

# Neurorehabilitation and Neural Repair

<http://nnr.sagepub.com>

---

## The Role of Corticospinal Tract Damage in Chronic Motor Recovery and Neurorehabilitation: A Pilot Study

Annette Sterr, Shan Shen, Andre J. Szameitat and Katherine A. Herron  
*Neurorehabil Neural Repair* 2010; 24; 413  
DOI: 10.1177/1545968309348310

The online version of this article can be found at:  
<http://nnr.sagepub.com/cgi/content/abstract/24/5/413>

---

Published by:



<http://www.sagepublications.com>

On behalf of:



American Society of Neurorehabilitation

Additional services and information for *Neurorehabilitation and Neural Repair* can be found at:

**Email Alerts:** <http://nnr.sagepub.com/cgi/alerts>

**Subscriptions:** <http://nnr.sagepub.com/subscriptions>

**Reprints:** <http://www.sagepub.com/journalsReprints.nav>

**Permissions:** <http://www.sagepub.com/journalsPermissions.nav>

**Citations** <http://nnr.sagepub.com/cgi/content/refs/24/5/413>

# The Role of Corticospinal Tract Damage in Chronic Motor Recovery and Neurorehabilitation: A Pilot Study

Neurorehabilitation and  
Neural Repair  
24(5) 413–419  
© The Author(s) 2010  
Reprints and permission: <http://www.sagepub.com/journalsPermissions.nav>  
DOI: 10.1177/1545968309348310  
<http://nnr.sagepub.com>



Annette Sterr, PhD,<sup>1</sup> Shan Shen, PhD,<sup>1</sup> Andre J. Szameitat, PhD,<sup>2</sup> and Katherine A. Herron, MSc<sup>1</sup>

## Abstract

**Background.** With diffusion-tensor imaging (DTi) it is possible to estimate the structural characteristics of fiber bundles in vivo. This study used DTi to infer damage to the corticospinal tract (CST) and relates this parameter to (a) the level of residual motor ability at least 1 year poststroke and (b) the outcome of intensive motor rehabilitation with constraint-induced movement therapy (CIMT). **Objective.** To explore the role of CST damage in recovery and CIMT efficacy. **Methods.** Ten patients with low-functioning hemiparesis were scanned and tested at baseline, before and after CIMT. Lesion overlap with the CST was indexed as reduced anisotropy compared with a CST variability map derived from 26 controls. Residual motor ability was measured through the Wolf Motor Function Test (WMFT) and the Motor Activity Log (MAL) acquired at baseline. CIMT benefit was assessed through the pre–post treatment comparison of WMFT and MAL performance. **Results.** Lesion overlap with the CST correlated with residual motor ability at baseline, with greater deficits observed in patients with more extended CST damage. Infarct volume showed no systematic association with residual motor ability. CIMT led to significant improvements in motor function but outcome was not associated with the extent of CST damage or infarct volume. **Conclusion.** The study gives in vivo support for the proposition that structural CST damage, not infarct volume, is a major predictor for residual functional ability in the chronic state. The results provide initial evidence for positive effects of CIMT in patients with varying, including more severe, CST damage.

## Keywords

constraint-induced movement therapy, diffusion tensor imaging, chronic hemiplegia, upper limb, stroke rehabilitation, fractional anisotropy

## Introduction

The amount of residual corticospinal tract (CST) has long been implicated in the recovery of motor function after stroke.<sup>1–4</sup> We explored this idea with a recently developed neuroimaging technique<sup>5</sup> that allows noninvasive mapping of corticofugal fibers to quantify the integrity of these fiber tracks in vivo. The method uses a combination of diffusion-weighted imaging and tractography to first establish the trajectory of corticofugal fiber bundles, and subsequently infers CST damage through a voxel-based quantification of the overlap between the lesion and a CST variability map determined in healthy controls. We applied this methodology to assess the relation of CST damage and residual motor recovery in a cohort of chronic stroke patients who were selected on the basis of low-functioning hemiparesis rather than lesion characteristics. We reasoned that greater overlap of the lesion with the CST would be indicative of greater CST damage and hence be associated with poorer motor ability. We further tested the proposition<sup>2</sup> that the

extent of the infarct lesion rather than CST damage may be related to the level of motor deficit.

To test this hypothesis, the absolute volume of the infarct lesion (ie, across the whole brain) was calculated. We inferred that if CST damage was the critical determinant for motor recovery, CST damage but not infarct volume would be associated with residual motor ability. Stinear et al<sup>3</sup> further proposed that CST damage may be a predictor for functional improvements achieved through practice-based motor rehabilitation in the chronic state. This view builds on the theory that CST integrity is intrinsically linked to

<sup>1</sup>University of Surrey, Guildford, United Kingdom

<sup>2</sup>Ludwig Maximilian University, Munich, Germany

### Corresponding Author:

Annette Sterr, Department of Psychology, University of Surrey, Guildford, GU2 2XH, UK  
E-mail: [a.sterr@surrey.ac.uk](mailto:a.sterr@surrey.ac.uk)

recovery because of its instrumental role in functional reorganization.<sup>5-7</sup> We therefore queried whether the efficacy of neuroplasticity-facilitating rehabilitation techniques may depend on the level of CST damage. This idea was explored by studying the outcome of neurorehabilitation with constraint-induced movement therapy (CIMT) in relation to the extent of CST damage and infarct volume.

To address the questions above, we followed the methods used by Newton et al<sup>5</sup> and first determined the CST variability map in a cohort of 26 healthy volunteers and then modeled the ipsilateral CST in 10 chronic stroke patients presenting with low-functioning upper-limb hemiparesis. CST damage was quantified by calculating the voxels for which the infarct lesion overlapped with the CST variability map. A measure of lesion volume was obtained by labeling voxels with significantly reduced anisotropy. Residual functional ability was determined by an ecologically valid real-world measure of functional ability, the Motor Activity Log<sup>8</sup> (MAL) and the Wolf Motor Function Test<sup>9</sup> (WMFT). These data were then correlated with indices of CST damage/infarct volume to explore the association with long-term functional outcome as well as CIMT benefit.

## Method

### Participants

A total of 26 right-handed healthy individuals (6 men, 20 women; mean age = 22.8 years, ranging from 19 to 35 years), and 10 stroke patients (7 men, 3 women; mean age = 53.5 years, ranging from 30 to 69 years) participated in the study.

Patient participants were recruited through flyers and newspaper and Web advertisements. Control participants were recruited through e-mail lists and flyers. Patient respondents were prescreened by phone and attended a subsequent screening session at the University of Surrey in which information on physical and mental health history was obtained. The criteria for patient selection were (a) first-ever stroke with chronicity >12 months; (b) low-functioning status (Frenchay Arm Test<sup>10</sup> <2, minimal wrist movement [<10% against gravity], no more than 10° finger extension); (c) Mini-Mental State score<sup>11</sup> >25; and (d) ability to understand the therapist and to communicate needs. Patients were selected on the basis of symptom presentation not the location of the lesion, which in most cases was unknown to their general practitioner (family doctor in the United Kingdom). The study was approved by the Thames Valley Multi-Centre Research Ethics Committee. Written informed consent was obtained from each participant.

### Study Schedule and Behavioral Parameter Extraction

Subjects received a 10-day course of CIMT with 3 hours of daily shaping training provided in one-to-one sessions.<sup>12</sup>

The WMFT, a comprehensive laboratory-based test of motor function, and the MAL, a subjective assessment of everyday activities, were used to measure motor ability 2 weeks prior to intervention (baseline), as well as before (pre) and after (post) the 2-week intervention. Outcome parameters comprised the functional ability score (WMFT-FA) and median performance time (WMFT-PT, in seconds) for the WMFT, and the amount of use (MAL-AOU) and quality of use (MAL-QOU) for the MAL. WMFT data were scored from videotapes by researchers blinded to the time of testing. Residual motor ability was indexed by averaging baseline and pretreatment measures (residual ability scores). Treatment-induced improvement was indexed as the difference between pretreatment and posttreatment scores (outcome scores). Structural magnetic resonance imaging (MRI) data were acquired at pre-CIMT testing.

### MRI Data Acquisition

A 3T Siemens Trio scanner (Erlangen, Germany) was used to acquire high-resolution T1 images with an MPRAGE (magnetization prepared rapid acquisition gradient echo pulse) sequence with repetition time (TR) = 1830 milliseconds, echo time (TE) = 4.43 milliseconds, inversion time = 1100 milliseconds, flip angle = 11°, field of view = 256 mm, 176 slices, voxel size = 1 × 1 × 1 mm<sup>3</sup>, and in-plane matrix = 256 × 256. Diffusion-weighted images (DWI) were acquired with a single-shot diffusion-weighted echo-planar imaging sequence, with diffusion gradients along 12 directions ( $b_0 = 0$ , 1 image and  $b_1 = 1000$  s/mm<sup>2</sup>, 12 images) and TR = 8900 milliseconds, TE = 100 milliseconds, number of averages = 4, 55 slices, voxel size = 2.5 × 2.5 × 2.5 mm<sup>3</sup>, and in-plane matrix = 88 × 128.

### Preprocessing

The DWI was motion corrected and realigned to the mean image using the diffusion toolbox in SPM5 (<http://sourceforge.net/projects/spmtools>). Corrected images were normalized to MNI space. A brain mask was used to remove ghost artifacts. The gradient information of each image was updated by reorientation, which applied the rotations performed during realignment and normalization to the gradient direction vectors. Diffusion tensor eigenvalues and eigenvectors were calculated to generate fractional anisotropy (FA) maps for each participant<sup>13,14</sup> using DTIstudio<sup>15</sup> (<https://www.dtistudio.org>).

### Fiber Tracking of Corticospinal Tract

Fiber tracking was performed in MNI space. The DTIstudio software was also used for fiber tractography based on the fiber assignment by continuous tracking (FACT) method.<sup>16,17</sup> The two seed areas were drawn manually on FA maps using

region of interest (ROI) selection tools provided in DTIstudio (<https://www.dtistudio.org/>). Fiber tracking started from all voxels with a threshold of FA >0.2 and a tract-turning angle <41°. Following the protocol used by others,<sup>3,5,18,20,21</sup> the CST was reconstructed for each control participant from 2 ROI, the cerebral peduncles and the precentral gyrus (including the anterior bank of the central sulcus), identified in the FA maps. Because of noise in the images, the CST was only tracked in 22 participants. For each individual, the CST obtained for the left and the right hemisphere were saved as binary mask. The CST masks of the 22 participants were subsequently summed across participants to produce a trajectory variability map for each hemisphere, similar to the methods used by Newton et al.<sup>5</sup>

### Lesion Identification Based on Fractional Anisotropy Maps

This step was performed with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>). Fractional anisotropy maps were smoothed with a Gaussian kernel of full-width at half-maximum (FWHM) = 8 mm. The smoothed map of each patient was compared with the average map derived from controls on a voxel by voxel basis using one-way analyses of variance (ANOVAs). Brain volume, age, and gender were included as covariates. Lesioned tissue was identified as significant anisotropy reduction ( $P < .001$ , uncorrected). A binary lesion mask was then generated for every patient. Lesion volume was parameterized as the sums of voxels with significantly reduced anisotropy identified in the FA map. Identified lesions were validated by visual inspection of T1-weighted images.

### Calculation of CST Damage in Patients

Each lesion mask was overlaid onto either the left or right trajectory variability map of the CST determined in the control cohort. The extent of their overlap was measured as overlap volume between the lesion and the CST variability map with

$$\text{Overlap volume} = \sum_{j=1}^N \frac{\text{Sum of weighted voxel numbers in the region of overlap}_{j\text{th axial slice}}}{\text{Sum of weighted voxel numbers in the CST map}_{j\text{th axial slice}}},$$

where  $N$  is the number of axial slices in each image.

This parameter sums up the portion of the voxel numbers forming the region of overlap to the region of CST on each axial slice, where the voxel numbers are weighted by the CST variability maps. Note that this index has no unit because it measures the sum of the overlap ratio.

### Statistics

Pearson correlations were calculated between indices of CST damage/infarct volume and residual recovery scores to test the association with (a) long-term recovery and (b) outcome scores to test the association with treatment benefit.

### Results

The trajectory variability maps of the left and right hemispheric CST for the control group are depicted in Figure 1. Lesion overlap with the CST ranged from 4.53 to 18.28 (mean = 9.62, standard deviation = 4.95).

### CST Damage and Residual Motor Ability

The mean MAL scores ( $1.13 \pm 1.0$  units for quality of movement [QOM] and  $1.03 \pm 1.0$  units for amount of use [AOU]) suggested low levels of affected arm use in everyday situations. The WMFT confirmed that abilities with the affected arm were generally poor (functional ability score [FA] =  $4.4 \pm 1.3$  units; median performance time (PT) =  $17.3 \pm 26.3$  seconds). Statistical analysis of the association of motor ability parameters with CST damage revealed significant correlations of lesion overlap with both WMFT measures (FA,  $r = -.82$ ,  $P < .01$ ; RT,  $r = .83$ ,  $P < .01$ ). For the MAL indices correlations were not significant (QOM,  $r = -.47$ ,  $P = .17$ ; AOU,  $r = -0.4$ ,  $P = .24$ ). An example of lesion overlap with the CST variability map is presented in Figure 2. Bivariate scatterplots showing the association of lesion overlap and WMFT parameters are presented in Figure 3.

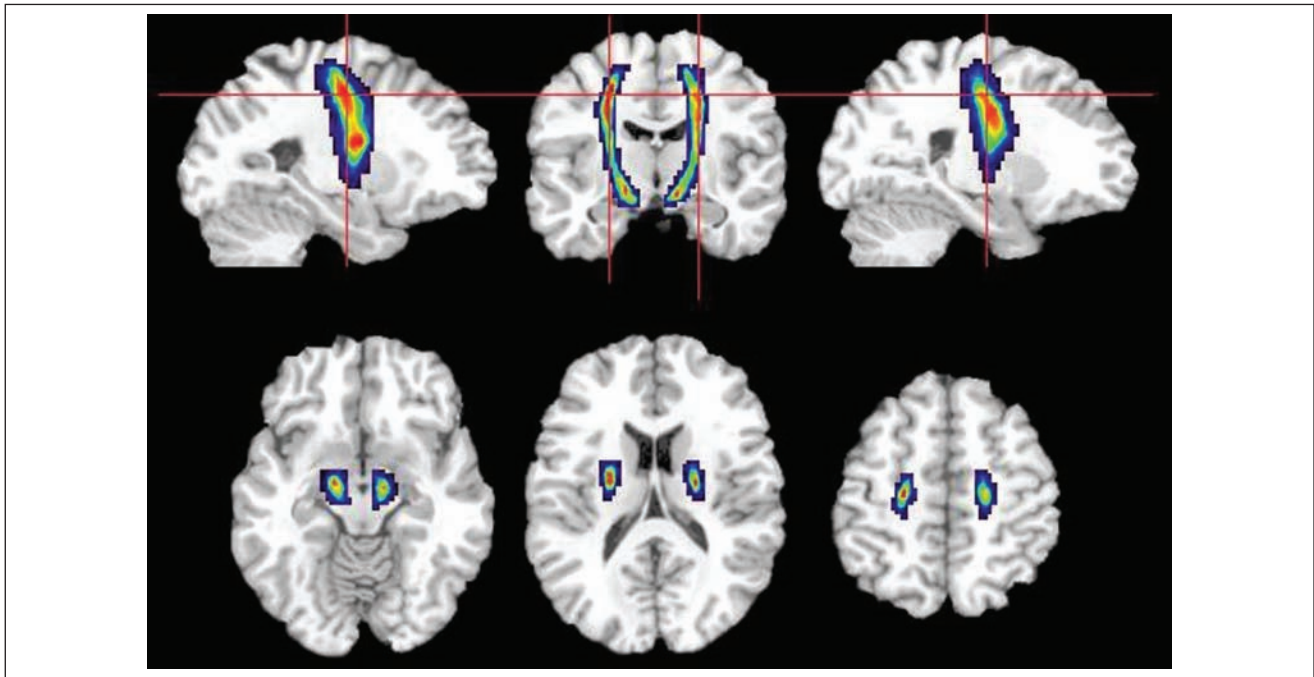
### CST Damage and CIMT Outcome

Motor ability improved significantly with CIMT. Measures at baseline and pretreatment were not significantly different. For the pretreatment versus posttreatment comparisons significant effects were found for MAL (MAL-AOU,  $t = -6.2$ ,  $P < .001$ ; MAL-QOM,  $t = -7.8$ ,  $P < .001$ ) and WMFT-FA ( $t = -4.8$ ,  $P < .01$ ) and a trend for WMFT-RT ( $t = 2.0$ ,  $P = .070$ ). Correlation analysis thereby suggested that the treatment-induced improvements in motor ability were not systematically associated with CST overlap (WMFT-FA,  $r = -0.11$ ,  $P = .76$ ; WMFT-PT,  $r = -.08$ ,  $P = .83$ ; MAL-QOM,  $r = .27$ ,  $P = .44$ ; MAL-AOU,  $r = .07$ ,  $P = .86$ ).

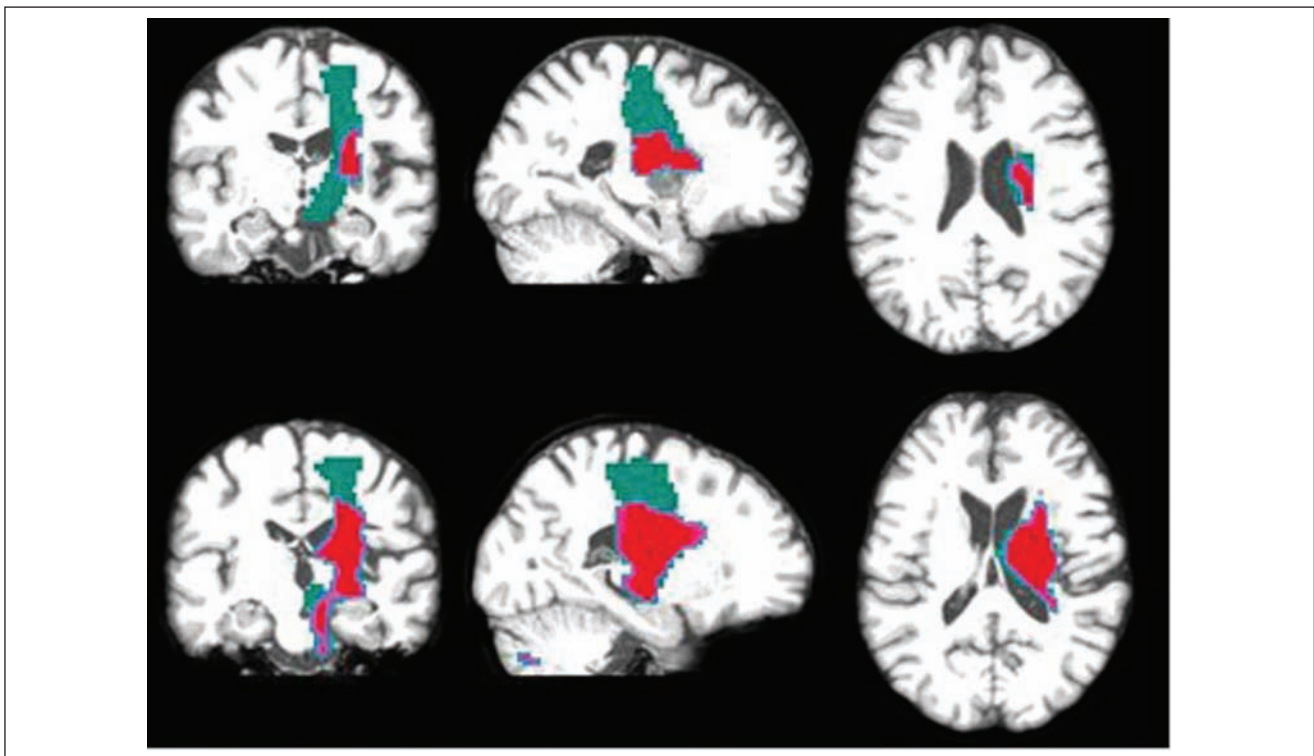
### Infarct Lesion Volume

The absolute lesion volume, quantified as the sum of lesioned voxels on the FA maps, showed no significant association with residual motor ability (WMFT-FA,  $r = -.5$ ,  $P = .141$ ; WMFT-PT,  $r = -.24$ ,  $P = .50$ ; MAL-QOM,  $r = .02$ ,  $P = .96$ ; MAL-AOU,  $r = .05$ ,  $P = .90$ ) or treatment benefit (WMFT-FA,

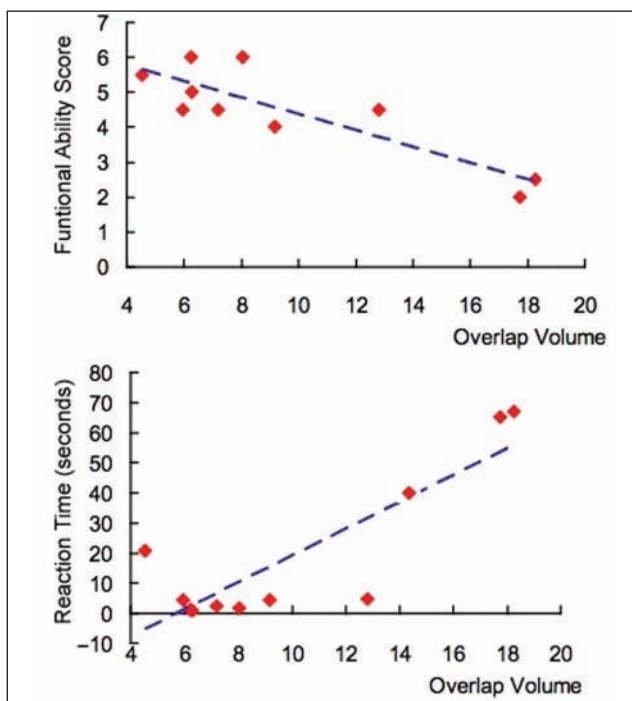




**Figure 1.** Trajectory variability maps of CST displayed on a T1-weighted image. Color bar shows number of subjects the CST was tracked in each voxel (range from 1 to 22). The top column shows sagittal slices  $x = -23$  and  $x = 25$  on the side of coronal slice  $y = -13$ . The bottom column shows axial slices  $z = -13$ ,  $z = 15$ , and  $z = 49$ .



**Figure 2.** Examples showing lesions indicated by the reduced anisotropy (red) overlaid on trajectory variability maps of the corticospinal tract (CST; green). Top row patient 1,  $x = 24$ ,  $y = -14$ ,  $z = 23$ ; bottom row patient 3,  $x = 21$ ,  $y = -19$ ,  $z = 16$ .



**Figure 3.** Association of performance in the Wolf Motor Function Test with lesion overlap. Upper panel shows the functional ability parameter (indicative of movement quality), higher values indicate better ability. Lower panel shows the average time patients needed to perform the tasks; shorter times reflect better performance.

$r = -.001$ ,  $P = .99$ ; WMFT-PT,  $r = -.12$ ,  $P = .75$ ; MAL-QOM,  $r = .16$ ,  $P = .65$ ; MAL-AOU,  $r = .38$ ,  $P = .28$ ).

## Discussion

The present study aimed to assess the hypothesis that CST damage is critical for long-term motor recovery using a method that affords a quantitative *in vivo* estimation of the overlap between infarct lesion and corticospinal tract.<sup>5</sup> We further asked whether the level of CST damage may be relevant for motor improvements obtained through training-based rehabilitation (CIMT). Our data suggest that patients with greater overlap of the infarct lesion with the CST variability map tended to have poorer residual ability. At the same time, the volume of the area damaged by the stroke, that is, the size of the infarct lesion, was not associated with the level of residual ability. Our data therefore provide further evidence for the assumption that the structural integrity of the CST is critical for the long-term recovery of motor function, whereas the size of the stroke is of minor influence for the restitution of upper-limb ability. This is in line with earlier reports using different methods.<sup>1,2,4,7,22,23</sup>

With regard to the role of CST damage in CIMT outcome, our study suggests that—at least in low-functioning

patients—treatment benefits were unrelated to CST damage and infarct lesion volume. Notably, CST damage was quite varied in our cohort with a 4-fold difference between some individuals. However, in all cases significant improvements in upper-limb function were obtained confirming earlier findings that CIMT significantly improves motor ability in patients with low-functioning hemiparesis,<sup>9,24-26</sup> with improvements being evident in the real-world setting (indicated by the MAL) as well as the laboratory environment (indicated by the WMFT). This result suggests that patients with various degrees of CST damage and lesion characteristics may benefit from the intervention and that CIMT can be an effective treatment protocol even when CST damage is quite substantial. To investigate the interaction of CIMT and CST damage in more detail would require larger cohorts with a wider range of preintervention motor ability.

A recent article by Stinear et al<sup>3</sup> suggests that motor treatment benefit depends on CST integrity, a conclusion that at first glance contradicts the findings of the present study. However, in the experiment by Stinear et al<sup>3</sup> motor ability preintervention spanned a much wider range than in the cohort of the present study (all low functioning). Furthermore, the experiment did not use therapist-assisted one-to-one treatment, as does CIMT, but used a self-directed practice of a block-stacking task. Their patients with poorer residual ability may have found it much harder to manage the block-stacking task, compared with the higher-functioning patients during practice. Differences across studies relating structure and behavior are likely to be affected by the dose and type of training task, the outcome measure relevant to the task, and the limitations of defining small changes in residual CST fibers in relation to differences below a certain, as yet unknown, level of residual motor function. Rather than being theoretically contradictory, the empirical discrepancy between the present data and the data of Stinear et al<sup>3</sup> raises interesting questions on the interaction of structural, behavioral, and psychological parameters of motor rehabilitation.

The clinical effectiveness of CIMT is thought to be mediated by brain plasticity processes that include enhancement of the neural representation for the upper-limb movements studied.<sup>27-32</sup> The absence of an association between CIMT benefit and residual CST fibers suggests that training-induced gains can be mediated by a range of levels of intact ipsilateral corticofugal fibers. In addition to map plasticity, for example, optimal axonal transmission rates may be increased by thickening of the myelin sheath that may also be induced by training.<sup>33</sup>

## Conclusion

This pilot study of 10 patients with chronic low-functioning hemiparesis shows that greater CST damage, but not infarct

volume, is associated with poorer performance in motor function, but the reduced density of CST fibers may not limit the potential efficacy of CIMT in these patients. The most critical variable is probably the amount of functional reorganization, which is modulated by the amount, timing, and type of motor rehabilitation efforts. Longitudinal structural neuroimaging studies are necessary to unravel the interaction of CST damage, motor impairment, and therapeutic outcomes with rehabilitation interventions.

### Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Funding

This study was funded by the Medical Research Council, UK awarded to A. Sterr. We are grateful to Andre Lynch for help with patient recruitment and training. We want to thank the anonymous reviewers for their stimulating comments.

### References

- Fries W, Danek A, Scheidtmann K, Hamburger C. Motor recovery following capsular stroke: role of descending pathways from multiple motor areas. *Brain*. 1993;116:369-382.
- Pineiro R, Pendlebury ST, Smith S, et al. Relating MRI changes to motor deficit after ischemic stroke by segmentation of functional motor pathways. *Stroke*. 2000;31:672-679.
- Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain*. 2007;130:170-180.
- Werring DJ, Toosy AT, Clark CA, et al. Diffusion tensor imaging can detect and quantify corticospinal tract degeneration after stroke. *J Neurol Neurosurg Psychiatry*. 2000;69:269-272.
- Newton JM, Ward NS, Parker GJ, et al. Non-invasive mapping of corticofugal fibres from multiple motor areas—relevance to stroke recovery. *Brain*. 2006;129:1844-1858.
- Ward NS, Newton JM, Swayne OB, et al. The relationship between brain activity and peak grip force is modulated by corticospinal system integrity after subcortical stroke. *Eur J Neurosci*. 2007;25:1865-1873.
- Ward NS, Newton JM, Swayne OB, et al. Motor system activation after subcortical stroke depends on corticospinal system integrity. *Brain*. 2006;129:809-819.
- Uswatte G, Taub E, Morris D, Vignolo M, McCulloch K. Reliability and validity of the upper-extremity Motor Activity Log-14 for measuring real-world arm use. *Stroke*. 2005;36:2493-2496.
- Wolf SL, Thompson PA, Morris DM, et al. The EXCITE trial: Attributes of the Wolf Motor Function Test in patients with subacute stroke. *Neurorehabil Neural Repair*. 2005;19:194-205.
- De Souza LH, Hewer RL, Lynn PA, Miller S, Reed GA. Assessment of recovery of arm control in hemiplegic stroke patients. 2. Comparison of arm function tests and pursuit tracking in relation to clinical recovery. *Int Rehabil Med*. 1980;2:10-16.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
- Sterr A, Elbert T, Berthold I, Kolbel S, Rockstroh B, Taub E. Longer versus shorter daily constraint-induced movement therapy of chronic hemiparesis: an exploratory study. *Arch Phys Med Rehabil*. 2002;83:1374-1377.
- Jones DK, Horsfield MA, Simmons A. Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magn Reson Med*. 1999;42:515-525.
- Skare S, Hedehus M, Moseley ME, Li T-Q. Condition number as a measure of noise performance of diffusion tensor data acquisition schemes with MRI. *J Magn Reson*. 2000;147:340-352.
- Jiang H, van Zijl PC, Kim J, Pearlson GD, Mori S. DtiStudio: Resource program for diffusion tensor computation and fiber bundle tracking. *Comput Methods Programs Biomed*. 2006;81:106-116.
- Xue R, van Zijl PC, Crain BJ, Solaiyappan M, Mori S. In vivo three-dimensional reconstruction of rat brain axonal projections by diffusion tensor imaging. *Magn Reson Med*. 1999;42:1123-1127.
- Mori S, Crain B, Chacko V, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol*. 1999;45:265-269.
- Okada T, Mikuni N, Miki Y, et al. Corticospinal tract localization: Integration of diffusion-tensor tractography at 3-T MR imaging with intraoperative white matter stimulation mapping—preliminary results. *Radiology*. 2006;240:849-857.
- Okada T, Miki Y, Fushimi Y, et al. Diffusion-tensor fiber tractography: intraindividual comparison of 3.0-T and 1.5-T MR imaging. *Radiology*. 2006;238:668-678.
- Burgel U, Amunts K, Hoemke L, Mohlberg H, Gilsbach JM, Zilles K. White matter fiber tracts of the human brain: three-dimensional mapping at microscopic resolution, topography and intersubject variability. *Neuroimage*. 2006;29:1092-1105.
- Hagmann P, Thiran J-P, Jonasson L, et al. DTI mapping of human brain connectivity: statistical fibre tracking and virtual dissection. *Neuroimage*. 2003;19:545-554.
- Wenzelburger R, Kopper F, Frenzel A, et al. Hand coordination following capsular stroke. *Brain*. 2005;128:64-74.
- Lindberg PG, Skejo PH, Rounis E, et al. Wallerian degeneration of the corticofugal tracts in chronic stroke: a pilot study relating diffusion tensor imaging, transcranial magnetic stimulation, and hand function. *Neurorehabil Neural Repair*. 2007;21:551-560.
- Sterr A, Freivogel S. Motor-improvement following intensive training in low-functioning chronic hemiparesis. *Neurology*. 2003;61:842-844.

25. Sterr A, Freivogel S. Intensive training in chronic upper limb hemiparesis does not increase spasticity or synergies. *Neurology*. 2004;63:2176-2177.
26. Taub E, Uswatte G, King DK, Morris D, Crago JE, Chatterjee A. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. *Stroke*. 2006;37:1045-1049.
27. Askim T, Indredavik B, Vangberg T, Håberg A. Motor network changes associated with successful motor skill relearning after acute ischemic stroke: a longitudinal fMRI study. *Neurorehabil Neural Repair*. 2009;23:295-304.
28. Boake C, Noser EA, Ro T, et al. Constraint-induced movement therapy during early stroke rehabilitation. *Neurorehabil Neural Repair*. 2007;21:14-24.
29. Levy CE, Nichols DS, Schmalbrock PM, Keller P, Chakeres DW. Functional MRI evidence of cortical reorganization in upper-limb stroke hemiplegia treated with constraint-induced movement therapy. *Am J Phys Med Rehabil*. 2001;80:4-12.
30. Schaechter JD, Kraft E, Hilliard TS, et al. Motor recovery and cortical reorganization after constraint-induced movement therapy in stroke patients: a preliminary study. *Neurorehabil Neural Repair*. 2002;16:326-338.
31. Szaflarski JP, Page SJ, Kissela BM, Lee JH, Levine P, Strakowski SM. Cortical reorganization following modified constraint-induced movement therapy: a study of 4 patients with chronic stroke. *Arch Phys Med Rehabil*. 2006;87:1052-1058.
32. Sawaki L, Butler AJ, Xiaoyan L, et al. Constraint-induced movement therapy results in increased motor map area in subjects 3 to 9 months after stroke. *Neurorehabil Neural Repair*. 2008;22:505-513.
33. Fields RD. White matter in learning, cognition and psychiatric disorders. *Trends Neurosci*. 2008;31:361-370.