST ($B = 109.58$; $p = 0.016$) and contralesional ACR ($B = 42.69$; $p = 0.039$), with an effect of male sex, but no education and age; $r^2 = 0.571$, indicating moderate accuracy. Movement time was predicted by CC genu ($B = -1810.03$; $p = 0.003$) ipsilesional-SLF ($B = -917.45$; $p = 0.015$), contralesional pons-CST ($B = 1744.31$; $p = 0.016$), and ipsilesional PLIC-CRT ($B = -380.54$; $p = 0.037$), with male sex and high education supporting better performance; $r^2 = 0.755$, indicating good accuracy.

Discussion

Clinical assessment of ILH

We assessed behavioral performances of the less-affected hand (ILH) in 29 patients at 1 month post-stroke. Since the degree of ILH impairment may depend on the type of task that is tested [10], we used three tasks with different motor and visuomotor processes. PPT, grip, and movement time were impaired in 41.4%, 58.6%, and 24.1%, respectively, highlighting that ILH impairment is frequent, in line with

Fig. 2 Overlap of stroke lesions in the 29 patients. Axial slices are displayed with for z MNI coordinates. Left lesions are represented on the left side and right lesions on the right side of each slice (neurologic convention). Note that ipsilesional SCR and SLF were damaged in all patients, and PLIC, ALIC, and ACR in 70% of them

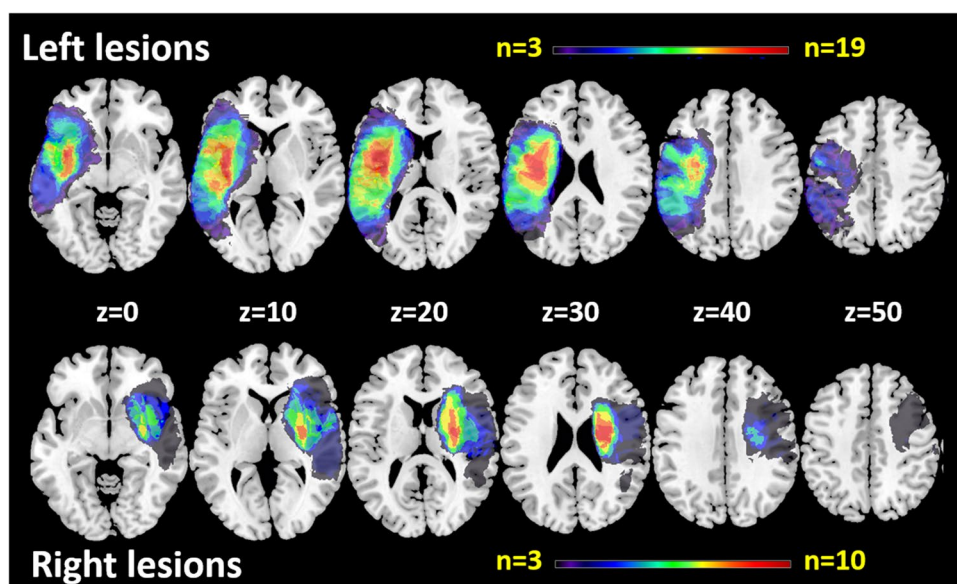


Table 3 Linear regression models for ILH PPT, GRIP, and MST, with bootstrapping based on 1000 samples

Variables	r^2 change	B	Bootstrap					
			Bias	SE	p	95% CI		
						Lower	Upper	
PPT		$r^2=0.696$						
(Constant)		– 1.69	– 0.16	4.79	0.696	– 12.30	7.02	
Education		0.32	– 0.01	0.17	0.065	– 0.02	0.65	
Age	0.450	– 0.08	0.00	0.05	0.067	– 0.17	0.02	
Sex		– 1.16	– 0.22	1.04	0.251	– 3.57	0.63	
i-PLIC	0.182	17.95	0.82	5.22	0.002	8.24	29.15	
i-SLF	0.120	20.52	0.46	6.78	0.008	8.80	36.36	
GRIP		$r^2=0.571$						
		B	Bootstrap					
Variables	r^2 change		Bias	SE	p	95% CI		
						Lower	Upper	
Constant		– 18.10	– 1.98	21.03	0.329	– 66.47	17.71	
Sex		– 14.89	– 0.66	3.79	0.001	– 24.01	– 8.54	
Age	0.327	– 0.12	0.01	0.14	0.318	– 0.38	0.18	
Education		0.35	0.02	0.50	0.484	– 0.55	1.38	
c-ACR	0.233	109.58	5.48	42.65	0.016	36.52	206.99	
i-CP-CST	0.088	42.69	0.02	18.67	0.039	4.09	78.76	
MST		$r^2=0.755$						
		B	Bootstrap					
Variables	r^2 change		Bias	SE	p	95% CI		
						Lower	Upper	
Constant		1172.19	52.11	431.26	0.008	398.01	2202.31	
Education		– 17.66	0.00	6.36	0.009	– 29.74	– 3.14	
Age	0.351	– 1.83	– 0.26	3.57	0.612	– 9.02	5.39	
Sex		135.87	0.83	58.95	0.035	24.22	261.94	
genu-CC	0.243	– 1810.03	– 47.30	419.95	0.003	– 2632.43	– 925.48	
i-SLF	0.103	– 917.45	– 18.63	308.59	0.015	– 1539.04	– 323.94	
c-pons-CST	0.074	1744.31	– 5.22	672.29	0.016	260.57	2947.88	
i-PLIC-CRT	0.045	– 380.54	– 5.18	170.54	0.037	– 719.31	– 75.81	

SE indicates standard error; 95% CI, 95% confidence interval; Tracts: ipsilesional (i-) and contralesional (c-). ROIs: *PLIC* posterior limb of the internal capsule, *CP* cerebral peduncle, *SLF* superior longitudinal fasciculus, *genu-CC* genu body of the corpus callosum, *ACR* anterior corona radiata

previous studies [6, 8, 10, 15, 41]. Among the multiple tasks described in the literature exploring post-stroke ILH impairment, PPT impairment is the most commonly described, while more heterogeneous results are reported for handgrip strength [6, 15] and movement time [42]. Here, the low frequency of MST suggests that this test may be an insensitive measure compared to kinematic measures, [42, 43], and that visuomotor components of ILH impairment may have been underestimated.

We measured FA in the main tracts related to hand motor function [29, 30, 44] and found that all ROIs but pons and PLIC ROIs of the contralesional CST had lower FA values in patients than in healthy participants, indicating microstructural damage to contralesional and interhemispheric white matter tracts following stroke that may compound ILH function.

ILH performances correlated with clinical motor and sensory scores highlighting that ILH impairment scales with

sensorimotor stroke severity and Barthel index. The effect of stroke severity was particularly strong for ILH PPT that correlated with the paretic PPT and lesion volume, while trends were observed for grip and MST.

Correlation analyses between ILH and FA in ROIs of the motor network also revealed task dissociations. PPT (including reach movements requiring visuomotor processes and precise grasp requiring motor processes), MST (visuomotor reaching task), and grip strength (pure motor task) were predicted by a combination of different tracts of the motor network. This argues against the idea that a single mechanism may account for ILH impairment that varies in terms of modality and degree.

Mechanisms of ILH impairment

Our findings showed that, depending on the task, several tracts including the CST, c-ACR, CC, i-SLF, and to a lesser extent i-CRP, were associated with ILH impairment.

We found moderate to strong correlations between the three ILH scores and i-CST, while no significant correlation was observed with contralesional CST-CR and CST-PLIC, suggesting that motor processes of ILH impairment are driven by the ipsilesional CST. Furthermore, i-CST predicted ILH impairment, explaining 18.2 and 8.8% of the PPT and grip variance, respectively. Anatomically, the uncrossed fibers of the ipsilesional CST (Fig. 1-S3A) descending in the dorsal funiculus terminate in the ventromedial intermediate zone to propriospinal neurons connected to distal motoneurons through intersegment spinal interneurons. Although the ventromedial intermediate zone is related to the motor function of the trunk and arms [45], propriospinal neurons may connect with distal motoneurons through intersegment spinal interneurons and thus be involved in the motor control of dexterous hand movements [46]. Moreover, other corticospinal pathways projecting to the reticular formation such as the CRP terminate bilaterally to the propriospinal neurons of the ventral and lateral intermediate zone and contribute to motor performance [47]. Our findings, showing that i-PLIC-CRP was a factor of MST performance, strengthen the hypothesis that ipsilesional descending pathways participate in ILH impairment.

ILH scores were also correlated with FA in the bilateral ALIC, ACR, and CC. Linear models showed that c-ACR was a significant factor of handgrip impairment, explaining 23.3% of the variance. ACR has been linked to cognition and particularly to attention in adults with brain injury [48]. Moreover, a part of ACR fibers originate in the SMA, descend through the ALIC [49], and then merge with the CST in the CP [13], which continues in the pons and medulla to decussate at the pyramid caudal end [13, 50]. The involvement of SMA in simple motor tasks is documented by stroke studies, with SMA lesions leading to mild motor deficits [50], and i-SMA fMRI-related activity supporting motor recovery [17, 51]. Therefore, motor control components of ILH impairment may also implicate the contralesional CST through transcallosal and c-ACR fibers from premotor and/or prefrontal areas (Fig. 1-S3.B).

We found that all ILH scores strongly correlated with the CC including the genu, which predicted MST and explained 24.3% of the variance. A role of the CC is motor coordination of bimanual [52] and unilateral hand motor movements through the balance of excitatory and inhibitory interhemispheric interactions [14]. The ipsi- and contralesional motor areas exert a reciprocal influence through transcallosal fibers [53], as evidenced in tracer studies showing reciprocal transcallosal connections for both MI and SMA [54]. In

nonhuman primates, SMA lesions impaired the ILH motor program through transcallosal connections to contralesional SMA [55]. Taken together, our findings concur with previous stroke studies [6, 56], suggesting that the information is shared with the contralesional hemisphere through transcallosal fibers, before travelling through the descending motor pathways. This is consistent with the recent literature proposing an active and specific role of the ipsilateral hemisphere in the planning and execution of voluntary movements [19].

ILH impairment also correlated with decreased FA in bilateral SLF and i-SLF predicted PPT and MST explaining 12.0 and 10.3% of the variance, respectively. These findings support the theory that ILH impairment relates to the bilateral hemispheric control of unilateral movement [6, 10, 14, 15]. In this view, the damaged hemisphere would alter movements of both ILH and paretic hands. In the literature, unimanual motor tasks implicating visuomotor components yield bilateral activity in the frontoparietal network [14, 57–59]. In our study, PPT and MST that require visuomotor control (in contrast to handgrip) were associated with the SLF, a key structure of the frontoparietal network connecting parietal, premotor, and motor frontal areas in both human [60–62] and nonhuman primates [13]. Furthermore, our findings that i-SLF disruptions alter ILH with visuomotor processing are supported by previous works showing an essential role for the SLF in motor planning and kinematic components of movement execution in 30 right-handed healthy participants [44].

Interestingly, ILH impairment did not correlate with cognitive deficits and was not significantly improved in patients without cognitive deficit, suggesting that cognitive impairment did not influence ILH impairment in this study. Nevertheless, as patients with severe apraxia or neglect were excluded from our study, we may have underestimated the effects of cognitive impairment related to apraxia and neglect on ILH impairment [22].

There were significant correlations between lesion volume and MST, with a trend for PPT and grip. Surprisingly, few studies, if any, have explored the relationships between lesion volume and ILH impairment in humans. Our findings are consistent with nonhuman macaque experiments [63] reporting that reaching ILH tasks were compounded by lesion volume.

Limitations

The small sample size is the main limitation of this study. However, this is the first study exploring the microstructural WM disruptions to understand the underlying mechanisms of ILH impairment following stroke. Also, the homogeneity of our population in terms of age, absence of leukoaraosis, and stroke severity and territory may

have compensated, at least for a part, for this limitation. Nevertheless, the small sample may explain why we did not observe any effect of the lesion side, in contrast with others [7]. Another limitation relates to ILH impairment patients' perception. When patients with impaired ILH were asked if they noticed that their ILH was impaired, most of them answered that their ILH function was worse than before stroke, but much better than the contralateral hand. However, we did not record all patients' answers.

Conclusion

This study showed that motor-related tract disruptions predict ILH impairment, with a pattern related to the processes engaged in each task: tasks with motor processing were associated with the ipsilateral CST suggesting the involvement of uncrossed CST fibers, while tasks with visuomotor processing were related to i-SLF supporting hand motor control. In addition, our findings revealed a role for the contralesional hemisphere that may modulate the planning and execution of hand movements through prefrontal/premotor areas and transcallosal interactions. Taken together, ILH impairment may result from the summation of several WM disruptions, supporting the concept of degeneracy of the motor network. Our results provide a theoretical basis for integrating ILH impairment in rehabilitation programs to improve functional recovery and for research interventions, such as neuromodulation.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request criteria.

Declarations

Ethics approval Institutional review board approval by the Institutional Review Board (CPP: 07-CHUG-25).

Consent to participate A written informed consent from all patients or relatives was obtained before their participation in the study.

Consent to publish All the authors have read and approved the submission.

Competing interest The authors have no conflict of interest to declare.

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