Whole Brain White Matter Microstructure and Upper Limb Function: Longitudinal Changes in Fractional Anisotropy and Axial Diffusivity in Post-Stroke Patients

Journal of Central Nervous System Disease
Volume 11: 1–9

DOI: 10.1177/1179573519863428
SAGE

Nicodemus Edrick Oey[1,3], Geoffrey Sithamparapillai Samuel[2], Joseph Kai Wei Lim[3], Antonius MJ VanDongen[3], Yee Sien Ng[2] and Juan Zhou[3,4]

[1]Singapore Health Services, Singapore. [2]Department of Rehabilitation Medicine, Singapore General Hospital, Singapore. [3]Programme in Neuroscience and Behavioural Disorders, Center for Cognitive Neuroscience, Duke-NUS Medical School, Singapore. [4]Clinical Imaging Research Center, Agency for Science, Technology and Research (A*STAR), Singapore.

ABSTRACT

BACKGROUND: Diffusion tensor imaging (DTI) magnetic resonance imaging (MRI) measuring fractional anisotropy (FA) and axial diffusivity (AD) may be a useful biomarker for monitoring changes in white matter after stroke, but its associations with upper-limb motor recovery have not been well studied. We aim to describe changes in the whole-brain FA and AD in five post-stroke patients in relation to kinematic measures of elbow flexion to better understand the relationship between FA and AD changes and clinico-kinematic measures of upper limb motor recovery.

METHODS: We performed DTI MRI at two timepoints during the acute phase of stroke, measuring FA and AD across 48 different white matter tract regions in the brains of five hemiparetic patients with infarcts in the cortex, pons, basal ganglia, thalamus, and corona radiata. We tracked the progress of these patients using clinical Fugl-Meyer Assessments and kinematic measures of elbow flexion at the acute phase within 14 (mean: 9.4 ± 2.49) days of stroke symptom onset and at a follow-up appointment 2 weeks later (mean: 16 ± 1.54) days.

RESULTS: Changes in FA and AD in 48 brain regions occurring during stroke rehabilitation are described in relation to motor recovery. In this case series, one patient with a hemipontine infarct showed an increase in FA of the ipsilateral and contralateral corticospinal tract, whereas other patients with lesions involving the corona radiata and middle cerebral artery showed widespread decreases in perilesional FA. On the whole, FA and AD seemed to behave inversely to each other.

CONCLUSIONS: This case series describes longitudinal changes in perilesional and remote FA and AD in relation to kinematic parameters of elbow flexion at the subacute post-stroke period. Although studies with larger sample sizes are needed, our findings indicate that longitudinally measured changes in DTI-based measurements of white matter microstructural integrity may aid in the prognostication of patients affected by motor stroke.

KEYWORDS: Diffusion tensor imaging, MRI, stroke, central nervous system, fractional anisotropy

RECEIVED: September 2, 2018. **ACCEPTED:** June 23, 2019.

TYPE: Original Research

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Biomedical Research Council, Singapore (BMRC 04/1/36/372 to J.Z.), the National Medical Research Council, Singapore (NMRC/CBRG/0088/2015 to J.Z.), and Duke-NUS Graduate Medical School Signature Research Program funded by Ministry of Health, Singapore.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Nicodemus Edrick Oey, Singapore Health Services, 8 College Road, Singapore 169857, Singapore. Email: Nicodemus.oey@gmail.com

Introduction

Motor recovery after stroke is related to lesion location and the structural integrity of white matter pathways.[1] Diffusion tensor imaging (DTI) measures the diffusion of water molecules along a fibrous neural tract, enabling the characterization of Wallerian Degeneration—a key process underlying white matter microstructural damage and consequent lack of motor recovery.[2] Diffusion-tensor-imaging-measured fractional anisotropy (FA), which quantifies the degree of directionality of water diffusion in cerebral white matter, is a surrogate measurement of the integrity of its local microstructure. Fractional anisotropy is known to correlate with motor recovery,[3] implying that FA may be useful in predicting function.[4] Indeed, correlations of single-timepoint FA with motor recovery have been shown in stroke patients undergoing rehabilitation.[5] However, though rFA provides an advantage over FA by taking a ratio of FA between lesioned and non-lesioned hemispheres, it does not provide information on the change in FA over time—in short, longitudinal changes in FA have rarely been studied. Another metric, known as axial diffusivity (AD), measures the predominant diffusivity in the direction of white matter tracts and has been relatively understudied.

The role of DTI metrics in prognosticating upper limb motor outcome have been reviewed.[6] Most studies have focused on the role of the measured ratio of lesioned to non-lesioned FA (rFA) in specific white matter tracts, such as the corticospinal tract (CST), in predicting long-term motor outcome.[7] One study reported that cross-sectional FA measurements of the

Table 1. Patient profile, primary lesion location, and clinical scores at baseline and follow up.

ID	AGE RANGE	H	BASELINE	FOLLOW-UP	LESION LOCATION	FMA (B)	FMA (FU)
A	70-75	R	12 days	19 days	Right hemipons	24	(50)#
B	70-75	R	12 days	18 days	Right posterior lentiform	50	(54)
C	60-65	R	6 days	16 days	Left corona radiata*	48	(63)#
D	60-65	R	7 days	12 days	Right thalamus	62	(65)
E	35-40	L	10 days	14 days	Left middle cerebral artery	62	(65)

Legend: H, handedness (L, left-handed, R, right-handed), Baseline, number of days after symptom onset. Follow-up, number of days that elapsed between baseline and follow-up scan.
FMA, Total Fugl-Meyer scores; B, score at baseline; FU, score at follow up.
*Dominant hemisphere.
#Clinically significant change in score.[19,20]

CST distal to the stroke lesion 80 hours within stroke onset did not have predictive value to motor outcomes at 3 months as measured by the Fugl-Meyer Assessment (FMA) score, but longitudinal comparisons of FA were not performed.[8] Another study showed correlations between initial rFA in the CST and superior longitudinal fasciculus with clinical measures of hemiparesis and cognition in stroke recovery.[9] In a groundbreaking study that looked at longitudinal changes in DTI parameters, Groisser et al.[10] showed that subacute decreases in FA predicted chronic hand dexterity, and importantly showed that another metric, known as AD, at the acute stroke phase correlated strongly with subacute and chronic motor function.

Despite the encouraging findings of these studies, the relationship between longitudinally measured FA and AD changes and concomitant motor recovery has not been clear.[11] Technical issues include the fact that DTI techniques such as fiber-tracking have so far relied on analyzing predefined brain locations and therefore may not reflect changes occurring in other parts of the brain.[12] Furthermore, it is still unclear whether clinical scores such as the FMA or kinematic measurements of upper extremity function as measured by accelerometers may be better correlates of neural recovery.[13] In this study, we used both clinical measures of FMA scores and kinematic measures of elbow flexion and extension movement through the use of wearable gyrometers. Kinematic parameters have been shown to correlate well with clinical scores[14] and may have the added benefit of being more sensitive,[15] allowing for the detection of potentially meaningful performance gains that would have otherwise been unnoticed.[16] We aimed to observe how changes in FA and AD longitudinally evolved over a 2-week period after acute stroke in relation to clinico-kinematic changes.

As the main outcome measure, we reported detailed analyses of elbow movements, as the elbow joint is critical for the positioning of the hand in space and for reaching: a function that is often impaired in stroke due to weakness[17] and spasticity.[18] Beyond the ceiling effect of the FMA, the kinematic-based parameters of movement speed and smoothness were examined in great detail in parallel with changes in FA and AD of the CST as well as in 47 other brain regions.

In this proof-of-principle case series, we combined the use of DTI magnetic resonance imaging (MRI), clinical assessment, and kinematic measures of elbow flexion to explore the utility of DTI in detecting longitudinal changes in white matter microstructure and their relationship to changes in elbow function.

Methods

Patient selection

Patients were recruited from a tertiary stroke rehabilitation unit, based on inclusion criteria, such as first episode ischemic stroke within the last 21 days, minimum power of 2 in the upper limb muscles on the Medical Research Council scale, and the ability to provide informed consent. All patients received standard-of-care 1 hour daily sessions of occupation and physical therapy, with an additional 1-hour long session of kinematic training, between baseline and follow-up MRI scans, with the exact time that elapsed between the baseline and follow-up scans being listed in Table 1 and Figure 1. Five patients, which are henceforth identified as patient A, B, C, D, and E, were selected to represent motor stroke due to lesions in the pons, basal ganglia, corona radiata, thalamus, and middle cerebral artery, respectively. Other patient information including initial National Institute of Health Stroke Scale (NIHSS) scores, Modified Ranking Scale (mRS) scores, treatment history, baseline power, and comorbidities are listed in Supplementary Table S1. We earnestly thank all patients for their voluntary participation in this study. All consent-taking and human subject participation was conducted in accordance to the ethical principles expressed in the Declaration of Helsinki and in the Singhealth Institutional Review Board CIRB Ref 2013/323/F. The Institutional Review Board of Singapore Health Services (Singhealth CIRB Ref 013/323/F) specifically approved the conduct of the study. Recruited patients gave written informed consent after a research assistant explained in detail the objective, methodology, and logistics of the study. Patients were specifically informed that their involvement in the study would not in any way compromise their clinical care.

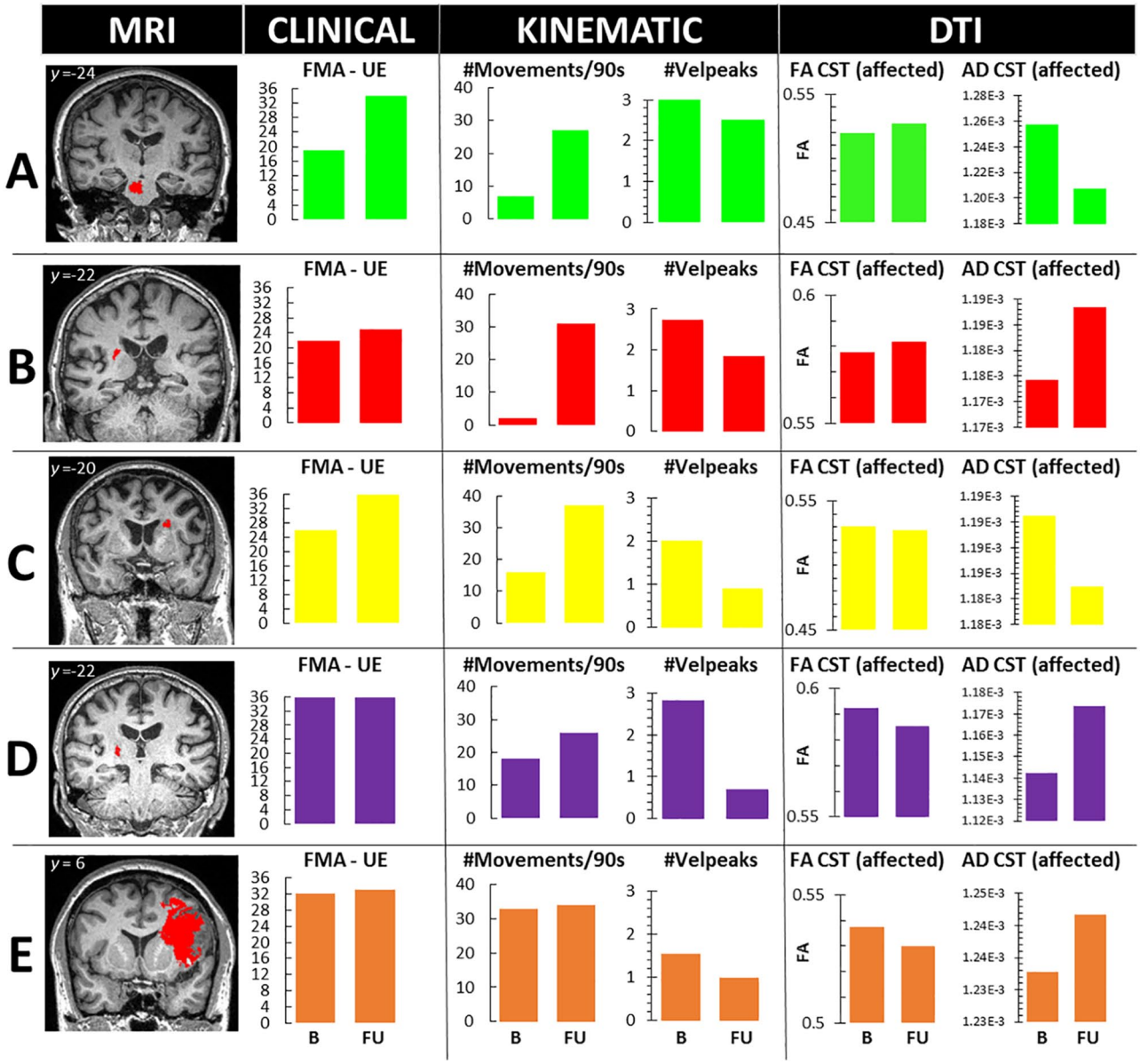

Figure 1. Lesion location, clinical, kinematic, and DTI changes from baseline to follow-up.

Image acquisition and tract-based spatial statistics

Multimodal MRI scans including DTI were performed at two different timepoints for each patient: the baseline scan which occurred within 1 to 14 days of symptom onset, and the follow-up scan which occurred on average 2 weeks after the baseline scan (range: 12-19 days, Table 1). Magnetic resonance imaging was performed on a 3T Siemens Magnetom Trio System (Siemens, Erlangen, Germany). High-resolution T1-weighted Magnetization-Prepared Rapid Gradient Echo (MPRAGE) was used for obtaining sequences (192 continuous sagittal slices, TR/TE/TI = 2300/2.98/900 ms, flip angle = 9°, FOV = 256 × 240 mm^2, matrix = 256 × 240, isotropic voxel size = 1.0 × 1.0 × 1.0 mm^3, bandwidth = 240 Hz/pixel). Diffusion tensor imaging was performed using a diffusion-weighted echo-planar imaging (EPI) sequence (61 noncollinear diffusion gradient directions at b = 1000 s/mm^2, eight volumes of b = 0 s/mm^2, TR/TE = 8400/90 ms, FOV = 220 × 220 mm^2, matrix = 96 × 96, 68 contiguous slices, and voxel size = 2.3 × 2.3 × 2.3 mm^3). Diffusion tensor imaging data for were preprocessed using FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl), and corrected using eddy[21] through affine registration of diffusion-weighted images to the first b = 0 volume.[22] Voxel-wise processing of FA data was carried out using tract-based spatial statistics (TBSS).[23] Fractional anisotropy and AD data from 48 brain regions of interest (ROIs) based on the Johns Hopkins white matter atlas were calculated at baseline and follow-up, and a percent delta change was calculated by subtracting the baseline value from follow-up and obtaining a ratio (Follow-up—Baseline/Baseline) and multiplying it by 100 (Figure 2). With

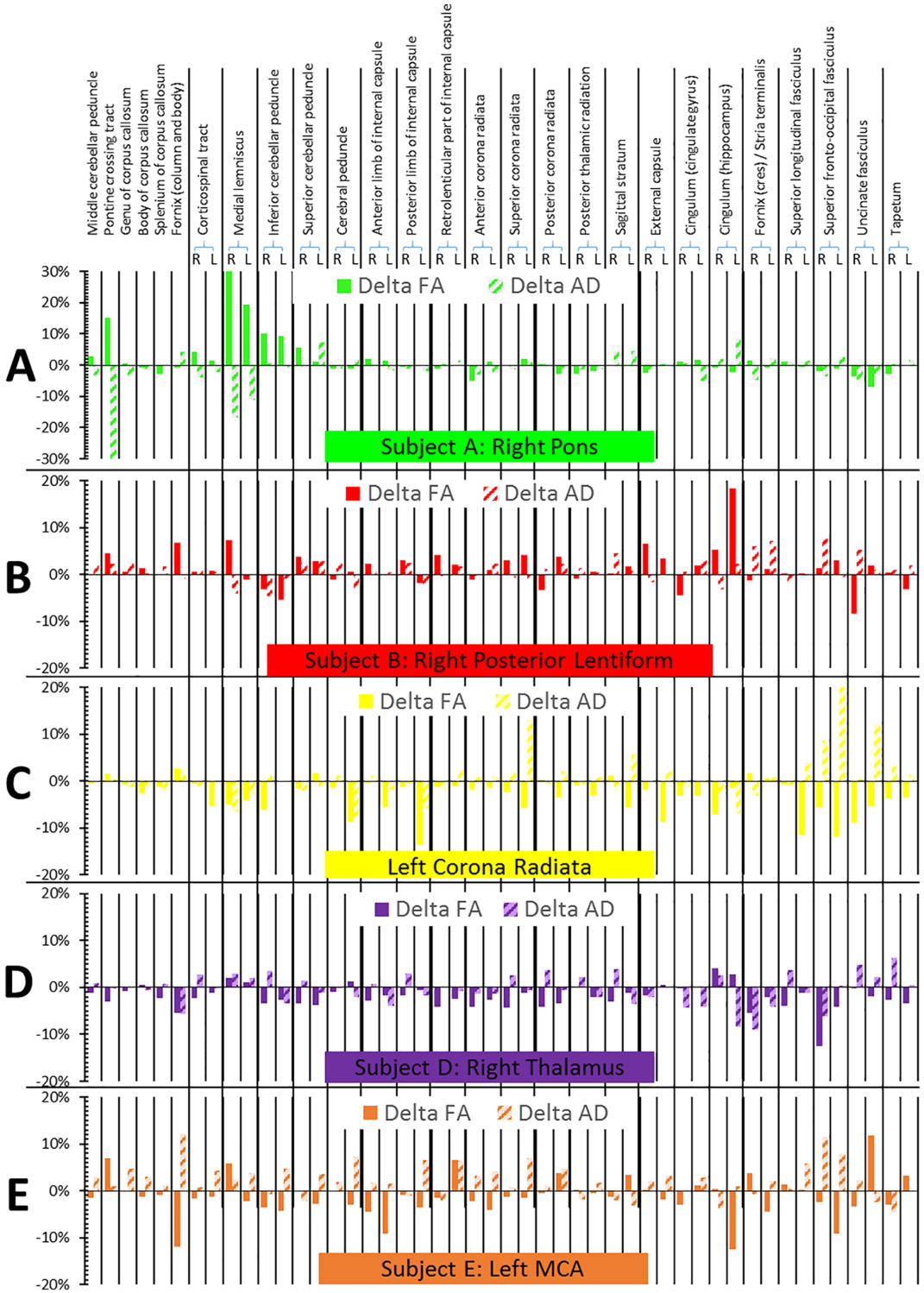

Figure 2. Lesion-dependent region-specific white matter microstructure changes in acute stroke: comparison of longitudinal FA and AD.

respect to the CST, a more comprehensive ROI was used for analysis (Supplementary Figure S3).

Clinical measures of upper limb function

To track clinical improvement, trained clinical neurology fellows and occupational therapists assessed each patient's performance at baseline and follow-up using the FMA: a well-established outcome measure for motor recovery which assesses movement synergy, reflexes, and coordination, all of which contribute to a global measure of limb function after stroke.[24] Total upper extremity FMA scores were analyzed at baseline which occurred within 14 (mean: 9.4±2.49) days of stroke symptom onset and at a follow-up appointment 2 weeks later (mean: 16±1.54) days.

Kinematic measures of upper limb function

Kinematic measures of quality of elbow movement were obtained by equipping each patient with two wearable inertial measurement unit (IMU) sensors (MPU-9150 chip, InvenSense, San Jose, CA), mounted at the mid-shaft of the humerus and the distal forearm proximal to the wrist. In addition to 1 hour of standard physiotherapy each day, patients enrolled in the study were given an extra hour of kinematic training. In these sessions which occurred every weekday between the baseline and follow-up MRI scans, we presented to patients an augmented reality setup where patients are seated in front of a computer screen which shows the patient's arm as an avatar and a number of "reaching targets" which depict food items (Supplementary Figure S1). Patients were asked to do repetitive elbow flexion and extension movements which are designed to simulate arm movements during the act of reaching out for food.[25] In each session lasting 1 hour on the weekdays above and beyond conventional physiotherapy, patients were asked to complete as many reaching movements as they can in up to 10 trials of 90-second intervals each, with 5 minutes of rest allowed in between trials. Registered three-dimensional coordinates at the humerus and distal forearm resulted in a highly detailed data set of arm location and velocities during repetitive elbow movements (Supplementary Table S2). In each of these 90-second trials, we measured several kinematic parameters including: (1) the total number of successful elbow flexion movements, defined as the completion of a full reaching movement followed by full flexion to bring the hand to the mouth completed within 90 seconds; (2) the speed of movements, defined as the amount of time (in milliseconds) it takes for the patient to complete the reaching movement; and (3) the number of velocity correction peaks (please see Supplementary Table S2 for other kinematic parameters such as hand-path ratio). The average total number of flexion movements completed in a limited span of time is an important metric as not only is it thought to be related to stamina and power, repetition is needed to promote recovery of neural tracts.[26] In this study, only the number of successful complete extension and flexion of the elbow were charted to minimize the possibly confounding effects of incomplete or less purposeful movements (Supplementary Figure S2, Supplementary Table S2). To measure the smoothness of movements, we quantified the number of velocity correction peaks: a parameter that is inversely correlated with movement quality on the premise that the movement of stroke patients often comprises frequent submovements or correction attempts due to deficits in motor output pathways and ascending sensory feedback.[27] As such, we obtained a kinematic measure of movement smoothness by transforming angular velocities into "velocity peaks" (#velpeaks[28]). In all cases, an average of 10 trials was obtained for both number of successful movements as well as velocity peaks, with the standard errors of mean calculated (Supplementary Table S2). Statistical analyses were performed by comparing the means using a paired two-tailed *t*-test using the software GraphPad Prism. By taking an average of 10 trials during each session, we reduced the possibility that the kinematic measures of movement speed and smoothness might be confounded by factors such as fatigue, familiarity, and training.

Results

Clinical, kinematic, and imaging measures at baseline and follow-up

Demographic, lesion-specific variables, as well as clinical and kinematic measures at baseline and follow-up of the five patients with diverse lesion locations are listed in Table 1. Total FMA scores (FMA) were tabulated at baseline (B) and at follow-up (FU), with higher numbers corresponding to better performance and a maximum score of 66, with clinically important differences for the FMA scores being defined as 4.25 to 7.25 units according to a previous study.[19] A graphical summary of the lesion site along with the upper extremity function subscale score (FMA-UE) and kinematic measures of average total number of elbow movements completed in 90 seconds and velocity correction peaks is shown in Figure 1. Juxtaposed with these clinical and kinematic measures are FA and AD changes in the CST and posterior limb of the internal capsule (PLIC), as single-timepoint FA in these regions was previously shown to be correlated to motor deficit and outcome,[7,29] whereas longitudinal loss of AD was prognostic of chronic motor outcome. The evolution of FA and AD in all 48 brain regions examined is given in Figure 2.

Each patient's stroke lesion is depicted in representative coronal slices with a red overlay, with the normalized coordinate corresponding to the slice chosen displayed on the top left. Individual increments in total FM scores (FMA-UE) are shown in graphical format for each patient, both at baseline (B) and follow-up (FU). Subsequent columns depict kinematic parameters as measured by wearable gyrometers: number of movements, hand-path ratio, and number of velocity correction peaks. In the extreme right panel, changes in FA and AD in the affected CST are shown.

FA and AD of brain regions surrounding the stroke lesion show dynamic changes depending on lesion location

We evaluated the relationship between the location of the lesion and FA changes across 48 brain regions, and observed location-dependent recovery patterns in white matter tract microstructure (Figure 2). A spatially confined lesion, such as that seen in patient A (pons) and patient B (lentiform nucleus) was associated with perilesional increases in FA. After 2 weeks of rehabilitation, patient A with the right hemipontine infarct showed increases in the FA of distal motor pathways including the perilesional pontine crossing tract, descending bilateral CSTs, and bilateral medial lemnisci (Figure 3). Patient B who had a left-sided basal ganglia lesion had increases in the FA but

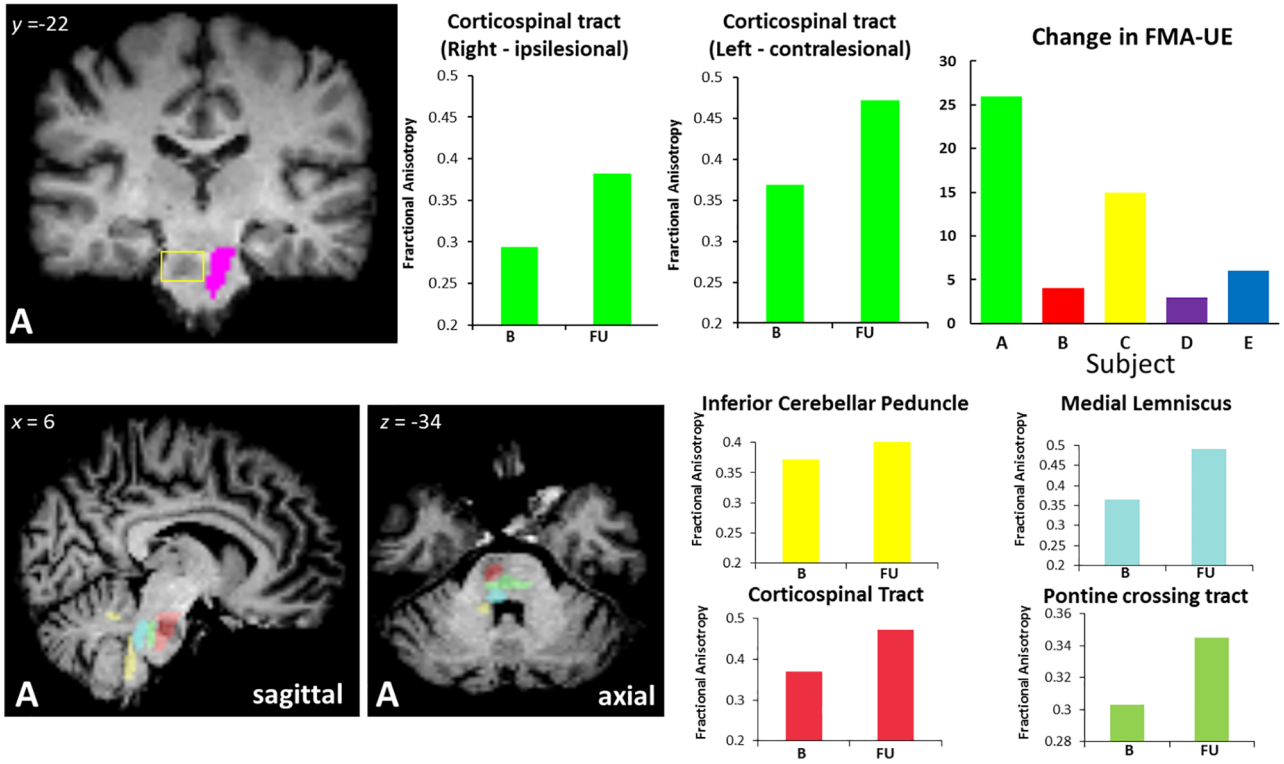

Figure 3. Contralateral and perilesional white matter tract FA changes may be associated with improvements in FMA-UE in patient A with a pontine lesion.

reductions in AD of the perilesional ipsilateral PLIC. On the contrary, patient E who had an MCA infarct and patient C who had a corona radiata infarct showed widespread decreased FA throughout many different white matter tracts perilesionally and remotely. This globally reduced FA after a larger territory stroke may reflect extensive Wallerian Degeneration of descending pathways secondary to a larger ischemic insult. In contrast to FA, the AD metric increased in the corona radiata and internal capsule ROIs (Figure 2, patients C and E). Finally, we observed that laterality is easily demonstrated by using whole-brain DTI analysis: in patient C with a left corona radiata infarct, reduction in FA of the left CST was seen to be more prominent than the right CST. In patient D who suffered a right-sided thalamic lesion, AD recovery was observed only in the right but not the left CST. The same patient D, however, showed recovery of both FA and AD in the right and left medial lemnisci, which carry positional and vibration sense fibers from both sides of the body to the contralateral hemispheres of the brain.

Based on 48 standard ROIs defined in John Hopkins University templates,[30] we calculated the FA change and AD change (%) in each ROI at 2 weeks follow-up compared to baseline, indicated by "Delta FA" on the y-axis. Each row corresponds to each of the five acute stroke patients (see Table 1 and Figure 1 for their lesion locations).

Patient A with a hemipontine infarct showed longitudinally increased FA of both ipsilateral and contralateral CST and surrounding white matter tracts.

In patient A with an infarct located in the right hemipons, we saw an increase in FA of the CST of the ipsilesional (right) but also of the contralesional side (left) after 2 weeks of rehabilitation. Furthermore, patient A also showed longitudinal FA increases in surrounding white matter tracts such as pontine crossing tracts, inferior cerebellar peduncles, and the medical lemniscus (Figure 2). In an inverse manner, AD of the CST and medial lemniscus were shown to decrease (Figure 2).

Top panel: T1-weighted structural MRI of patient A, who had a right-sided pontine lesion (yellow box: lesion location magenta overlay: contralateral left CST ROI; corresponding normalized coordinates shown on the top left corner). Changes in FA of ipsilateral and contralateral CSTs were observed along with increased in FM-UE scores.

Bottom panel: patient A demonstrated increase in FA of perilesional areas such as in the CST (red), pontine crossing tracts (green), medial meniscus (blue), and inferior cerebellar peduncle (yellow).

Increase in internal capsule FA and increase in the number of flexion movements generated

Patient B, whose lesion is more proximally located in the right posterior lentiform nuclei, showed increased FA in the PLIC, which is distal to the lesion. This is in contrast to patient A who showed a decreased PLIC FA, which was proximal to patient A's pontine lesion. Compared to other patients in this

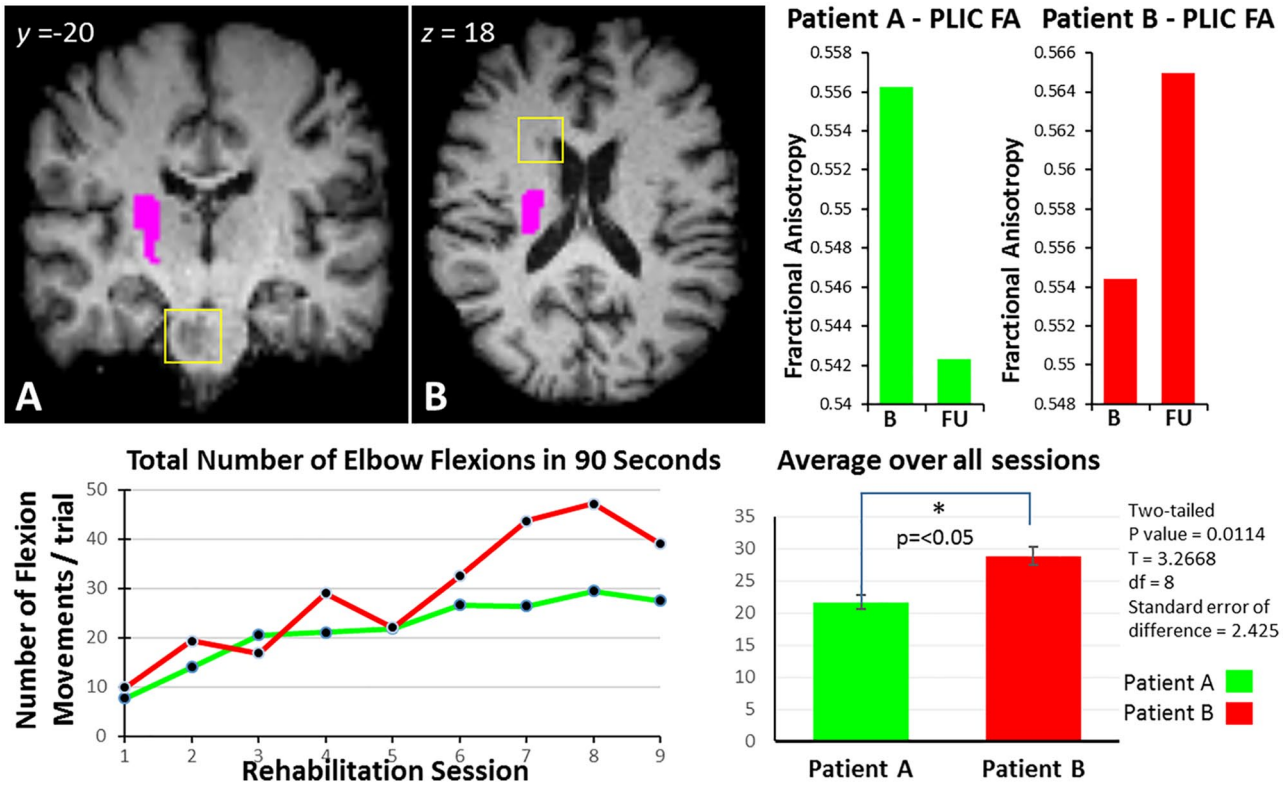

Figure 4. Distal PLIC FA increase in patient B corresponded to a greater increase in total number of successful elbow flexions.

series, we observed that patient B generated an increased average number of flexion movements over 90 seconds, which was statistically increased compared to patient A (Figure 4; paired two-tailed *t*-test, *P*-value = .0114, *T* = 3.2668, *df* = 8, standard error of difference = 2.425).

Top left panel: T1-weighted representative sections showing the lesion and pertinent ROIs for patient A with the right hemipontine (distal) lesion and patient B with the right posterior lentiform (proximal) lesion, with the corresponding normalized x, y, z coordinates given in the top left corner. Yellow overlay: lesion location. Violet overlay: PLIC ROI.

Top right panel: a comparison between patient A and B in terms of FA changes in the PLIC at baseline (B) and follow-up (FU), where Patient B showed an increase in PLIC FA after 2 weeks of rehabilitation.

Bottom panel: patient B showed a statistically greater increase in the number of flexion movements generated through time, as compared to patient A (time difference between sessions 1 and 10 = 2 weeks).

Specific increases in medial lemniscus FA corresponded to kinematic improvement in movement smoothness as measured by velocity correction peaks

In patient D, whose lesion was in the thalamus, no discernible change in clinical FMA scores was seen. However, patient D showed a measurable improvement in the FA of the bilateral medial lemnisci (Figure 2) and correspondingly had the largest improvement in the kinematic measure of velocity correction peaks, which is a measure that is related to the smoothness of movements (Figure 5).

Discussion

The trajectory of recovery undertaken by each patient in acute stroke is complex, necessitating a multi-disciplinary measure of imaging, kinematic, and clinical parameters. In this prospective observational study, we found that in each of the five patients with different lesion locations, lesion-dependent patterns of FA and AD changes were observed with differing degrees of clinical and kinematic improvement over a 2-week time period (Figure 2).

In terms of perilesional white matter tract changes, this study adds on to the body of knowledge gained from prior studies[6] by examining the longitudinal increase in FA, which may potentially be related to performance gain in kinematic measures of elbow flexion and FMA scores such as that seen in patient A in this cohort (Table 1, Figure 3). The increase or decrease in FA and AD over time at the individual patient level seemed to depend on whether the lesion is proximal or distal to the white matter tract (Figures 2 and 3), which may be related mechanistically to Wallerian degeneration.

Following up on a previous study which showed that cross-sectional reduced FA of the CST correlated with poor motor

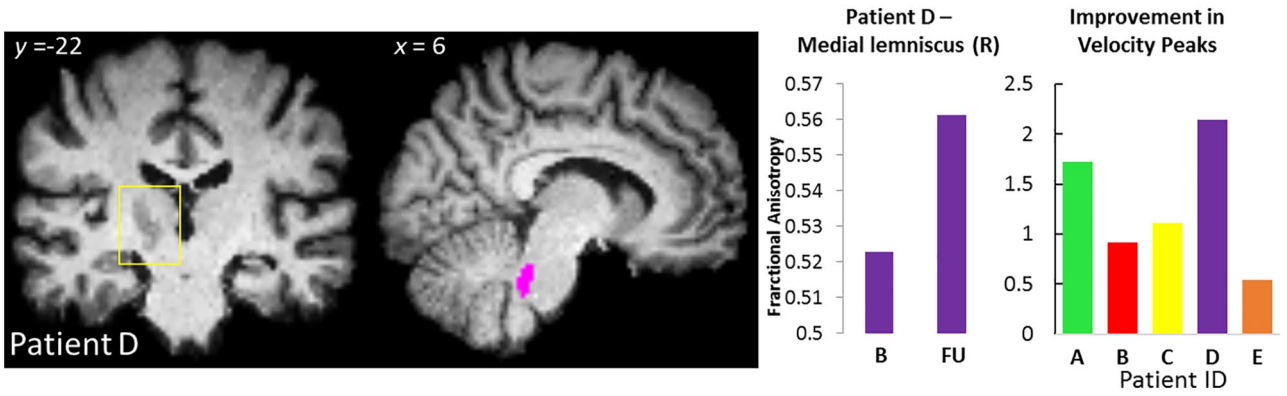

Figure 5. Medial lemniscus FA and improvement in velocity peaks.
From left to right: a representative T1-weighted slice showing the location of the thalamic lesion in patient D (yellow square), with the medial meniscus ROI being highlighted in violet and the corresponding x, y, z coordinates shown on the top left. A graph of FA improvement in the ipsilateral medial meniscus in patient D. Improvement in the kinematic measurement of velocity peaks shows that patient D had the highest improvement in the kinematic measure of velocity peaks. (B, baseline; FU, follow-up.)

outcome,[2] we report here longitudinal increases in FA of the CST and surrounding white matter tracts that seemed to parallel improvement in clinical FMA scores as seen in patient A in our cohort, though statistical analysis could not be performed due to small sample size (Figure 3). In accordance with a prior study that determined the importance of single-time-point FA of the PLIC to predict poor motor outcome,[29] we found that longitudinal increases in PLIC FA, which was seen only in Patient B in this cohort, corresponded instead to a sizable improvement in the total number of movements generated in a set amount of time (Figure 4), which is a measure of arm endurance that may not be apparent in clinical tools such as the FMA in view of its ceiling effect.

With regard to differences in FA and AD in the acute phase of stroke, we describe an inverse relationship between FA and AD: FA increases in the acute phase are almost mirrored by a concomitant decrease in AD (Figure 2). Such a relationship has not been described and would require further study to determine its significance.

Other findings from this longitudinal study have hitherto been less well studied: we saw in patient D with a thalamic infarct increases in medial lemniscus FA which was accompanied in this patient by a measurable improvement in the kinematic parameter of velocity correction peaks as well as in the coordination subscale of the FMA despite showing negligible change in total FMA scores. These results suggest that certain clinical tests and/or kinematic measures may be more appropriate or more sensitive in detecting dynamic improvements in arm function which may not have been apparent otherwise.

An advantage of using the TBSS technique is the ability to detect changes occurring in remote regions in the brain: in all patients, we were able to monitor FA and AD changes in the contralateral CST as well as regions as far removed as the uncinate fasciculus (Figure 2), which has been reported to be an indicator for apathy, low mood, and depression,[31] and the superior longitudinal fasciculus (Figure 2), which has been correlated with cognitive function after stroke.[9]

Several limitations of this early longitudinal DTI study include the fact that patient recruitment during the acute stroke period was logistically challenging. Furthermore, as this is a preliminary case series with inferences derived from observations of individual cases, a larger study cohort size and statistical analysis will be needed to explore the validity and generalizability of the inferences reported. Although our observations of FA changes in individual patients seem to suggest that degeneration and subsequent recovery of white matter tracts can be investigated using DTI,[32] generalization of these individual changes would likely require statistical analyses to establish a clinically important change. In addition, the rigorous measurements of kinematic performance using augmented reality and wearable gyrometers were relatively new and less developed in an acute hospital setting. Finally, the length of time between baseline and follow-up was on average 13 days; therefore, any improvement that might have taken place beyond the 2-week observational period of this study would not have been reported here.

Conclusions

This longitudinal DTI study shows for the first time changes in perilesional and remote FA in relation to kinematic parameters of elbow flexion, thereby bringing to light the potential of using TBSS-measured FA in multiple brain regions across time coupled with kinematic measures of arm function to potentially correlate imaging data with motor performance in patients with diverse lesion locations. Gyrometer-derived kinematic scores of the upper extremity may be more sensitive to minute changes that are not apparent on clinical scores and thus may be tested further as more sensitive objective markers of clinical improvement. Follow-up trials may benefit from kinematic measures in a larger group of patients during acute stroke rehabilitation to see whether the changes observed at the individual level can be correlated to motor performance but also functional outcomes especially in populations with poor prognoses. Although this study is limited in its follow-up to approximately 2 weeks,

detailed analyses of longitudinal FA in the subacute and chronic phases of stroke can potentially identify certain trends of improvement in specific subscales such as coordination or movement smoothness.[33] Detailed analysis of these kinematic-neuroimaging relationships in larger samples may pave the way for individualized rehabilitation of stroke patients.

Author Contributions

NEO and AMJV conceptualized, wrote, and performed the study. GSS and NYS were the stroke clinicians who recruited subjects and provided technical expertise. JZ and JLKW performed the MRI scans and analyses.

Supplemental Material

Supplemental material for this article is available online.

ORCID iD

Nicodemus Edrick Oey https://orcid.org/0000-0001-5302-8400

REFERENCES

1. Crafton KR, Mark AN, Cramer SC. Improved understanding of cortical injury by incorporating measures of functional anatomy. *Brain*. 2003;126:1650–1659.
2. Moller M, Frandsen J, Andersen G, Gjedde A, Vestergaard-Poulsen P, Ostergaard L. Dynamic changes in corticospinal tracts after stroke detected by fibre-tracking. *J Neurol Neurosurg Psychiatry*. 2007;78:587–592.
3. Puig J, Pedraza S, Blasco G, et al. Wallerian degeneration in the corticospinal tract evaluated by diffusion tensor imaging correlates with motor deficit 30 days after middle cerebral artery ischemic stroke. *AJNR Am J Neuroradiol*. 2010;31:1324–1330.
4. Radlinska B, Ghinani S, Leppert IR, Minuk J, Pike GB, Thiel A. Diffusion tensor imaging, permanent pyramidal tract damage, and outcome in subcortical stroke. *Neurology*. 2010;75:1048–1054.
5. Wen H, Alshikho MJ, Wang Y, et al. Correlation of fractional anisotropy with motor recovery in patients with stroke after postacute rehabilitation. *Arch Phys Med Rehabil*. 2016;97:1487–1495.
6. Kumar P, Yadav AK, Misra S, Kumar A, Chakravarty K, Prasad K. Prediction of upper extremity motor recovery after subacute intracerebral hemorrhage through diffusion tensor imaging: a systematic review and meta-analysis. *Neuroradiology*. 2016;58:1043–1050.
7. Puig J, Blasco G, Daunis-I-Estadella J, et al. Decreased corticospinal tract fractional anisotropy predicts long-term motor outcome after stroke. *Stroke*. 2013;44:2016–2018.
8. Doughty C, Wang J, Feng W, Hackney D, Pani E, Schlaug G. Detection and predictive value of fractional anisotropy changes of the corticospinal tract in the acute phase of a stroke. *Stroke*. 2016;47:1520–1526.
9. Koyama T, Domen K. Diffusion tensor fractional anisotropy in the superior longitudinal fasciculus correlates with functional independence measure cognition scores in patients with cerebral infarction. *J Stroke Cerebrovasc Dis*. 2017;26:1704–1711.
10. Groisser BN, Copen WA, Singhal AB, Hirai KK, Schaechter JD. Corticospinal tract diffusion abnormalities early after stroke predict motor outcome. *Neurorehabil Neural Repair*. 2014;28:751–760.
11. Jang SH. A review of diffusion tensor imaging studies on motor recovery mechanisms in stroke patients. *NeuroRehabilitation*. 2011;28:345–352.
12. Schaechter JD, Perdue KL, Wang R. Structural damage to the corticospinal tract correlates with bilateral sensorimotor cortex reorganization in stroke patients. *Neuroimage*. 2008;39:1370–1382.
13. Gebruers N, Truijen S, Engelborghs S, De Deyn PP. Prediction of upper limb recovery, general disability, and rehabilitation status by activity measurements assessed by accelerometers or the Fugl-Meyer score in acute stroke. *Am J Phys Med Rehabil*. 2014;93:245–252.
14. Yang Q , Yang Y, Luo J, Li L, Yan T, Song R. Kinematic outcome measures using target-reaching arm movement in stroke. *Ann Biomed Eng*. 2017;45:2794–2803.
15. Bigoni M, Baudo S, Cimolin V, et al. Does kinematics add meaningful information to clinical assessment in post-stroke upper limb rehabilitation? a case report. *J Phys Ther Sci*. 2016;28:2408–2413.
16. Van Dokkum L, Hauret I, Mottet D, Froger J, Metrot J, Laffont I. The contribution of kinematics in the assessment of upper limb motor recovery early after stroke. *Neurorehabil Neural Repair*. 2014;28:4–12.
17. Wing AM, Lough S, Turton A, Fraser C, Jenner JR. Recovery of elbow function in voluntary positioning of the hand following hemiplegia due to stroke. *J Neurol Neurosurg Psychiatry*. 1990;53:126–134.
18. Ada L, O'Dwyer N, O'Neill E. Relation between spasticity, weakness and contracture of the elbow flexors and upper limb activity after stroke: an observational study. *Disabil Rehabil*. 2006;28:891–897.
19. Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther*. 2012;92:791–798.
20. Lang CE, Edwards DF, Birkenmeier RL, Dromerick AW. Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Arch Phys Med Rehabil*. 2008;89:1693–1700.
21. Andersson JL, Jenkinson M, Smith S. *Non-linear optimisation*. FMRIB technical report TR07JA1. Oxford, UK: FMRIB Centre, University of Oxford; 2007.
22. Cortese S, Imperati D, Zhou J, et al. White matter alterations at 33-year follow-up in adults with childhood attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2013;74:591–598.
23. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*. 2006;31:1487–1505.
24. Sullivan KJ, Tilson JK, Cen SY, et al. Fugl-Meyer assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. *Stroke*. 2011;42:427–432.
25. Samuel GS, Oey NE, Choo M, et al. Combining levodopa and virtual reality-based therapy for the rehabilitation of upper limb after acute stroke: pilot study part II. *Singapore Med J*. 2016;58:1–25.
26. Lang CE, Macdonald JR, Reisman DS, et al. Observation of amounts of movement practice provided during stroke rehabilitation. *Arch Phys Med Rehabil*. 2009;90:1692–1698.
27. Bosecker C, Dipietro L, Volpe B, Krebs HI. Kinematic robot-based evaluation scales and clinical counterparts to measure upper limb motor performance in patients with chronic stroke. *Neurorehabil Neural Repair*. 2010;24:62–69.
28. Holden MK, Dyar TA, Dayan-Cimadoro L. Telerehabilitation using a virtual environment improves upper extremity function in patients with stroke. *IEEE Trans Neural Syst Rehabil Eng*. 2007;15:36–42.
29. Puig J, Pedraza S, Blasco G, et al. Acute damage to the posterior limb of the internal capsule on diffusion tensor tractography as an early imaging predictor of motor outcome after stroke. *AJNR Am J Neuroradiol*. 2011;32:857–863.
30. Hua K, Zhang J, Wakana S, et al. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage*. 2008;39:336–347.
31. Huang P, Xu X, Gu Q , et al. Disrupted white matter integrity in depressed versus non-depressed Parkinson's disease patients: a tract-based spatial statistics study. *J Neurol Sci*. 2014;346:145–148.
32. Pierpaoli C, Barnett A, Pajevic S, et al. Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *Neuroimage*. 2001;13:1174–1185.
33. Pila O, Duret C, Laborne FX, Gracies JM, Bayle N, Hutin E. Pattern of improvement in upper limb pointing task kinematics after a 3-month training program with robotic assistance in stroke. *J Neuroeng Rehabil*. 2017;14:105.