IOP Publishing J. Neural Eng. 22 (2025) 026019 https://doi.org/10.1088/1741-2552/adbe3c

Journal of Neural Engineering

RECEIVED
8 October 2024

REVISED
25 February 2025

ACCEPTED FOR PUBLICATION
8 March 2025

PUBLISHED
18 March 2025

PAPER

Rehabilitation with hybrid assistive limb improves upper limb paralysis in patients with cerebral hemorrhage by repairing axonal injury of the corticospinal tract

Masahiko Nishimura[1], Shigetaka Kobayashi[2], Tomomi Kuninaka[2], Yohei Hokama[2], Hideki Nagamine[2] and Shogo Ishiuchi[1,*]

[1] Department of brain healthcare, advanced medical research center, faculty of medicine, University of the Ryukyus, 1076, Kyuna, Ginowan-city, Okinawa 901-2725, Japan
[2] Department of Neurosurgery, Graduate School of Medicine, University of the Ryukyus, 1076, Kyuna, Ginowan-city, Okinawa 901-2725, Japan
[*] Author to whom any correspondence should be addressed.

E-mail: ishogo@med.u-ryukyu.ac.jp

Keywords: hybrid assistive limb, hemiplegic upper extremity, rehabilitation, diffusion tractography, cerebral hemorrhage, wearable exoskeleton

Supplementary material for this article is available online

Abstract

Objective. Effective rehabilitation for upper limb paralysis in patients with intracerebral hemorrhage mediated by hemiplegia has not yet been established. We evaluated the effectiveness of upper limb functional training using a wearable-type exoskeleton driven by bio-electric signals using upper limb motor function scores and tractography of the corticospinal tract (CST). *Approach.* Nine patients with putamen and seven with thalamus hemorrhage were trained using the hybrid assistive limb (HAL) of the wearable exoskeleton. Among the participants, 12 individuals were patients with severe hemiplegic, indicated by a Fugl–Meyer assessment (FMA) score of 10. We also investigated the relationship between improvement in upper limb function and changes in mean diffusivity, axial diffusivity, radial diffusivity (RD), or fractional anisotropy (FA) in the CST. *Main results.* Following HAL training, upper limb function scores increased in all patients. We observed a clinically significant improvement in nine patients, with a mean effect size of 26 ± 12.7. HAL training was effective in improving upper limb function in patients with an FA ratio (the affected/unaffected side) $\geqslant 0.86$ in the CST. Patients with clinically significant improvements had a mean $16 \pm 15\%$ increase in FA ratio in the CST. Patients with greater improvement in upper-limb function tended to have lower RD values in the CST, and the effect size of the RD value and FMA was demonstrated to be negatively correlated ($rs = -0.54$). An increase in FA ratio and a decrease in RD values in the CST of the cerebral peduncle are significant findings that suggest improvements in upper limb function. *Significance.* These findings highlight the effectiveness of HAL training in improving upper-limb dysfunction in patients with subacute cerebral hemorrhage. Improvement of upper limb function by assistive actuation with the wearable exoskeleton based on bio-electric signals may be caused by the promotion of the restoration of white matter integrity of the CST.

1. Introduction

Putamen and thalamic hemorrhages account for approximately 60%–70% of all intracerebral hemorrhages (ICHs) [1–3]. Eighty-five percent of patients with putamen and thalamic hemorrhage develop contralateral hemiparesis because of impairment of the corticospinal tract (CST) [1, 4]. The recovery of upper limb motor dysfunction is delayed compared with that of lower limb dysfunction. Lower limbs are generally used for sitting, standing, and walking. Several patients learn not to use the paralyzed upper limbs, considering their capability to perform activities of daily living with the unaffected upper limbs [5, 6]. Therefore, therapists face difficulties in treating upper limb dysfunction in stroke survivors [7, 8].

Despite reports on the partial effectiveness of arm-based training, neurodevelopmental approach, and constraint-induced movement therapy for upper limb motor paralysis in an RCT study, researchers have questioned the efficacy of their treatments for severe paralysis [9, 10]. The effectiveness of robot-assisted therapy for improving upper limb paralysis has recently been reported [11–16]. The single-joint type of hybrid assistive limb (HAL-SJ) assists elbow joint movement based on the bioelectric potential signal (BES) generated by the wearer's voluntary movement [17, 18]. The advantage of this wearable exoskeleton is that it synchronizes the assistive actuation of the HAL-SJ with the patient's spontaneous movements, encouraging their participation in the motor learning of the elbow joint [19–21]. The HAL-SJ training was effective in improving elbow movement. However, its effect on hand or finger function remains unknown [19, 22, 23].

Stroke-mediated upper extremity paralysis and CST injury are closely linked [24–26]. Imaging evaluation of the CST with diffusion tensor imaging (DTI) is effective for functional prediction of upper limb paralysis [27–32]. DTI captures the three-dimensional diffusion of water molecules in white matter [33–35]. The parameters that represent anisotropic diffusion are defined as eigenvalues (λ1, λ2, and λ3) in the three-dimensional direction. From these eigenvalues, we calculated the diffusion coefficients with the mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) for an anisotropy index. Changes in FA and the diffusion coefficient indicate plasticity of the white matter microstructure after motor learning [36, 37]. There are few reports on the impact of rehabilitation on the CST.

Our aim was to investigate the efficacy of upper limb functional training using robot-assisted therapy and changes in the connectivity of white matter tracts in patients with cerebral hemorrhage. We analyzed the relationship between HAL-SJ training and the fine structure of the CST and found that the neuroplastic changes in the CST were related to the improvement of upper limb motor function.

2. Methods

2.1. Participants

We recruited nine and seven patients with subacute putamen hemorrhage (putamen group, 50 ± 11 years) and thalamic hemorrhage (thalamus group, 60 ± 16 years old) with upper limb motor paralysis, respectively (Fugl–Meyer assessment (FMA) score average and standard deviation of 8.2 ± 10.2). The clinical features of the patients are presented in table 1.

Figure 1 show CT images of the participants. This study was approved by the ethical committee of the University of Ryukyus (No. 377) and was conducted in accordance with The Code of Ethics of the World Medical Association Declaration of Helsinki. Patients were informed of the study and provided informed consent.

Of the 16 patients enrolled in this study, case 2 underwent hematoma removal surgery. The remaining 15 patients underwent conservative treatments. The selected patients had aphasia, general cognitive impairment, or spatial neglect. Nonetheless, they were able to follow the instructions of the therapist and did not face any problems while performing upper limb function training with HAL-SJ.

2.2. Training for the upper limb function with HAL-SJ

Figure 2 depicts the appearance and attachment of the HAL-SJ. Electrodes for obtaining the BES were attached to the biceps and triceps on the patient's paralyzed side. For the HAL training, we attached the HAL-SJ to the upper limb on the paralyzed side and performed the following two training sessions: 1) flexion and extension motion of the elbow joint and 2) reaching by the upper limb. Patients who could sit performed exercises to reach with their limbs in chairs or wheelchairs. In contrast, those who could not sit performed the task in the supine position on the bed. The reaching task was performed against gravity, and the patient was instructed to touch the therapist's hand. The therapist's hand was positioned in front of the patient, and the movement direction of the reaching task was oriented toward the patient's front. The reaching task was repeated 30 times within a single training session. The torque of the actuator to support elbow joint movement was set to 19–24 Nm. The patients underwent HAL training for 30 min d^{-1}.

We examined upper limb function in patients using the FMA before and after HAL training [38]. FMA is considered significantly improved when an increase ⩾9 points is observed [39]. Patients with an increase in FMA score ⩾9 points were assigned to the improved group. In contrast, those with an increase in the FMA score <9 points were placed in the unimproved group.

2.3. The acquisition of DTI and preprocessing

DTIs were acquired using a whole-body 3T magnetic resonance imaging (MRI) scanner with a 32-channel head coil (Discovery 750MR, GE Healthcare, USA). The DTI single-shot echo planar imaging sequence and parameters were as follows: 29 non-collinear directions, TR = 9500 ms, TE = 82.1 ms, matrix

Table 1. Clinical features of the patients in this study.

Case	Age	Sex	CT classification	Lesion size(ml)	Lesion side	Higher-order cognitive dysfunction	Number of days from stroke onset to training initiation	Training sessions	Training days	The Fugl–Mayer assessment		
										Pre-HAL	Post-HAL	Effect size
Patients with putaminal hemorrhage												
Case 1	50	F	IVa	28.4	R	—	9	12	18	3	5	2
Case 2	69	F	Vb	43.6	R	Cognitive impairment	18	3	7	1	5	4
Case 3	38	F	IIIa	10.3	L	Transcortical motor aphasia	3	5	14	2	12	10
Case 4	60	F	IIIa	20.8	L		11	3	5	2	5	3
Case 5	43	M	IVa	60.0	R	Unilateral spatial neglect	35	5	13	5	9	4
Case 6	41	M	I	7.2	L	Transcortical motor aphasia	5	6	17	15	46	31
Case 7	49	F	IIIa	25.2	L	Motor aphasia	7	5	21	4	9	5
Case 8	56	M	I	5.1	L	—	3	15	37	40	62	22
Case 9	46	M	IVa	16.8	L	Motor aphasia	11	3	7	0	2	2
Patients with thalamic hemorrhage												
Case 10	61	M	IIb	4.8	L	—	6	2	2	20	56	36
Case 11	55	M	IIb	15.2	R	—	14	7	11	9	48	39
Case 12	56	M	IIa	2.7	R	—	4	4	7	6	18	12
Case 13	76	M	IIa	7.0	R	Cognitive impairment	3	8	20	5	17	12
Case 14	86	F	IIa	6.5	L	—	10	4	7	0	4	4
Case 15	40	M	IIa	4.8	R	—	1	5	17	14	58	44
Case 16	49	F	IIb	7.7	L	Transcortical motor aphasia	35	9	21	5	33	28

F, female; HAL, hybrid assistive limb; L, left hemisphere; M, male; and R, right hemisphere.

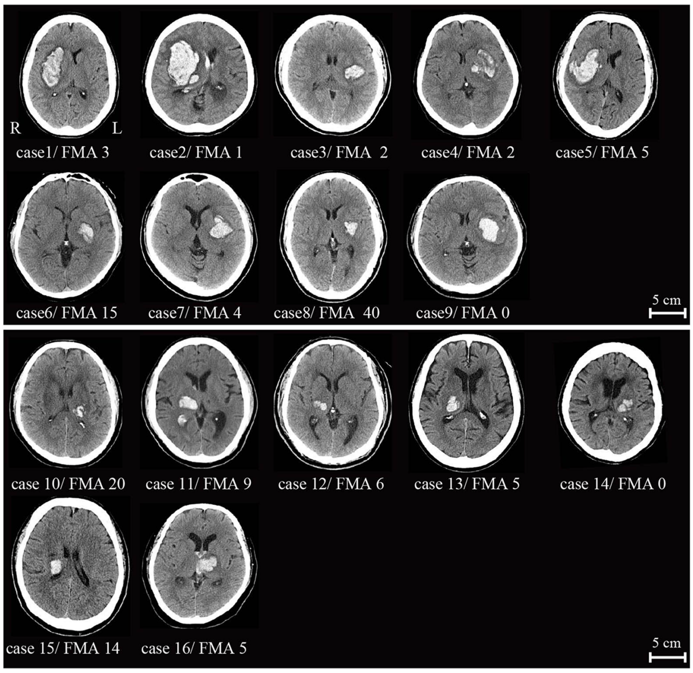

Figure 1. CT images of 16 patients with putaminal hemorrhage (cases 1–9) and those with thalamic hemorrhage (cases 10–16). The Fugl–Meyer assessment (FMA) values represent individual patient upper extremity function scores before training. L and R represent the left and right hemispheres, respectively. CT, computed tomography.

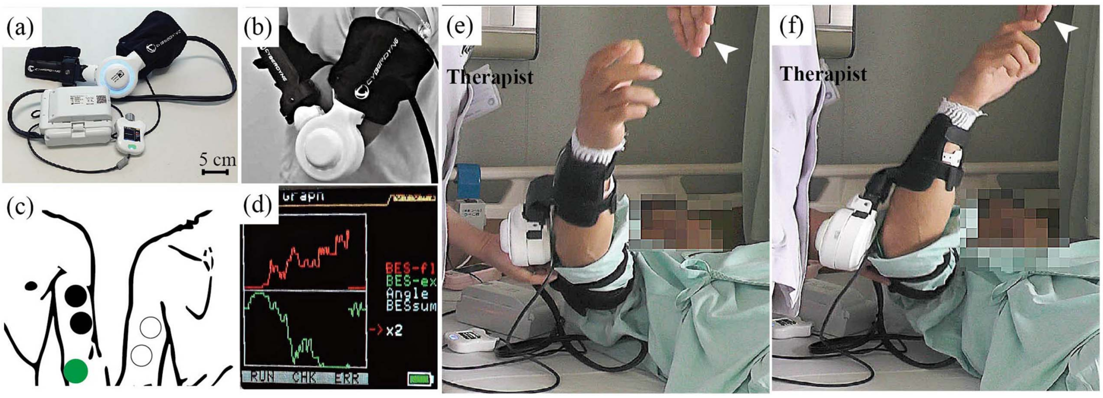

Figure 2. The appearance (a) and attachment (b) of single-joint type of hybrid assistive limb (HAL-SJ). Showing HAL-SJ attached to the upper limb by the brachium and forearm cuffs. The HAL-SJ will be driven by the BES. (c) Illustrating the electrode positions for generating BES to drive the HAL: the position on the elbow flexor muscles (black circles), elbow extensor muscles (white circles), and the ground electrode (green ones). (d) The BES waveform (red, elbow flexor; green, elbow extensor) during training. (e) and (f) Representative reaching task, showing start of training, and final view shown successfully the patient's finger can reach the target finger of the therapist (white arrowhead).

size = 128 × 128, field of view = 240 × 240 mm^2, voxel size = 1.875 × 1.875 × 2 mm^3, $b = 1000$ s mm^{-2}, and number of slices = 76.

We used DSI studio (http://dsi-studio.labsolver.org/) for tractography and analyzed the region of interest (ROI) of the CST. The DTI data were subjected to eddy current correction and normalization during preprocessing. We visualized the fiber tracking of the CST using the two-ROI method [40], using ROIs of the precentral gyrus and posterior limb of the internal capsule in the white-matter tractography atlas of Johns Hopkins University. The FA, MD, AD, and RD values were calculated for the posterior limb of the internal capsule, pyramidal tract, cerebral peduncle, and corona radiata, which are reportedly associated with motor function after stroke. Figure 3 depicts CST tractography and the ROI in a representative patient (case 7). We calculated the FA ratio (mean FA in the ROI of the lesioned hemisphere/mean FA in the ROI of the non-lesioned hemisphere) to minimize the dispersion of FA values due to individual differences. In addition, we focused on

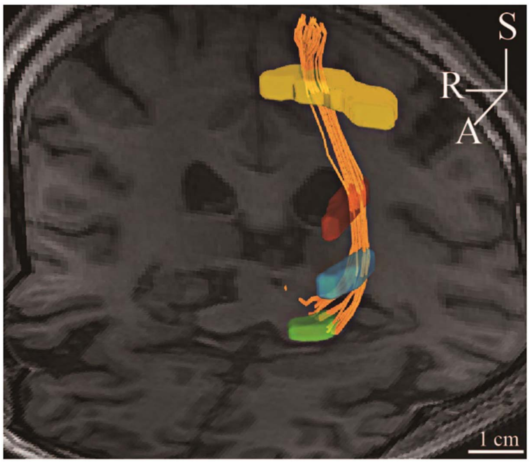

Figure 3. A three-dimensional image of the region of interest (ROI) on a T1-weighted image for calculating the fractional anisotropy values of the corticospinal tract (CST). Green, blue, red, and yellow areas indicate the cerebral peduncle, the posterior limb of internal capsule, corona radiata, and precentral gyrus, respectively. Orange cords indicate a CST passing through ROIs. White lines denote the following direction: anterior (A), right (R), and superior (S).

the cerebral peduncle, which is less affected by hematoma, and evaluated the association between the FMA score and FA values in the upper limb area of the CST [29, 30]. DTI data after HAL training could not be acquired for seven patients (cases 1, 4, 6, 9, 10, 12, and 14) due to their sudden transfer to another hospital or care facility.

2.4. Statistical analysis

We conducted the Mann–Whitney U test to compare the differences in age, the number of day from stroke onset to training initiation, the training session, the amount of hematoma, the score of upper limb function at the start of training, and the effect size of the FMA score between the putamen and thalamus hemorrhage groups. The ABC/2 method was used to calculate the hematoma [41]. We measured the FMA scores and tractography parameters before and after the HAL training using the Wilcoxon rank-sum test. Moreover, the FA, MD, AD, and RD of the improved and unimproved groups were compared using the Mann–Whitney U test.

We analyzed the relationship between the affected/unaffected FA ratio and FMA effect size using Spearman's correlation coefficient. A logistic regression analysis was performed to explain the prognostic model of upper limb function with age, hematoma, the number of days from stroke onset to training initiation, and training sessions as the explanatory variables, and clinically significant improvement in upper limb function as the objective variable. Moreover, we performed the analysis to predict the prognosis of upper limb function using the FA ratios of the posterior limb of the internal capsule, pyramidal tract, cerebral peduncle, and corona radiata as the explanatory variables. To analyze the factors influencing the effect size of FMA, a linear multiple regression analysis was conducted using age, hematoma volume, the number of days from stroke onset to training initiation, number of training sessions, and the FA ratio of the CST as independent variables. The statistical toolbox MATLAB R2014a (MathWorks) and JMP Pro14.1.0 (SAS Institute) were used for the analysis.

3. Results

3.1. Hemorrhage types in patients and training outcomes

Of the 16 patients who participated in this study, the classification of putamen hemorrhage was type I, IIIa, IVa, and Vb in two, three, three, and one patient, respectively [35]. In contrast, thalamic hemorrhage was of type IIa and IIb in four and three patients, respectively [42]. Twelve patients that had damaged internal capsules were severely paralyzed. The details of each patient are presented in table 1 and figure 1.

Patients 2, 5, and 14 underwent HAL training in a supine position on a bed because it was difficult to sit down alone. The therapist instructed the patients on the motion of the elbow joint while confirming the waveform of the BES on the display of the HAL-SJ. We observed an improvement in the BES of the triceps brachii and biceps brachii in cases 3, 6, 8, 10–12, 15, and 16. In contrast, the BES did not change in cases 1, 2, 5, 9, and 14.

Figure 4(a) depicts the alternation of FMA scores before and after HAL training; further details are provided in supplementary table 1. The mean FMA scores before and after HAL training were 8.2 ± 10.2 (score range: 0–40) and 24.3 ± 22.2 (score range: 2–62), respectively. The mean effect size was 16.1 ± 14.8. Following training, we observed clinically significant improvement in nine patients (cases 3, 6, 8, 10–13, 15,

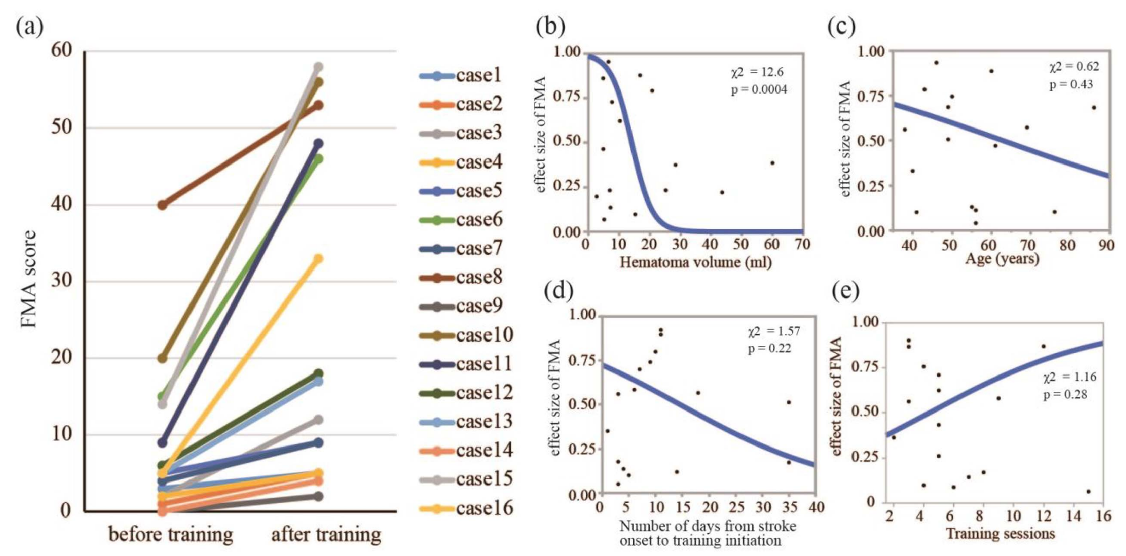

Figure 4. (a) The Fugl–Mayer assessment (FMA) scores before and after HAL training in each patient. The FMA scores for all patients have increased after HAL training. Logistic regression analysis curves for the effect size of FMA and hematoma volume (b), age (c), number of days from stroke onset to training initiation (d), and training session (e). The X-axis of the graph indicates hematoma volume (ml), the age (years), number of days from stroke onset to training initiation, and training sessions. The y-axis indicates the effect size of the FMA. Blue lines represent logistic curves. Black circles represent individual patients.

and 16), with a mean effect size of 26 ± 12.7 FMA. The shoulder and elbow subset scores of the FMA increased in all patients. Of these, eight (50%) and 11 (69%) patients showed improved finger and hand function, respectively.

3.2. The relationship between the prognosis of upper limb function and hemorrhage characteristics

The mean hematoma volume in the putamen hemorrhage group was significantly higher than that in the thalamic hemorrhage group (24.1 ± 18 ml vs. 7 ± 4 ml) ($p < 0.01$). The mean FMA effect size in the thalamic hemorrhage patient group was 25 ± 15.6, compared with 8.2 ± 9.3 in the putamen hemorrhage group ($p < 0.05$). Clinically significant improvements were observed in 86% and 33% of the patients in the thalamic hemorrhage and putamen hemorrhage groups, respectively. More patients in the thalamic hemorrhage group showed improvement in upper limb function than those in the putamen hemorrhage group (Fisher's exact test, $p < 0.05$; odds ratio, 0.05). There were no significant differences between the hemorrhage groups in terms of age, number of days from stroke onset to training initiation, number of HAL training sessions, or FMA score at the beginning of the training. The characteristics of both the hemorrhage groups are summarized in table 2.

There was a significant association between an increase in the hematoma size and a decrease in the FMA effect size. According to the logistic regression analysis (see figure 4(b)), the hematoma volume could explain the prognosis of upper limb function ($\chi^2 = 12.6$, $p < 0.001$). However, age, the period from the onset to the commencement of training, and the number of HAL training sessions could not explain the prognosis of upper limb function (figures 4(c)–(e)).

The patients were divided into two groups based on hematoma volume: those with a volume of less than 10 ml and those with 10 ml or more. The two groups were compared regarding age, gender, hematoma sites, the number of days from stroke onset to training initiation, number of training sessions, pre-training FMA scores, FMA effect size, and CST FA ratio (table 3). The group with a hematoma volume of less than 10 ml had a higher proportion of patients with thalamic hemorrhage (75%) and significantly higher mean values for pre-training FMA scores (13.3 ± 12.6), FA ratio (0.92 ± 0.02), and FMA effect size (23.6 ± 13.6) compared to the group with a hematoma volume of 10 ml or more (pre-training FMA score: 3.3 ± 2.8, FA ratio: 0.74 ± 0.15, FMA effect size: 8.6 ± 12.5; $p < 0.05$). Scatter plots of the FMA effect size against age, hematoma volume, the number of days from stroke onset to training initiation, number of training sessions, and CST FA ratio revealed significant correlations between the FMA effect size and hematoma volume ($r = -0.51$, $p = 0.04$) as well as between the FMA effect size and CST FA ratio ($r = 0.68$, $p = 0.005$) (see supplementary figure 1). Furthermore, potential interactions were suggested between age and CST FA ratio, hematoma volume and CST FA ratio, and the number of days to training initiation and the number of training sessions. A linear multiple regression analysis was performed with the FMA effect size as the dependent variable and age, hematoma volume,

Table 2. Summary of patients' characteristic.

	Putamen group ($n = 9$)	Thalamus group ($n = 7$)	p-value
Age (years)	50.2 ± 9.9	60.4 ± 15.8	0.2
Gender (male:female)	3:6	5:2	0.31
Hematoma volume (ml)	24.1 ± 18.0	7.0 ± 4.0	**0.01**
Number of days from stroke onset to training initiation	11.3 ± 10	10.4 ± 11.7	0.63
Number of training session	14.6 ± 7.7	12.1 ± 7.3	0.67
FMA score before training	8 ± 12.8	8.4 ± 6.7	0.26
Effect size of FMA	8.2 ± 9.3	25 ± 15.6	**0.03**

Showing mean values and standard deviation. A p-value with bold font indicates statistically significant.
FA, factional anisotropy; FMA, Fugl–Mayer assessment.

Table 3. The comparison of the recovery for patients with hematoma volume less than 10 ml or more than 10 ml.

	Less than 10 ml ($n = 8$)	More than 10 ml ($n = 8$)	*p-value*
Age (years)	58.1 (16.1)	51.3 (9.9)	0.40
Gender (male: female)	6:2	3: 5	0.31
The proportion of hematoma sites (putamen: thalamus)	25%:75%	87.5%:12.5%	**0.04**
Number of days from stroke onset to training initiation	8.4 (11.1)	13.5 (9.8)	0.07
Number of training session	6.6 (4.1)	5.4 (3.0)	0.51
FMA score before training	13.3 (12.6)	3.3 (2.8)	**0.03**
Effect size of FMA	23.6 (13.6)	8.6 (12.5)	**0.02**
FA ratio of pyramidal tract	0.92 (0.04)	0.74 (0.15)	**0.01**

Showing mean values and standard deviation. A p-value with bold font indicates statistically significant.
FA, factional anisotropy; FMA, Fugl–Mayer assessment.

Table 4. Summary of multiple liner regression model for effect size of FMA.

Explanatory variable (s)	Beta	Standard error	95% CI	Z-score	P-value
Intercept	−19.35	6.27	−31.47 to −6.601	3.09	**0.002**
Age	0.12	0.09	−0.08062 to 0.2913	1.29	0.2
Hematoma volume	0.23	0.09	0.06856–0.4108	2.67	**0.01**
Number of days from stroke onset to training initiation	0.006	0.08	−0.1403 to 0.1621	0.08	0.93
Number of training session	0.11	0.04	0.03193–0.1938	2.74	**0.001**
FA ratio of pyramidal tract	26.04	6.93	11.92–39.41	3.76	**0.0002**
Age and FA ratio of pyramidal tract	−0.17	0.1	−0.3618 to 0.05514	1.62	0.1
Hematoma volume and FA ratio of pyramidal tract	−0.26	0.09	−0.4525 to −0.08595	2.81	**0.005**
Number of days from stroke onset to training initiation and training session	−0.005	0.008	−0.1403 to 0.1621	0.61	0.54

A p-value with bold font indicates statistically significant.
FA, factional anisotropy. FMA, Fugl–Mayer assessment.

the number of days from stroke onset to training initiation, number of training sessions, CST FA ratio, and the interactions between age and CST FA ratio, hematoma volume and CST FA ratio, and the number of days from stroke onset to training initiation and the number of training sessions as independent variables (table 4). The regression analysis showed an R^2 value of 0.87, with an intercept estimate of -19.35 ($z = 3.09$, $p = 0.002$). Significant variables included hematoma volume, number of training sessions, CST FA ratio, and the interaction between hematoma volume and CST FA ratio ($p < 0.01$). Among these, the estimate for CST FA ratio was the highest (Beta = 26.04, $p = 0.0002$), showing a substantial difference compared to other estimates. These results indicate that the FMA effect size is influenced by CST FA ratio, hematoma volume, and the number of training sessions.

3.3. The relationship between the FA ratio of the CST and upper limb function outcomes

Figure 5 illustrates the association of the pyramidal tract with the upper limb in the FMA score after HAL training. Fiber tracking confirmed that the CSTs

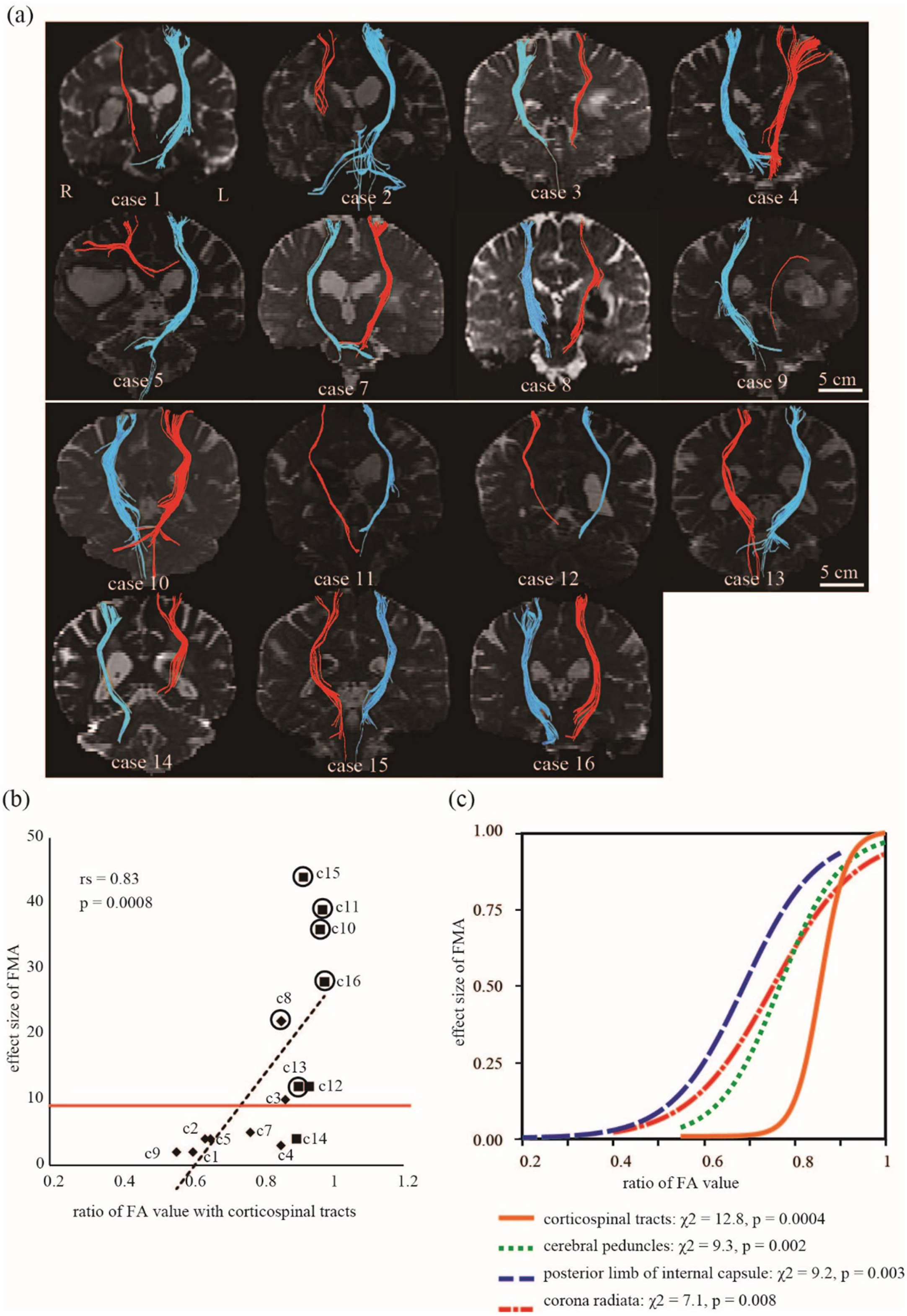

Figure 5. (a) Corticospinal tract (CST) images of patients with putaminal hemorrhage (cases 1–9) and those with thalamic hemorrhage (cases 10–16). The red and blue fibers represent the lesioned and non-lesioned CSTs, respectively. (b) A scatter plot depicting the ratio of the fractional anisotropy (FA) value on the lesioned/unlesioned side of the CST and the Fugl–Mayer assessment (FMA) effect size. The X-axis and the Y-axis indicate the ratio of the FA value on the CST and the FMA effect size, respectively. A dash line represents the straight line of linear approximation. The diamonds and squares indicate the FA value and FMA effect size for patients with putaminal hemorrhage and thalamic hemorrhage, respectively. The red line orthogonal to the Y-axis represents the clinically significant FMA effect size (9 points). Circles represent patients who were able to move their fingers before the hybrid assistive limb training. (c) Logistic regression analysis curves for the effect size of FMA and FA ratios of the CST (orange solid line), cerebral peduncles (green dotted line), the posterior limb of internal capsule (blue dashed line), and corona radiata (red dash dotted line). The X-axis and the Y-axis indicate the ratio of FA value and the FMA effect size, respectively. The scale bar indicates 5 cm.

of the lesioned and non-lesioned hemispheres were present in 11 patients (cases 1, 3, 4, 7, 8, 10–13, 15, and 16). Nonetheless, there were individual differences in the widths of CST bundles. The FMA effect size increased significantly after HAL training in 10 patients (63%). Despite confirming the CSTs of cases 1 and 7 in the lesioned hemispheres, their FMA effect did not improve significantly. Moreover, the FMA effect size was not clinically significant in four patients (cases 2, 5, 9, and 14), in whom the CST from the precentral gyrus to the cerebral peduncle could not be confirmed. Spearman's correlation analysis confirmed a significant positive correlation between the FA ratio (mean FA in the lesioned hemisphere/mean FA in the non-lesioned hemisphere) and the FMA effect size ($rs = 0.83$, $p < 0.001$; see figure 5(b)). Patients with a clinically significant increase in the FMA effect size had an FA ratio $\geqslant 0.86$ and voluntary finger movement at the beginning of training.

Logistic regression analysis was performed to determine the FA ratio of the CST in the cerebral peduncle, posterior limb of the capsule, radial corona, and the whole CST (figure 5(c)). This eventually helped us predict clinically significant improvements in upper limb function after training. The FA ratios of the whole CST ($\chi^2 = 12.8$, $p < 0.001$), cerebral peduncle ($\chi^2 = 9.3$, $p < 0.001$), posterior limb of the capsule ($\chi^2 = 9.2$, $p < 0.001$), and radial corona ($\chi^2 = 7.1$, $p < 0.001$) predicted an improvement in upper limb function. The FA ratio of the entire CST was most strongly associated with the FMA effect size.

3.4. Differences in parameters of the CST tractography between groups with and without improvement in upper limb function after HAL training

The differences in DTI parameters of the CST before and after HAL training were analyzed in the cerebral peduncles, which was less susceptible to hematoma. We calculated the FA values of the upper limb area in the cerebral peduncles for nine cases, with DTI images before and after HAL training (figure 6(a)). Figure 6(b) shows the FA values before and after training. The average FA value before and after the HAL training was 0.56 ± 0.11 and 0.58 ± 0.2, respectively, showing no substantial difference. The FA ratio of six cases (cases 3, 8, 11, 13, 15, and 16) with clinically significant improvement in upper limb function increased after training (the average rate of change in FA ratio, $15 \pm 16\%$). The FA ratio decreased in three cases (cases 2, 5, and 7), without an effective improvement in upper limb function (the average rate of change in FA ratio, $-19 \pm 26\%$) (see supplementary table 2).

We compared the CST tractography and the diffusion tensors of the upper limb area within the cerebral peduncle on the FA color map of patients with improved and unimproved upper limb function (figure 6(c)). While the blue color in the voxel on the FA color map means the vertical diffusion direction, a smaller blue shape indicates a larger diffusion coefficient. Following training, a black area without diffusion tensor was observed in the ROI on the cerebral peduncle color map of patients with unimproved upper limb function (figure 6(c), case 7). Similar results were observed in cases 2 and 5, with unimproved upper limb function, and the width of the CST in these patients was narrowed over the lateral ventricle in the affected hemisphere (see supplementary figure 2). In patients whose upper limb function improved, the blue shapes in the ROI of the cerebral peduncles became smaller after training, which reflects higher integrity of CST in superior-inferior direction. We observed an expansion of the CST in the lesioned hemisphere and an increase in fibers in the postcentral gyrus and precentral gyrus (figure 6(c), case 8, supplementary figure 2). Patients with increased diffusion tensor in the vertical direction, in other words, the axial surface to the CST, showed improved upper limb function.

Figure 7 and table 5 show the changes in DTI parameters of the CST in patients with and without improvements in upper limb function. Following the training, the RD value ($0.44 \pm 0.11\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$) significantly decreased in six patients (cases 3, 8, 11, 13, 15, and 16) with improved upper limb function than that before the training ($0.65 \pm 0.15\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$) (Mann–Whitney U test, $p < 0.05$). Three patients (cases 2, 5, and 7) with poor improvement displayed no significant difference in the mean RD values, before ($0.58 \pm 0.1\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$) and after ($0.71 \pm 0.13\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$) the training. Moreover, RD values of post-training in patients with improved upper extremity function ($0.44 \pm 0.11\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$) were lower than in those with poor improvement ($0.71 \pm 0.13\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$) ($p < 0.05$). Patients with greater decreases in RD values after HAL training tended to have higher FMA effect sizes ($rs = -0.54$, $p = 0.07$). All patients with clinically significant improvement (FMA effect size of $\geqslant 9$ points) had an RD value effect size of less than 0 points. No significant difference was observed between the AD and MD values of the CST before and after HAL training (supplementary table 3). In addition, there were no differences in the AD and MD values between the improved and unimproved patient groups. An increase in FA and a decrease in RD value were common in patients with clinically significant improvements in upper limb function.

4. Discussion

We aimed to assess the effectiveness of HAL training in improving upper limb dysfunction in patients with putamen and thalamic hemorrhage, as well as to examine its impact on the integrity of the CST during the training. We found that HAL training significantly

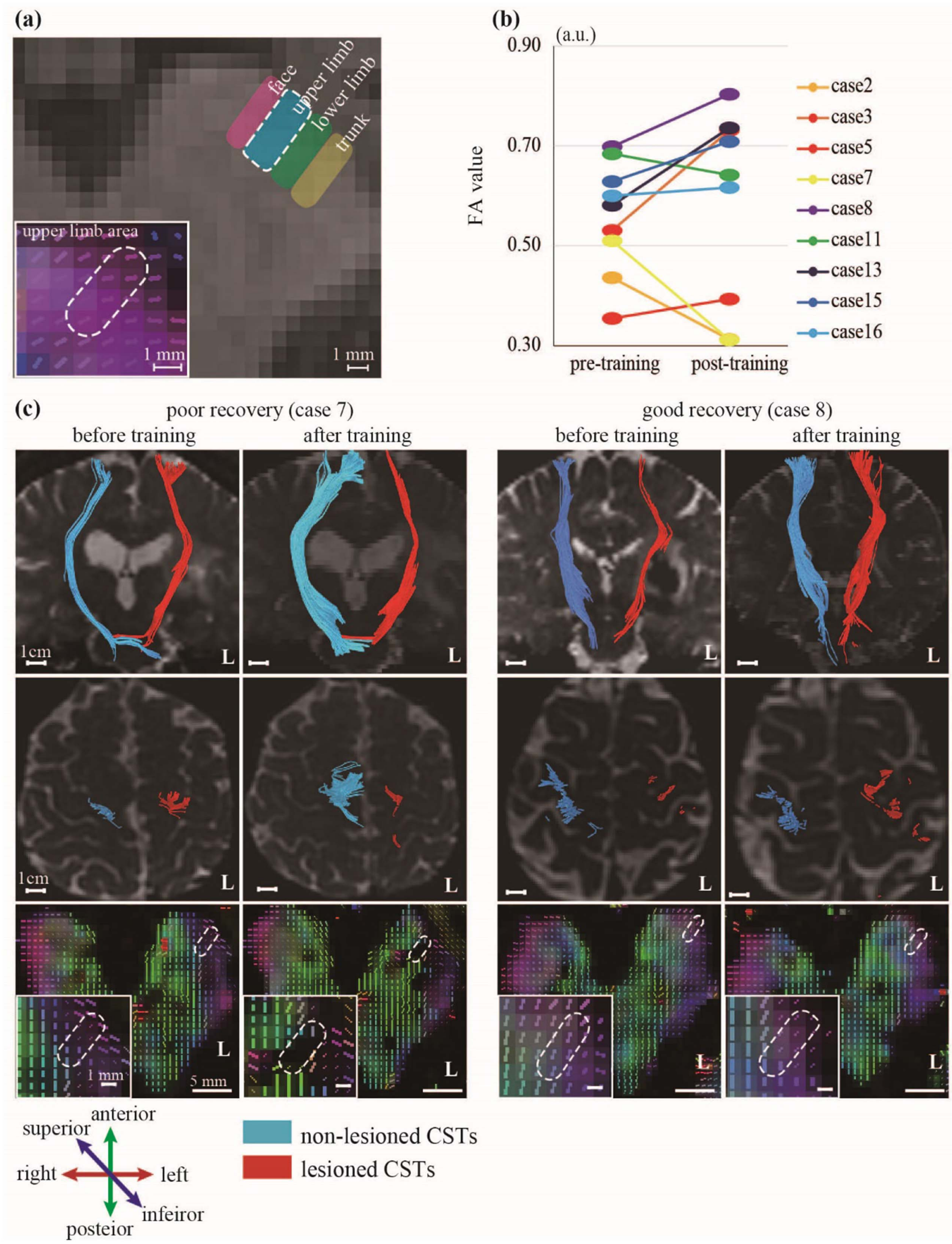

Figure 6. (a) A diagram showing the face (red), upper limbs (blue and dashed line), trunk (green), and lower limb (yellow) areas within the corticospinal tract (CST) of the cerebral peduncle. The inset image on lower left: the white dashed line represents an area of the upper limb in the enlarged view of the cerebral peduncle fractional anisotropy (FA) color map. The scale bar indicates 1 mm. (b) A graph depicting the FA ratio on the lesioned/unlesioned side of the upper limb area within the CST of the cerebral peduncle in nine patients, before and after the training. (c) Showing the representative cases with diffusion tensor tractography of CSTs and the diagram of the cerebral peduncle in poor or good recovery patients (case7 and 8). The upper and middle images depict the coronal and axial section images, respectively. The red and blue fibers represent the lesioned and non-lesioned CSTs, respectively. The lower images show the FA color map of the cerebral peduncle and the enlarged view of the upper limb area (white dashed line). Blue, green, and red colors in the FA color map indicate tensors in the vertical, anterior-posterior, and left-right directions, respectively. The scale bars on the FA color map of the cerebral peduncle and the enlarged view of the upper limb area indicate 5 mm and 1 mm, respectively.

improved the upper limb function in patients with severe hemiplegic ICH. Moreover, DTI tractography analysis after HAL training revealed an increase in FA and a decreased in RD in the CST in patients with improved upper limb dysfunction. These results suggest that HAL training with a BES-based cybernic device promotes white matter integration in the CST and contributes to the amelioration of upper-limb

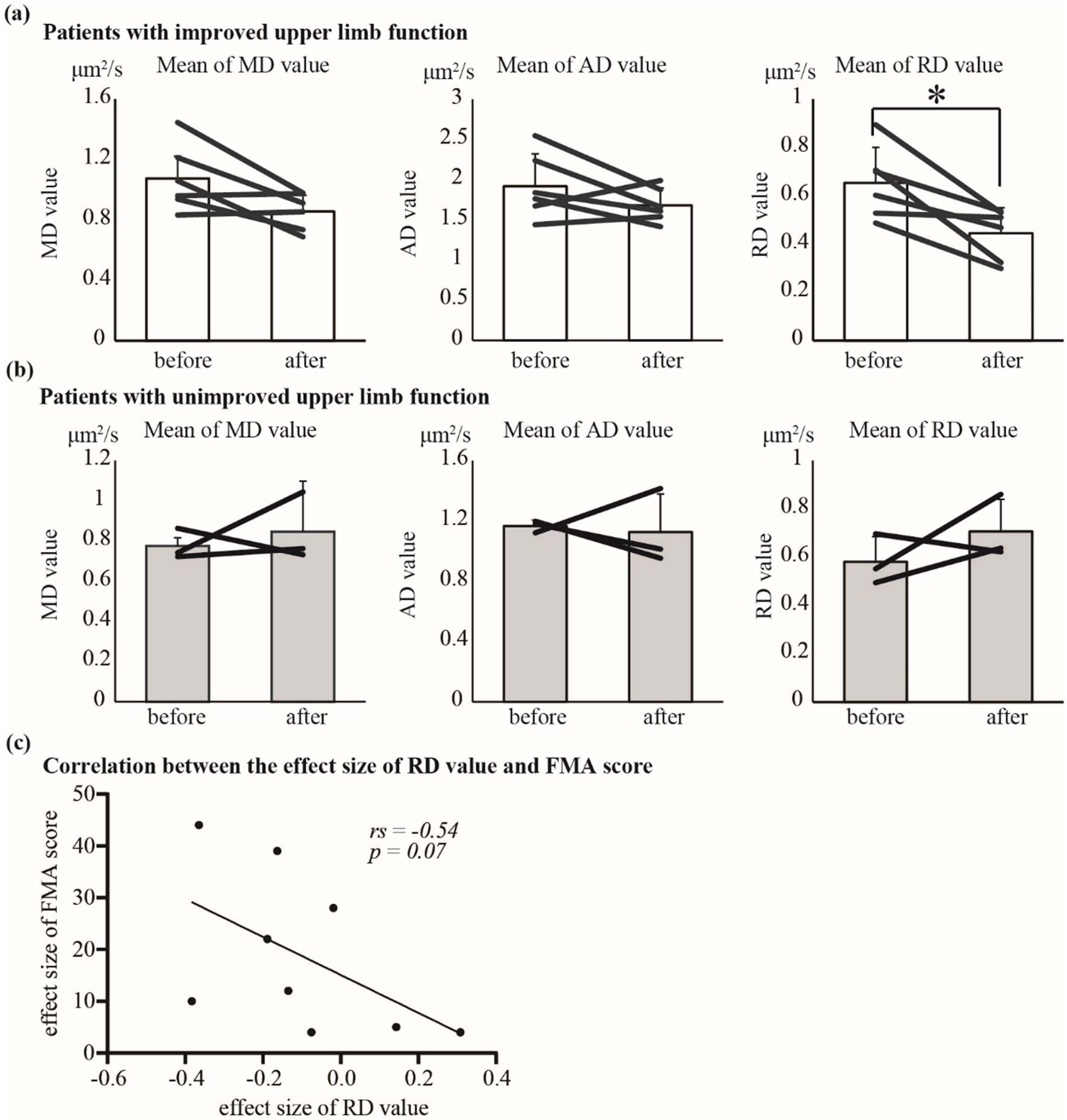

Figure 7. Bar graphs showing the mean values of diffusivity (MD), axial (longitudinal) diffusivity (AD), and radial diffusivity (RD) of the corticospinal tract before and after the training. (a) The upper graphs represent individual data and mean values for six patients with clinically significant improvement in the upper limb function. (b) The middle graphs represent those data for three patients with poor improvement in the upper limb function. (c) A scatter plot showing the effect size of RD and the Fugl–Mayer assessment (FMA). The X-axis and the Y-axis indicate the RD and the FMA effect size, respectively. A solid line represents the straight line of linear approximation. The effect size of RD and the FMA depicted a negative correlation. The dots indicate the effect size of RD and FMA for patients.

Table 5. Alternations in parameters of pyramidal tractography before and after HAL training in upper limb function improvement group and non-improvement group.

	Improved upper extremity function			Unimproved upper extremity function		
	Before HAL training	After HAL training	p-value	Before HAL training	After HAL training	p-value
FA	0.62 ± 0.06	0.71 ± 0.07	<0.05	0.43 ± 0.08	0.34 ± 0.05	n.s.
MD	1.07 ± 0.22	0.86 ± 0.12	n.s.	0.78 ± 0.08	0.85 ± 0.17	n.s.
AD	1.92 ± 0.4	1.68 ± 0.21	n.s.	1.17 ± 0.04	1.13 ± 0.25	n.s.
RD	0.65 ± 0.15	0.44 ± 0.11	<0.05	0.58 ± 0.1	0.71 ± 0.13	n.s.

Showing mean values and standard deviations of fractional anisotropy (FA), mean diffusivity (MD), axial (longitudinal) diffusivity (AD), and radial diffusivity (RD), and statistically significant differences before and after training. n.s., not significant.

motor paralysis in stroke patients. The significance of this study can be attributed to the establishment of new therapeutic strategies for neurorehabilitation.

The incorporation of a reaching task in the HAL training not only improved elbow function but also shoulder and hand function. Our results differed from those of conventional training methods for elbow joint movements with HAL [22]. In this study, HAL training was conducted to promote active movements in patients with the assistance of an exoskeleton robot driven by bioelectric signals generated at the initiation of voluntary movement. In conventional robot training, the paralyzed upper limb of the patient is passively guided by a robotic arm, resulting in minimal voluntary movement by the patient [11–16]. The reaching task involves the goal-directed action of reaching for an object, which in turn activates the ventral tegmental area and ventral striatum related to motivation [6, 43]. Activation of the ventral striatum and ventral tegmental area during the acute stage of stroke promotes improvement in upper-limb function [44]. After two weeks of training, the FMA score increased by an average of 16 points. Therefore, the incorporation of purposeful reaching tasks in HAL training is more effective in improving upper limb function than conventional robot and motor function training [6, 9, 11–16, 45].

Imagery training is effective for motor learning and rehabilitation [46]. However, a patient with a paralyzed limb finds it difficult to image the correct movement for limbs. Motion-assisted HAL based on a BES promotes the activation of the sensorimotor cortex by increasing the sensory input from proprioceptors of the muscle spindles and Golgi tendon organs [22]. Exercise support together with HAL training allows the patients to repeat precise exercises in the correct format. Moreover, the HAL-SJ-mediated enhancement of sensory feedback facilitates imagery training of the upper limb function. HAL training facilitates an imagery of purposeful upper extremity movements and motor relearning.

Tractography analysis revealed an association between enhancement of pyramidal FA and improvement in upper limb function. The FA of the pyramidal tract in stroke survivors sharply decreased by −24% and −34% after 2 and 4 weeks, respectively, despite conventional rehabilitation [47]. In the present study, the FA ratio in patients with improved upper limb function increased by an average of 15% during two weeks of HAL training. However, HAL training has a therapeutic effect compared to conventional rehabilitation. An FA ratio of 0.86 and voluntary finger movements are possible biomarkers for predicting improvement in upper limb function after HAL training [48].

A significant difference in upper limb functional improvement was observed between the thalamic hemorrhage group and the putaminal hemorrhage group, which was found to be related to hematoma volume and CST damage [49–52]. The average hematoma volume in the thalamic hemorrhage group was 7.0 ± 4.0 ml, which was smaller compared to the putaminal hemorrhage group. Tractography of the CST from the cortex to the midbrain was confirmed in all cases except case 14, suggesting minimal damage to the pyramidal tract. In contrast, the putaminal hemorrhage group had a significantly larger average hematoma volume of 24.1 ± 18.0 ml, with the hematoma extending into the internal capsule. Tractography analysis revealed disruption of the CST on the lesion side in 5 out of 8 cases. Based on hematoma volume, 75% of patients with volumes less than 10 ml were in the thalamic hemorrhage group, whereas 87.5% of patients with volumes of 10 ml or greater were in the putaminal hemorrhage group. Integrating these findings, differences in hematoma volume led to significant variations in CST FA ratios and pre-training FMA scores. Notably, patients with hematoma volumes below 10 ml exhibited less CST damage and higher FMA scores. Multiple regression analysis further identified CST FA ratio and hematoma volume as factors influencing FMA effect sizes after HAL training. These results suggest that factors crucial for improving upper limb function include smaller hematoma volumes, minimal CST damage, and preserved pre-training upper limb function [29, 30].

Following training, the FMA score increased in patients with pyramidal tract discontinuity. However, recovery of upper limb function was clinically ineffective. The results of tractography analysis of the CST in patients with poor recovery of upper limb function were consistent with those reported by Cho *et al* [53]. These patients had severely impaired trunk function and difficulty sitting. Disruption of the CST is a severe nerve injury and not only suggests impaired upper and lower extremities but also trunk function. In this study, HAL training alone had difficulty improving upper limb function in these patients. Upper limb function is controlled not only by the CST but also by the rubrospinal tract [53–56]. The reticulospinal tract is involved in trunk function and postural control. Therefore, rehabilitation of upper extremity function in stroke survivors with severely impaired CST may require HAL training in addition to neuromodulation to activate the reticulospinal and rubrospinal tracts [30].

Cognitive function plays an important role in HAL-based motor learning using [20]. Patients with poor improvement in upper-limb function had cognitive impairment and motor aphasia. Communication skills and cognitive functions form the basis for learning. Therefore, patients with impaired function find it difficult to acquire proper movements even with HAL training.

Our study has some limitations. Despite enrolling 16 patients, we could obtain DTIs from only nine of them. This necessitates an increased number of patients and verification of the effects of HAL training in the future. It is necessary to examine the effectiveness of HAL training in tests that compare upper-limb function training with other robotic devices or conventional training. Moreover, we found that it was difficult to improve upper limb function in patients with CST disruption. The involvement of the CST on the unaffected side and the rubrospinal tract in the improvement of upper limb function should be evaluated.

Furthermore, rehabilitation combined with drug-induced myelination or neural network promotion and neuromodulation therapy, such as transcranial magnetic stimulation should be considered for severe upper limb paralysis.

5. Conclusion

This study demonstrated that upper limb function training in the HAL is an effective rehabilitation method for upper limb motor paralysis following ICH. An FA ratio of 0.86 in the affected/unaffected CST was the boundary between clinically effective and ineffective cases. The RD value of patients with a clinically significant improvement in upper limb function decreased after training. These data support an association between changes in corticospinal tract integrity and improved upper-limb function with HAL training. To apply the results of this study to rehabilitation for upper limb motor paralysis in the future, it will be necessary to conduct tests on a larger number of cases and comparative tests with conventional training.

Data availability statement

These data cannot be made publicly available upon publication because they contain sensitive personal information. The data supporting the findings of this study are available upon reasonable request from the authors.

Acknowledgment

The authors wish to acknowledge Department of Radiology, University of the Ryukyus. Hospital for data acquisition on MRI. This work was supported by Grants-in-Aid for Scientific Research (B) (23390352) (to S I); Grants-in-Aid for Scientific Research (A) (17H01403) (to S.I.); Challenging Exploratory Research (24650168) (to S I); Grants-in-Aid for Scientific Research (C) (18K10783) (to M N) by the Ministry of Education, Culture, Sports, Science and Technology in Japan; the Industrial Disease Clinical Research Grants by the Ministry of Health, Labor and Welfare (14050101-01) (to S I); Special Account Budget for Education and Research (2011–2013, 2011–2015, 2014–2018, 2015–2019) (to S I); Grants for the Princess Takamatsu Cancer Fund (to S I); and the Grants for Takeda Science Foundation (to S I).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

ORCID iDs

Masahiko Nishimura https://orcid.org/0000-0002-9551-5650
Shigetaka Kobayashi https://orcid.org/0009-0000-7150-8336
Shogo Ishiuchi https://orcid.org/0000-0002-8967-2019

References

[1] Delcourt C *et al* 2017 Intracerebral hemorrhage location and outcome among INTERACT2 participants *Neurology* **88** 1408–14
[2] Panchal H N, Shah M S and Shah D S 2015 Intracerebral hemorrhage score and volume as an independent predictor of mortality in primary intracerebral hemorrhage patients *Indian J. Surg.* **77** 302–4
[3] Zimmerman R D, Maldjian J A, Brun N C, Horvath B and Skolnick B E 2006 Radiologic estimation of hematoma volume in intracerebral hemorrhage trial by CT scan *Am. J. Neuroradiol.* **27** 666 (PMID: 16552014)
[4] Nakayama H, Jorgensen H S, Raaschou H O and Olsen T S 1994 Recovery of upper extremity function in stroke patients: the Copenhagen stroke study *Arch. Phys. Med. Rehabil.* **75** 394–8
[5] Wolf S L, Lecraw D E, Barton L A and Jann B B 1989 Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients *Exp. Neurol.* **104** 125–32
[6] Li X, He Y, Wang D and Rezaei M J 2024 Stroke rehabilitation: from diagnosis to therapy *Front. Neurol.* **15** 1402729
[7] Bard G and Hirschberg G G 1965 Recovery of voluntary motion in upper extremity following hemiplegia *Arch. Phys. Med. Rehabil.* **46** 567–72
[8] Kwakkel G, Kollen B J, van der Grond J and Prevo A J 2003 Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke *Stroke* **34** 2181–6
[9] Platz T, Eickhof C, van Kaick S, Engel U, Pinkowski C, Kalok S and Pause M 2005 Impairment-oriented training or Bobath therapy for severe arm paresis after stroke: a single-blind, multicentre randomized controlled trial *Clin. Rehabil.* **19** 714–24
[10] van der Lee J H, Wagenaar R C, Lankhorst G J, Vogelaar T W, Deville W L and Bouter L M 1999 Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial *Stroke* **30** 2369–75
[11] Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J and Lingnau M L 2005 Computerized arm training improves the motor control of the severely affected arm after stroke: a single-blinded randomized trial in two centers *Stroke* **36** 1960–6
[12] Khan M A, Saibene M, Das R, Brunner I and Puthusserypady S 2021 Emergence of flexible technology in developing advanced systems for post-stroke rehabilitation: a comprehensive review *J. Neural Eng.* **18** 061003
[13] Klamroth-Marganska V *et al* 2014 Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial *Lancet Neurol.* **13** 159–66
[14] Miyasaka H, Orand A, Ohnishi H, Tanino G, Takeda K and Sonoda S 2016 Ability of electrical stimulation therapy to

improve the effectiveness of robotic training for paretic upper limbs in patients with stroke *Med. Eng. Phys.* **38** 1172–5

[15] Treger I, Faran S and Ring H 2008 Robot-assisted therapy for neuromuscular training of sub-acute stroke patients. A feasibility study *Eur. J. Phys. Rehabil. Med.* **44** 431–5

[16] Cardone D *et al* 2025 Robot-assisted upper limb therapy for personalized rehabilitation in children with cerebral palsy: a systematic review *Front. Neurol.* **15** 1499249

[17] Kawamoto H and Sankai Y 2005 Power assist method based on phase sequence and muscle force condition for HAL *Adv. Robot.* **19** 717–34

[18] Lee S and Sankai Y 2005 Virtual impedance adjustment in unconstrained motion for an exoskeletal robot assisting the lower limb *Adv. Robot.* **19** 773–95

[19] Fukuda H, Morishita T, Ogata T, Saita K, Hyakutake K, Watanabe J, Shiota E and Inoue T 2016 Tailor-made rehabilitation approach using multiple types of hybrid assistive limb robots for acute stroke patients: a pilot study *Assist. Technol.* **28** 53–56

[20] Nishimura F *et al* 2018 Efficacy of the visual evoked potential monitoring in endoscopic transnasal transsphenoidal surgery as a real-time visual function *Neurol. India* **66** 1075–80

[21] Saita K, Morishita T, Hyakutake K, Fukuda H, Shiota E, Sankai Y and Inoue T 2017 Combined therapy using botulinum toxin A and single-joint hybrid assistive limb for upper-limb disability due to spastic hemiplegia *J. Neurol. Sci.* **373** 182–7

[22] Saita K, Morishita T, Arima H, Hyakutake K, Ogata T, Yagi K, Shiota E and Inoue T 2018 Biofeedback effect of hybrid assistive limb in stroke rehabilitation: a proof of concept study using functional near infrared spectroscopy *PLoS One* **13** e0191361

[23] Hyakutake K, Morishita T, Saita K, Fukuda H, Shiota E, Higaki Y, Inoue T and Uehara Y 2019 Effects of home-based robotic therapy involving the single-joint hybrid assistive limb robotic suit in the chronic phase of stroke: a pilot study *BioMed Res. Int.* **2019** 5462694

[24] Hepp-Reymond M C and Wiesendanger M 1972 Unilateral pyramidotomy in monkeys: effect on force and speed of a conditioned precision grip *Brain Res.* **36** 117–31

[25] Murata Y and Higo N 2016 Development and characterization of a macaque model of focal internal capsular infarcts *PLoS One* **11** e0154752

[26] Schiemanck S K, Kwakkel G, Post M W, Kappelle L J and Prevo A J 2008 Impact of internal capsule lesions on outcome of motor hand function at one year post-stroke *J. Rehabil. Med.* **40** 96–101

[27] Groisser B N, Copen W A, Singhal A B, Hirai K K and Schaechter J D 2015 Corticospinal tract diffusion abnormalities early after stroke predict motor outcome *Neurorehabil. Neural Repair* **28** 751–60

[28] Jang S H 2011 A review of diffusion tensor imaging studies on motor recovery mechanisms in stroke patients *NeuroRehabilitation* **28** 345–52

[29] Koyama T, Tsuji M, Nishimura H, Miyake H, Ohmura T and Domen K 2013 Diffusion tensor imaging for intracerebral hemorrhage outcome prediction: comparison using data from the corona radiata/internal capsule and the cerebral peduncle *J. Stroke Cerebrovasc. Dis.* **22** 72–79

[30] Puig J *et al* 2013 Decreased corticospinal tract fractional anisotropy predicts long-term motor outcome after stroke *Stroke* **44** 2016–8

[31] Puig J *et al* 2017 Diffusion tensor imaging as a prognostic biomarker for motor recovery and rehabilitation after stroke *Neuroradiology* **59** 343–51

[32] Stinear C M, Barber P A, Petoe M, Anwar S and Byblow W D 2012 The PREP algorithm predicts potential for upper limb recovery after stroke *Brain* **135** 2527–35

[33] Basser P J and Pierpaoli C 2011 Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI *J. Magn. Reson.* **213** 560–70

[34] Moseley M E, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari H S, Wendland M F, Tsuruda J and Norman D 1990 Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system *Radiology* **176** 439–45

[35] Özarslan E, Vemuri B C and Mareci T H 2005 Generalized scalar measures for diffusion MRI using trace, variance, and entropy *Magn. Reson. Med.* **53** 866–76

[36] Sampaio-Baptista C *et al* 2013 Motor skill learning induces changes in white matter microstructure and myelination *J. Neurosci.* **33** 19499

[37] Wang X, Casadio M, Weber K A II, Mussa-Ivaldi F A and Parrish T B 2014 White matter microstructure changes induced by motor skill learning utilizing a body machine interface *NeuroImage* **88** 32–40

[38] Fugl-Meyer A R, Jääskö L, Leyman I, Olsson S and Steglind S 1975 The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance *Scand. J. Rehabil. Med.* **7** 13–31

[39] Arya K N, Verma R and Garg R K 2011 Estimating the minimal clinically important difference of an upper extremity recovery measure in subacute stroke patients *Top. Stroke Rehabil.* **18** 599–610

[40] Wakana S *et al* 2007 Reproducibility of quantitative tractography methods applied to cerebral white matter *Neuroimage* **36** 630–44

[41] Kothari R U, Brott T, Broderick J P, Barsan W G, Sauerbeck L R, Zuccarello M and Khoury J 1996 The ABCs of measuring intracerebral hemorrhage volumes *Stroke* **27** 1304–5

[42] Waga S and Yamamoto Y 1983 Hypertensive putaminal hemorrhage: treatment and results. Is surgical treatment superior to conservative one? *Stroke* **14** 480–5

[43] Hiraoka S *et al* 2017 Factors necessary for independent walking in patients with thalamic hemorrhage *BMC Neurol.* **17** 211

[44] Nishimura M, Yoshii Y, Watanabe J and Ishiuchi S 2009 Paralimbic system and striatum are involved in motivational behavior *NeuroReport* **20** 1407–13

[45] Sawada M, Kato K, Kunieda T, Mikuni N, Miyamoto S, Onoe H, Isa T and Nishimura Y 2015 Function of the nucleus accumbens in motor control during recovery after spinal cord injury *Science* **350** 98

[46] Lee K B, Kim J S, Hong B Y, Kim Y D, Hwang B Y and Lim S H 2015 The motor recovery related with brain lesion in patients with intracranial hemorrhage *Behav. Neurol.* **2015** 258161

[47] Tsuchimoto S, Shindo K, Hotta F, Hanakawa T, Liu M and Ushiba J 2019 Sensorimotor connectivity after motor exercise with neurofeedback in post-stroke patients with hemiplegia *Neuroscience* **416** 109–25

[48] Yu C, Zhu C, Zhang Y, Chen H, Qin W, Wang M and Li K 2009 A longitudinal diffusion tensor imaging study on Wallerian degeneration of corticospinal tract after motor pathway stroke *Neuroimage* **47** 451–8

[49] Yoshioka H, Horikoshi T, Aoki S, Hori M, Ishigame K, Uchida M, Sugita M, Araki T and Kinouchi H 2008 Diffusion tensor tractography predicts motor functional outcome in patients with spontaneous intracerebral hemorrhage *Neurosurgery* **62** 97–103

[50] Song S K, Sun S W, Ju W K, Lin S J, Cross A H and Neufeld A H 2003 Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia *Neuroimage* **20** 1714–22

[51] Feldman H M, Yeatman J D, Lee E S, Barde L H F and Gaman-Bean S 2010 Diffusion tensor imaging: a review for

pediatric researchers and clinicians *J. Dev. Behav. Pediatr.* **31** 346–56

[52] Zhu L L, Lindenberg R, Alexander M P and Schlaug G 2010 Lesion load of the corticospinal tract predicts motor impairment in chronic stroke *Stroke* **41** 910–5

[53] Cho S H, Kim S H, Choi B Y, Kang J H, Lee C H, Byun W M and Jang S H 2007 Motor outcome according to diffusion tensor tractography findings in the early stage of intracerebral hemorrhage *Neurosci. Lett.* **421** 142–6

[54] Morris R, Vallester K K, Newton S S, Kearsley A P and Whishaw I Q 2015 The differential contributions of the parvocellular and the magnocellular subdivisions of the red nucleus to skilled reaching in the rat *Neuroscience* **295** 48–57

[55] Ishida A, Isa K, Umeda T, Kobayashi K, Kobayashi K, Hida H and Isa T 2016 Causal link between the cortico-rubral pathway and functional recovery through forced impaired limb use in rats with stroke *J. Neurosci.* **36** 455–67

[56] Takenobu Y, Hayashi T, Moriwaki H, Nagatsuka K, Naritomi H and Fukuyama H 2014 Motor recovery and microstructural change in rubro-spinal tract in subcortical stroke *Neuroimage Clin.* **4** 201–8