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Compensatory role of the cortico-rubro-spinal tract in motor recovery after stroke

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ABSTRACT

Objectives: Studies on nonhuman primates have demonstrated that the cortico-rubro-spinal system can compensate for damage to the pyramidal tract (PT). In humans, so-called alternate motor fibers (aMF), which may comprise the cortico-rubro-spinal tract, have been suggested to play a similar role in motor recovery after stroke. Using diffusion tensor imaging, we examined PT and aMF in the context of human motor recovery by relating their microstructural properties to functional outcome in chronic stroke patients.

Methods: PT and aMF were reconstructed based on their origins in primary motor, dorsal premotor, and supplementary motor cortices in 18 patients and 10 healthy controls. The patients' degree of motor recovery was assessed using the Wolf Motor Function Test (WMFT).

Results: Compared to controls, fractional anisotropy (FA) was lower along ipsilesional PT and aMF in chronic stroke patients, but clusters of higher FA were found bilaterally in aMF within the vicinity of the red nuclei. FA along ipsilesional PT and aMF and within the red nuclei correlated significantly with WMFT scores. Probabilistic connectivity of aMF originating from ipsilesional primary motor cortex was higher in patients, whereas the ipsilesional PT exhibited lower connectivity compared to controls.

Conclusions: The strong correlations observed between microstructural properties of bilateral red nuclei and the level of motor function in chronic stroke patients indicate possible remodeling during recovery. Our results shed light on the role of different corticofugal motor tracts, and highlight a compensatory function of the cortico-rubro-spinal system which may be used as a target in future restorative treatments. *Neurology*® 2012;79:515–522

GLOSSARY

aMF = alternate motor fibers; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FWE** = family-wise error; **M1** = primary motor cortex; **PMd** = dorsal premotor cortex; **PT** = pyramidal tract; **ROI** = region of interest; **SMA** = supplementary motor area; **WMFT** = Wolf Motor Function Test.

Motor impairment after stroke has been related to the structural and functional integrity of corticospinal tracts.[1] Besides the pyramidal tract (PT), so-called alternate motor fibers (aMF) have been suggested to play a role in modulating recovery after stroke. Based on animal studies, it has been hypothesized that aMF comprise the cortico-rubro-spinal and cortico-reticulospinal systems.[2–4] However, anatomic evidence of those systems in man is sparse.[1]

Diffusion tensor imaging (DTI) allows for the reconstruction of monosynaptic and polysynaptic fiber bundles,[5,6] and lesion-induced alterations of dedicated tracts can be quantified[7] and related to impairment of motor function after stroke.[8–10] It has been demonstrated that DTI-derived measures of both PT and aMF explain more of the variance in motor outcome than the PT alone.[3] However, the methodology applied in the latter study did not allow for the detection of regional microstructural alterations so that no further inferences on aMF and their impact on recovery were possible. Furthermore, previous studies mainly focused on corticospinal tracts originating from the primary motor cortex (M1). In the current study, we extended

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Supplemental Data

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Table 1 Overview: patient group

Patient ID	Gender	Age, y	Lesion side	T_{post}, mo	Lesion location	Lesion size, cc	WMFT, sec[log]
1	F	77	L	64	C/SC	108.8	0.3
2	F	39	L	8	DWM	14.7	0.34
3	F	75	R	52	C/SC	39.0	1.74
4	M	71	R	6	BS	2.3	0.48
5	M	44	L	7	C/SC	246.3	1.41
6	M	62	L	14	C/SC	78.4	1.72
7	M	49	R	35	DWM	10.7	1.28
8	F	25	L	95	C/SC	49.9	0.01
9	M	40	L	45	C/SC	303.2	0.97
10	M	55	L	81	C/SC	143.3	0.34
11	M	62	L	28	C/SC	177.2	1.97
12	M	53	R	109	C/SC	268.5	0.42
13	M	48	R	14	DWM	2.7	0.84
14	M	45	L	15	DWM	328.9	1.15
15	F	60	R	54	C/SC	35.5	1.54
16	M	47	L	24	C/SC	241.4	1.58
17	M	25	R	7	BS	0.4	0.33
18	M	62	R	51	DWM	6.2	0.87
Mean ± SD		52.2 ± 15.0		39.4 ± 31.9		114.3 ± 116.7	0.96 ± 0.61

Abbreviations: BS = brainstem; C/SC = cortical/subcortical; DWM = deep white matter; T_{post} = time poststroke; WMFT = Wolf Motor Function Test Scores.

this focus in order to examine the differential contributions of primary and nonprimary motor regions[11,12] to the composition of PT and aMF. We aimed to test the hypotheses that 1) diffusivity measures of PT and aMF would differ between chronic stroke patients and healthy controls, and that 2) regional diffusivity properties in patients would be related to their degree of functional impairment.

METHODS

Subjects. Eighteen chronic stroke patients participated in this study (5 women; mean age ± SD 52.2 ± 15.0 years). Inclusion criteria were 1) occurrence of first ischemic stroke at least 5 months prior to enrolment without previous or subsequent cerebral ischemia; 2) Medical Research Council strength grade of ≤3/5 in extensor muscles of the affected upper extremity in the acute phase and persistent mild to moderate motor impairment; 3) no additional neurologic or psychiatric disorders. In addition, 10 healthy subjects (3 women; mean age 49.5 ± 20.7 years) were enrolled to be compared to the patient group. Characteristics of the patient group are provided in table 1.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local Institutional Review Board, and all participants gave written informed consent.

Functional motor assessment. Each patient underwent the Wolf Motor Function Test (WMFT), which consists of 15 time-based tasks and 2 tests of strength.[13] Similar to previous studies, completion times were log transformed to account for skewed data distribution.[14] The resulting score has a maximum value of 2.08 seconds[log] with lower values reflecting better function of the affected arm.

Image acquisition. Using a 3 T GE scanner, a T1-weighted anatomic sequence (voxel size: 0.93 × 0.93 × 1.5 mm^3) and a DTI sequence (2.5 × 2.5 × 2.5 mm^3; 50 contiguous axial slices covering the entire brain including the brainstem) with 30 non-collinear diffusion directions with a b value of 1,000 s/mm^2, and 6 with a b value of 0 s/mm^2, were acquired for all subjects in addition to other sequences.

Preprocessing of DTI data. Preprocessing and fiber tracking were performed with FSL (http://www.fmrib.ox.ac.uk/fsl). A 3-dimensional affine registration was applied to correct for eddy currents and head motion[15] and followed by brain extraction.[16] Probability distributions of fiber directions were then calculated, allowing estimates of 2 directions per voxel.[17] Directional diffusivities were determined as $\lambda_1 > \lambda_2 > \lambda_3$, and fractional anisotropy (FA) was calculated from these eigenvalues. Axial diffusivity ($\lambda_\parallel$) corresponds to λ_1, radial diffusivity ($\lambda_\perp$) to $(\lambda_2 + \lambda_3)/2$.[18] We normalized individual FA images to the FSL template (1 × 1 × 1 mm^3) using linear and nonlinear algorithms. The resulting transformation matrices were also used to normalize λ maps.

Probabilistic tractography. In order to reconstruct different portions of PT and aMF according to their origins in primary and nonprimary motor cortices, 3 different regions of interest (ROIs) were drawn on the same axial slice in the subcortical white matter. The border between primary (M1) and dorsal premotor cortices (PMd) cannot be easily determined since their cytoarchitectonic boundaries do not correspond to gross-

anatomic landmarks.[19] The M1 ROI was therefore defined at the posterior bank of the precentral gyrus from the deepest point of the central sulcus to the lateral crest of the precentral gyrus. The anterior bank of the precentral gyrus and the lateral aspect of the adjacent superior frontal gyrus comprised the PMd ROI. The anterior border of the PMd ROI coincided with the rostral end of the supplementary motor cortex (SMA) ROI. The SMA ROI was drawn on the medial aspect of the superior frontal gyrus; the anterior border was determined by a vertical line through the anterior commissure perpendicular to a line connecting the anterior and posterior commissures,[20] and the posterior border was marked by a vertical line through the posterior commissure.[21] According to previous work, 2 different pontine ROIs were used in order to differentiate PT (basis pontis) and aMF (tegmentum pontis).[3] All ROIs were manually defined on the individual FA maps in native space.

Using the brainstem ROIs as seed regions and the posterior limb of the ipsilateral internal capsule and subcortical ROIs as waypoint masks, we reconstructed 6 different tracts in both hemispheres: fibers originating from each of the motor regions, passing through the internal capsule and descending to either the anterior (^{M1}PT, ^{PMd}PT, ^{SMA}PT) or posterior pons (^{M1}aMF, ^{PMd}aMF, ^{SMA}aMF). Sagittal exclusion masks were applied in the corpus callosum and along the midline in the brainstem to include only unilateral fibers. A coronal exclusion mask was added at the posterior bank of the central sulcus to restrict tractography to fibers originating in motor cortices.

Probabilistic maps were generated by iterations of the streamline process.[22] For every seed voxel in the brainstem ROIs, 5,000 "particles" were propagated through the multi-tensor field. The number of particles that pass a certain voxel on their way to the subcortical ROIs indicates its probability to be connected with the seed mask. The resulting maps of streamline intensities were then constrained[23] to voxels with more than 1% of the individual robust range. After their reconstruction, all tracts were overlaid onto the individual FA maps in order to visually inspect their course. Due to the considerable overlap of some lesions with ipsilesional corticospinal tracts in 9 patients, 26 of the overall 216 tracts could not be properly reconstructed (^{M1}aMF: n = 2; ^{PMd}aMF: n = 3; ^{SMA}aMF: n = 3; ^{M1}PT: n = 2; ^{PMd}PT: n = 8; ^{SMA}PT: n = 8), most likely due to a poorly informed dispersion of probabilistic streamlines in white matter regions affected by the stroke.[11] They were excluded from further analyses.

Tractography-based analysis. We performed 1) an analysis of tract-specific diffusivity properties, 2) an analysis of tract-specific probabilistic connectivity, and 3) a voxelwise FA analysis of delineated tracts.

For tract-specific analyses, individual tracts were binarized and used to extract FA as well as λ values in native space. This allowed us to compare tract-specific diffusivity values between the patient and control groups and, within the patient group, between lesional and contralesional hemispheres.

Second, group differences in tract-specific connectivity were assessed for corticospinal fibers descending unilaterally from the subcortical ROIs to the ipsilateral brainstem ROIs ("unilateral" fibers) and for corticospinal fibers crossing the midline cranial to the brainstem ROIs in the pons or midbrain ("crossing" fibers). To reconstruct these "crossing" fibers, tractography was rerun using the brainstem ROIs as described above and the contralateral internal capsule and contralateral subcortical ROIs as waypoint masks. Parts of the exclusion mask cranial to the brainstem ROIs were deleted to allow streamlines to cross the midline at the level of the midbrain and the brainstem. We then extracted tract-specific values of probabilistic connectivity by averaging streamline intensities from every voxel within "unilateral" and "crossing" tracts and compared them between groups. PT fibers originating in cortical motor areas and "crossing" in the midbrain/pons most likely represent collaterals innervating pontine nuclei, whereas crossing aMF most likely correspond to the crossing rubro-spinal tract.[1]

Third, we spatially normalized the patients' tracts in order to build canonical tracts for voxelwise within-group correlation analyses and between-group comparisons. Brain images and tracts of patients with right-hemispheric lesions were mirrored along the midline. Canonical tracts were thresholded so that only voxels which were common to at least 50% of the patients (i.e., n = 9/18) were included. We applied nonparametric permutation methods[24] for every voxel within these tracts. Monte Carlo permutation-based tests were run to compare FA values between the groups. Furthermore, we tested for correlations between WMFT scores and FA values within the patient group. To avoid an arbitrary initial cluster-forming threshold, we used threshold-free cluster enhancement[25] for final voxelwise inference. For each cluster showing significant between-group FA differences, underlying axial and radial diffusivities were compared using 2-sample *t* tests.

RESULTS

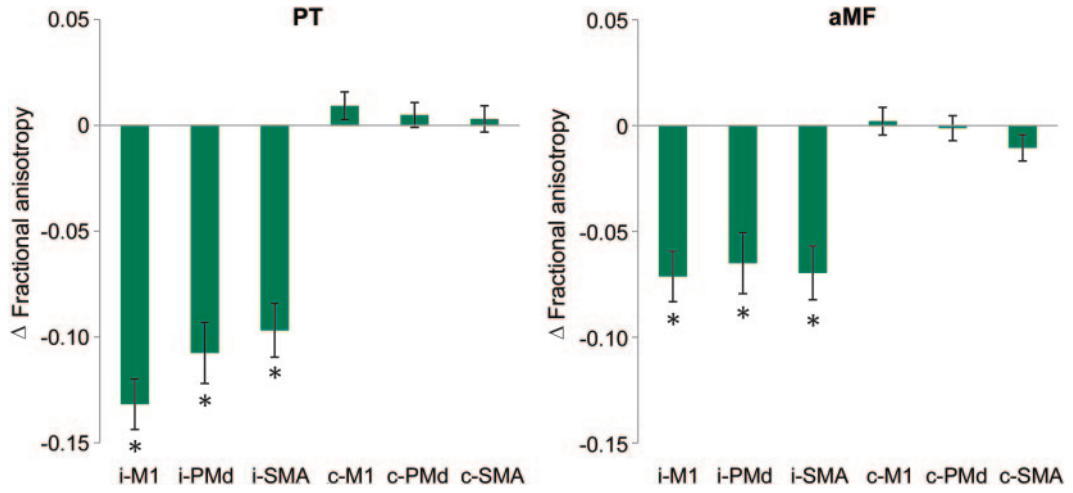
Tract-specific diffusivity measures. The patients' ipsilesional tracts exhibited lower FA values as compared to controls (all $p < 0.012$). No significant differences were found in tract-specific FA of contralesional tracts comparing patients with healthy controls (all $p > 0.27$; figure 1).

Probabilistic connectivity of "unilateral" tracts. aMF originating in ipsilesional M1 exhibited higher probabilistic connectivity in patients as compared to controls [$t(15) = 2.304$, $p = 0.036$]. In contrast, connectivity of the PT originating in ipsilesional M1 tended to be lower in the patient group [$t(23) = -1.596$, $p = 0.124$]. Similarly, PT and aMF originating in ipsilesional PMd or SMA as well as contralesional tracts did not differ significantly between the patient and control groups, although trends for higher connectivity were observed for ipsilesional ^{SMA}aMF (see figure 2 for details).

Probabilistic connectivity of tracts crossing at the midbrain/brainstem level. aMF originating in ipsilesional PMd/SMA and crossing in the midbrain/brainstem showed higher connectivity as compared to the same tracts in control subjects [^{PMd}aMF: $t(10) = 2.259$, $p = 0.048$; ^{SMA}aMF: $t(9) = 2.489$, $p = 0.034$], whereas crossing aMF originating in ipsilesional M1 or contralesional M1/PMd/SMA did not differ from controls ($p > 0.19$).

The PT, on the other hand, exhibited higher connectivity of "crossing" fibers originating from all 3 contralesional motor areas as compared to the same tracts in controls [^{M1}PT: $t(18) = 2.180$, $p = 0.043$; ^{PMd}PT: $t(17) = 2.630$, $p = 0.018$; ^{SMA}PT: $t(16) = 2.182$, $p = 0.044$], whereas fibers from ipsilesional

Figure 1 Between-group differences in fractional anisotropy (FA)



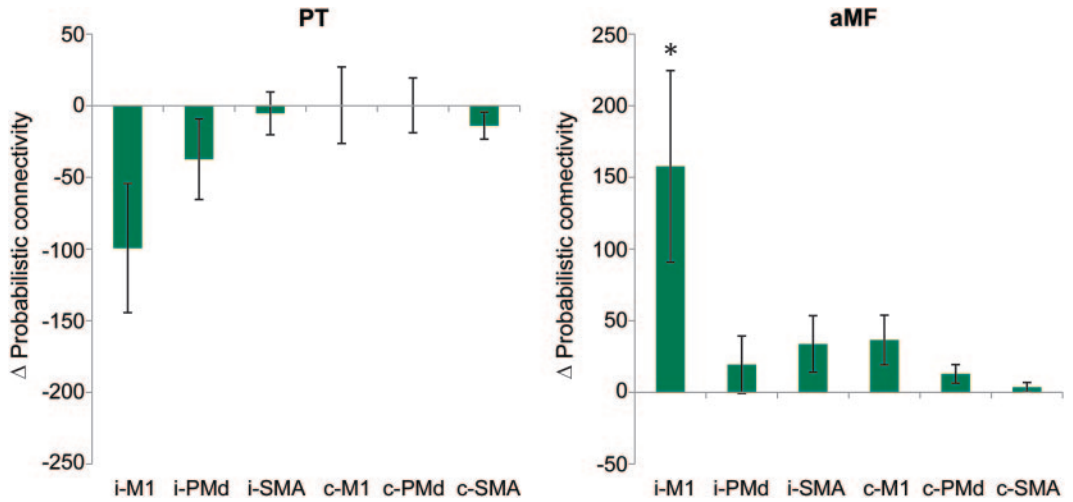
Differences in tract-specific FA between patients and controls ($FA_{patients} - FA_{controls}$; FA of controls was averaged across hemispheres). Error bars indicate SEM. Asterisks mark significant differences between the patient and control groups ($p < 0.05$). aMF = alternate motor fibers; c = contralesional; i = ipsilesional; M1 = primary motor cortex; PMd = dorsal premotor cortex; PT = pyramidal tract; SMA = supplementary motor area.

motor areas did not (^{M1}PT and ^{SMA}PT: $p > 0.73$); only the ^{PMd}PT showed a trend for decreased connectivity [$t(10) = -2.068$, $p = 0.063$]. Degrees of freedom and p values were adjusted in all t tests in which Levene's test indicated unequal variances.

Voxelwise analysis. Voxelwise between-group comparisons revealed lower FA values in multiple locations along ipsilesional PT and aMF in patients as compared to controls ($p < 0.05$; family-wise error [FWE]-corrected). In the contralesional hemisphere, lower FA values were found only in a cluster slightly cranial to the internal capsule within PT and aMF ($p < 0.05$; FWE-corrected).

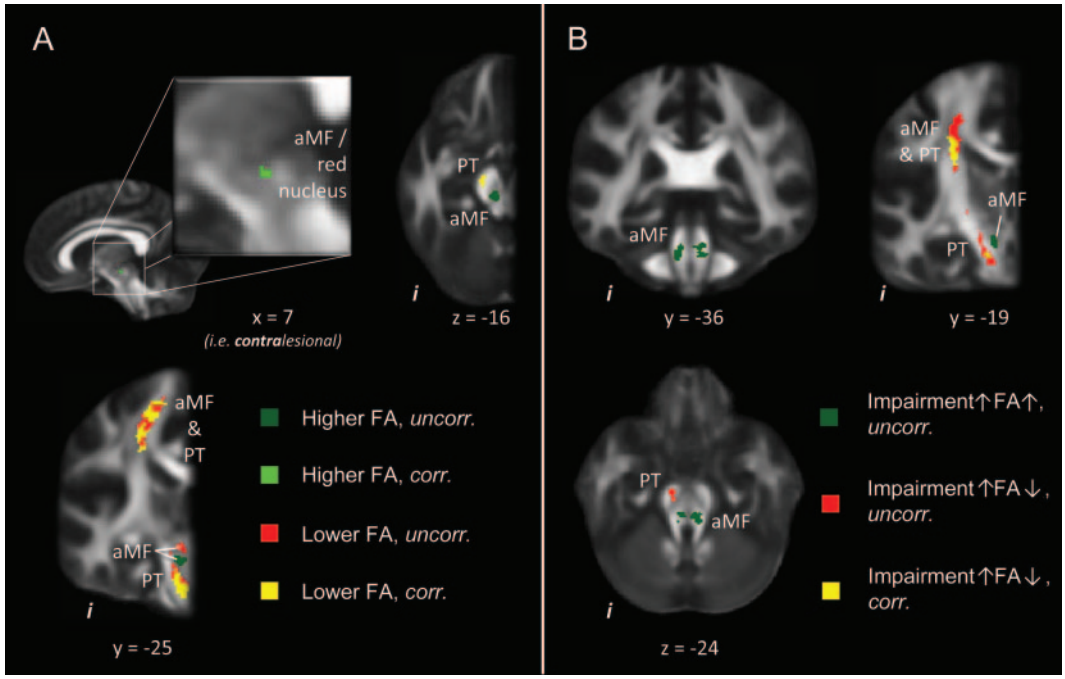
Higher FA values in the patients as compared to the controls were found only in the vicinity of contralesional and ipsilesional red nuclei within the aMF (table e-1 on the *Neurology*® Web site at www.neurology.org; figure 3). Higher FA values were associated with lower $\lambda_{\perp}$ [contralesional: $t(26) = 3.874$, $p < 0.001$; ipsilesional: $t(26) = -1.671$, $p = 0.107$] but not $\lambda_{\parallel}$ ($p > 0.37$ in both hemispheres).

Figure 2 Between-group differences in probabilistic connectivity



Differences in tract-specific probabilistic connectivity between patients and controls ($connectivity_{patients} - connectivity_{controls}$; connectivity of controls was averaged across hemispheres). Error bars indicate SEM. Asterisk marks significant differences between the patient and control groups ($p < 0.05$). aMF = alternate motor fibers; c = contralesional; i = ipsilesional; M1 = primary motor cortex; PMd = dorsal premotor cortex; PT = pyramidal tract; SMA = supplementary motor area.

Figure 3 Regions with between-group differences in fractional anisotropy (FA) and correlations between FA and Wolf Motor Function Test (WMFT)



(A) Clusters with significant FA differences between the patient and control groups, and (B) clusters with significant correlations between FA and WMFT scores in the patient group. aMF = alternate motor fibers; corr. = family-wise error-corrected; i = ipsilesional; impairment ↑ FA ↑ = the higher the WMFT scores, the higher the FA values; impairment ↑ FA ↓ = the higher the WMFT scores, the lower the FA values; PT = pyramidal tract; uncorr. = uncorrected; x, y, z = coordinates in Montreal Neurological Institute space.

Voxelwise correlation analyses yielded significant results for voxels along all ipsilesional corticospinal tracts ($p < 0.05$, FWE-corrected): the higher the FA, the lower the WMFT scores (note that lower WMFT scores reflect better motor function). Further clusters with significant correlations were found in the vicinity of bilateral red nuclei ($p < 0.05$, uncorrected): the lower the FA, the lower the WMFT scores (table e-2; figure 3).

DISCUSSION In the current study, we report a specific pattern of FA differences between chronic stroke patients and healthy controls along ipsilesional corticospinal tracts (PT and aMF) and in the ipsilesional and contralesional red nuclei. These between-group differences were complemented by significant correlations of DTI-derived measures and motor activity scores in the patient group, which may indicate a compensatory role of aMF and its rubral relay station for motor recovery after damage to the corticospinal system.

Higher FA values in ipsilesional and contralesional red nuclei of chronic stroke patients may reflect structural remodeling in the course of motor recovery. This notion is supported by significant correlations between FA and WMFT in clusters within the red nuclei and the adjacent white matter. Experimental animal studies have demonstrated that recovery of motor function after PT lesions can be mediated by the rubro-spinal tract[26,27] and is associated with a change in the synaptic organization of efferent neurons in the red nucleus.[28] Similar observations have been made in humans after stroke. Despite severe PT damage, motor evoked potentials from ipsilesional motor cortex could be elicited in the affected limb of chronic stroke patients,[4] and patients were able to independently control individual fingers of their affected hands.[2] Based on these studies and the findings of our current study, we postulate a compensatory role of aMF for those stroke patients with severe PT damage but relatively high levels of functional recovery.[2–4] Additional evidence comes from a DTI study reporting higher FA values in ROIs in the ipsilesional red nucleus in subacute stroke patients as compared to healthy controls.[29] Similarly, we found higher FA values in red nuclei of chronic stroke patients. Rather than using predefined ROIs, our analysis employed voxelwise testing of whole tracts independent of a priori hypotheses. Furthermore, we found FA alterations in bilateral red nuclei and

strong correlations with measures of motor function, extending those previous results.

A few clusters of significant FA differences between the groups as well as clusters showing correlations between FA and WMFT did not survive FWE correction, such as the clusters in the ipsilesional red nucleus. However, considering that voxels along ipsilesional PT and aMF generally exhibited lower FA as compared to the control group, it is a striking finding that the only clusters with higher FA values were localized within the red nuclei. Whereas lower FA values can be interpreted as being indicative of degenerative processes,[7,8] clusters of higher FA values within the red nuclei may reflect plastic remodeling as has been demonstrated in healthy subjects.[30]

The significantly higher FA values in bilateral red nuclei of chronic stroke patients as compared to healthy controls were primarily driven by lower radial diffusivity. Axial diffusivity did not show significant between-group differences. The interpretation of such gray matter diffusivity alterations is challenging because they are relatively unexplored.[31] However, the iron content of gray matter has been shown to influence diffusivity measures.[32] It is open to speculation that changes in iron content may be associated with the extent of tissue compaction[31] during structural remodeling. Furthermore, diffusivity alterations may indicate the presence of interstitial fluid accumulation or a higher degree of tissue compaction due to dendritic arborization, axonal ramification, synaptogenesis, or glial proliferation,[31–33] which led to the hypothesis that FA increase reflects synaptic reorganization.[33]

The significantly lower FA values along ipsilesional PT and aMF in the patients can be attributed to higher axial and radial diffusivities, which is characteristic for chronic white matter degeneration.[34,35] Interestingly, tract-specific differences in diffusivity measures were most prominent for tracts originating in the primary motor cortex in our study. Furthermore, correlations between tract-specific FA values and WMFT scores were only significant for ^{M1}PT and ^{M1}aMF, which emphasizes the important role of fibers originating in M1 for the functional integrity of the motor system. Due to the topographic organization of corticospinal tracts,[36] stroke patients with lesions in the posterior limb of the internal capsule are more severely impaired with respect to the function of their upper extremities the more posterior the lesion is localized.[37] Our data support this finding and demonstrate that also lesions not restricted to the internal capsule or the primary motor cortex appear to alter those fibers originating in M1 more thoroughly than fibers originating from PMd and SMA in patients who were severely affected in the acute phase after stroke (figure e-1). Furthermore, we found a more pronounced decrease of FA values in the PT than in aMF, indicating that the PT might be more prone to degenerative processes than aMF after ischemic lesions. This has been described previously[3] and might be best explained by the composition of aMF which presumably contain a heterogeneous group of polysynaptic fibers.

In addition to diffusivity measures, alterations of probabilistic connectivity measures can inform the study of plastic remodeling and degenerative processes in the human brain.[38] Consistent with the diffusivity analysis, unilateral PT originating in ipsilesional motor areas showed a lower tract-specific connectivity in patients as compared to controls. Within those tracts, fibers originating in M1 showed a more prominent decrease in tract-specific connectivity as compared to fibers originating in PMd and SMA. In turn, aMF descending unilaterally from ipsilesional M1 exhibited a significantly higher probabilistic connectivity as compared to healthy controls. Similarly, aMF originating in ipsilesional motor areas and crossing to the contralesional side at the midbrain/brainstem level showed a higher probabilistic connectivity in stroke patients. We therefore suggest that aMF represent the crossed and uncrossed cortico-rubro-spinal tract.[1] Their increased probabilistic connectivity in chronic stroke patients may reflect structural adaptations of the red nucleus caused by compensatory input to this relay station in the midbrain, which has also been reported in neonatal rats with lesions to the PT as a result of lesion-induced sprouting.[39] Although the patients in our study had variable lesion locations, part of the ipsilesional M1 was intact in most patients as indicated by the fact that corticospinal tracts descending from ipsilesional M1 could be reconstructed in the majority (16/18). Together with the results of the connectivity analysis, this suggests that intact portions of ipsilesional M1 may be the most important origin of those cortico-rubral fibers that undergo plastic changes during motor recovery.

Increased connectivity of PT fibers originating in contralesional motor areas and "crossing" at the midbrain/pons level most likely represents axon collaterals innervating pontine nuclei.[1] Since axonal sprouting has been described as one form of plastic remodeling,[40] it can be speculated that the higher connectivity of fibers "crossing" at the midbrain and brainstem level observed in our study is due to enhanced innervation of pontine nuclei in stroke patients.

We interpret the FA alterations in the vicinity of bilateral red nuclei in our chronic stroke patients as a result of preceding plastic remodeling during motor recovery. The strong correlation of local FA values with WMFT scores suggests that the observed diffu-

sivity alterations are functionally meaningful. The analysis of probabilistic connectivity complements these findings and further substantiates our interpretation that ipsilesional aMF undergo plastic remodeling after stroke. Our study sheds light on the role of different corticofugal motor tracts in poststroke reorganization and opens avenues for the development of restorative treatments targeting the presumed compensatory function of the cortico-rubro-spinal system.

AUTHOR CONTRIBUTIONS

T. Rüber: drafting the manuscript, analysis or interpretation of data, statistical analysis. G. Schlaug: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision, obtaining funding. R. Lindenberg: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision.

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DISCLOSURE

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