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Synergistic but independent: The role of corticospinal and alternate motor fibers for residual motor output after stroke

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ABSTRACT

Background: Brain imaging has shown that not only the cortico-spinal tract (CST), but also alternate corticofugal motor fibers (aMF), such as the cortico-rubro-spinal and cortico-reticulo-spinal tract, influence residual motor output after stroke. So far, studies mainly have investigated each tract separately. A combined analysis of CST and aMF with assessment of their interactive role, i.e., that structural integrity of one tract influences the functional role of the structural integrity of the other, is pending.

Methods: 39 late subacute stroke patients (aged 59.4 ± 12.0 years, 100 ± 11 days after stroke) were included. Probabilistic tractography was used to reconstruct CST and aMF. Fractional anisotropy (FA) was calculated as a measure of microstructural integrity. Multiple-linear-regression analysis was used to associate tract-related FA with residual motor output and to determine interactions between CST and aMF.

Results: Both CST (coefficient = 3.93, $p < 0.0001$) and aMF (coefficient = −4.43, $p = 0.003$) of the affected hemisphere significantly contributed to residual motor output. An interaction of their impacts with a consecutive influence on motor output was not detected ($p = 0.882$). Thus, these data suggest that aMF and CST explain residual motor output in stroke patients in a synergistic, but mainly independent manner.

Conclusions: The structural states of the CST and also – to a smaller degree – of the aMF correlate with residual motor output in late subacute stroke patients. Based on this statistical modeling with all inherent limitations, the novel finding of an absence of a significant interaction between both tracts in regard of their functional role, suggests that both corticofugal pathways act synergistically but largely independently. These findings add to the understanding of the functional role of different corticofugal motor fibers and their interactions for motor output after stroke.

1. Introduction

Structural brain imaging has significantly enhanced our understanding of how brain networks react to focal lesions caused by e.g., an ischemic stroke (Lindenberg et al., 2010; Rüber et al., 2012; Schaechter et al., 2009; Schulz et al., 2015b). For a comprehensive review see Koch and colleagues (Koch et al., 2016). Apart from the cortico-spinal tract (CST) with its significant and well-established role for residual motor output and recovery processes, studies in animals (Belhaj-Saïf and Cheney, 2000; Lawrence and Kuypers, 1968a, 1968b; Zaaimi et al., 2012) and more recently also in humans (Lindenberg et al., 2012; Rüber et al., 2012; Takenobu et al., 2014; Yeo and Jang,

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2010), have evidenced that alternate corticofugal motor fibers (aMF), such as the cortico-rubro-spinal and cortico-reticulo-spinal tract, might be also important for the residual function of the upper extremity after stroke. It has been shown that these fiber show microstructural alterations in the chronic stage after stroke (Lindenberg et al., 2010; Rüber et al., 2012; Schaechter et al., 2009) and play a functional role in the recovery process (Lindenberg et al., 2010; Rüber et al., 2012; Takenobu et al., 2014; Yeo and Jang, 2010) and for improvement with treatment (Lindenberg et al., 2012). For instance, one study has shown that residual motor output could be better inferred based on the integrity of CST and aMF together than CST alone (Lindenberg et al., 2010). Whole-brain voxel-wise analyses have reported significant structure-function-relationships for white matter of aMF and in areas in and around the red nucleus (Rüber et al., 2012; Takenobu et al., 2014). Notably, it has been recently speculated that aMF might influence residual motor function depending on the residual state of the CST (Bradnam et al., 2013), an hypothesis which has not yet experimentally addressed in detail. To this extent, structural imaging has rarely considered a combined analysis of CST and aMF and, even more importantly, has neglected so far a statistical evaluation of interactions between the state of CST and aMF in relation to residual motor function, i.e., that the structural integrity of one tract might influence the functional role of the other. Despite its inherent limitation to simplify the research problem, to be susceptible for confounders or epiphenomena and to be not able to prove causality, such combined analyses might be helpful to better understand CST and aMF structural plasticity and their functional relevance in the light of partly conflicting data for tract-related microstructure or the presence of associations with motor function after stroke (Rüber et al., 2012; Schaechter et al., 2009). Therefore, the present study was designed (1) to reconstruct the CST and aMF applying diffusion-tensor imaging and probabilistic tractography in late subacute stroke patients, (2) to estimate the microstructural integrity of both tracts and (3) to investigate not only whether aMF integrity would explain variance in residual motor output in addition to that explained by the CST, but also whether there might be a significant cross-network interaction between both corticofugal tracts.

2. Materials and methods

2.1. Participants & clinical testing

39 patients (aged 59.4 ± 12.0 years, range 35–80; 20 male; four left-handed) with first-ever ischemic stroke (17 in the dominant hemisphere) were recruited about three months after onset (mean 100 ± 11 days, range 80–129). Patients showed a broad range of supratentorial cortical, subcortical and cortico-subcortical stroke lesions. They were evaluated by means of grip force (calculated as the ratio between the affected and unaffected hand, mean value 0.2 ± 0.3, range 0–1.2) and the upper limb score of the Fugl-Meyer assessment (mean value 40.1 ± 19.3, range 4–66). In order to calculate a more general motor score including distal and proximal motor components, both measures were combined to one composite motor output score (MO) by principal component analysis (1st principal component explaining 75% of variance in both measures) as applied in previous trials (Schulz et al., 2015b). Table 1 summarizes the clinical data for all patients. Available brain imaging data of 26 healthy participants of similar age (66 ± 10.1 years, range 48–79), gender (15 male, $X^2 = 0.06$, $p = 0.80$, Pearson's Chi^2 test) and handedness (all right-handed, $X^2 = 1.34$, $p = 0.25$) from a previous study on cortico-cerebellar structural connectivity were used for the reconstruction of the CST and aMF (Schulz et al., 2015a). The present study was approved by the local ethics committees. All participants gave written informed consent according to the Declaration of Helsinki. Written informed consent was obtained from all participants and ethical approval was provided by the Institutional Review Board of Samsung Medical Center (IRB No.2015-07-02).

2.2. Brain imaging

In the stroke patients, diffusion-weighted images were acquired using a 3T Phillips ACHIEVA MRI scanner (Philips Medical Systems, Best, Netherlands) located at the Samsung Medical Center, Seoul, Korea. Seventy-five axial slices were obtained covering the whole brain with gradients ($b = 1000\ s/mm^2$) applied along 45 non-collinear directions with the following sequence parameters; repetition time = 8770 ms, echo time = 60 ms, field of view = 220 × 220 mm, slice thickness = 2.25 mm, in-plane resolution = 1.96 × 1.96 mm. Details of the MRI scanner and imaging sequences used for the controls, obtained at the University Medical Center Hamburg-Eppendorf, Hamburg, Germany, are given elsewhere (Schulz et al., 2015a).

2.3. Image processing & probabilistic tractography

The FSL software package 5.1 (http://www.fmrib.ox.ac.uk/fsl) was used to analyze the diffusion-weighted data. In brief, after correcting for eddy currents and head motion, brains were skull stripped and fractional anisotropy (FA) maps were calculated for each participant fitting the diffusion tensor model at each voxel (Behrens et al., 2003). The FA maps were then registered non-linearly to the Montreal Neurological Institute (MNI) standard space applying FSL's *flirt* and *fnirt*. Herein, stroke lesions were masked out and were not considered during the registration process. Probabilistic tractography was conducted in the 26 controls (Schulz et al., 2015a) to reconstruct the CST and aMF originating from the primary motor cortex (M1). For both tracts, individual seed masks for each hemisphere were placed in the hand knob area M1 in each participant using an established semi-automated pipeline. These masks were biased to the hand representation and standardized in size and relationship to the white/gray matter boundary; details are given elsewhere (Schulz et al., 2015a). 50,000 streamlines were sent from M1 to the spinal target masks in the ventral medulla oblongata. *Waypoint* masks in MNI standard space included the posterior limb of the internal capsules and the cerebral peduncles. For the CST, a mask covering trajectories at the tegmentum pontis was added as an additional exclusion mask to the mid-sagittal and basal ganglia exclusion masks. For aMF, the additional exclusion mask was drawn in MNI standard space covering the pyramid fibers at basis pontis. After *probtrackx* tractography, CST and aMF output distributions of each control participant were thresholded at three different thresholds (0.5%, 1% and 2%, respectively, minimum 5) of the overall streamlines (*waytotal*) and binarized. The common group average for each tract was calculated for each of the three thresholds by taking the sum of all individual threshold- and subject-specific trajectories. Only those voxels were considered to belong to the common CST and aMF trajectories which were found in at least 65% of the subjects (Schulz et al., 2012). In both the stroke patients and controls, the binarized CST and aMF templates were finally used to estimate threshold-specific individual FA values at the level from the mesencephalon to the cerebral peduncle (MNI coordinates $z = -25$ to $z = -20$) as a measure of white-matter integrity (Beaulieu, 2002). Finally tract-related CST and aMF FA values were averaged across the three thresholds for each participant.

2.4. Statistical analysis

The data were analyzed using R statistical package 3.1.3. To compare the absolute FA values of CST and aMF in the stroke patients and controls, R's *lmer* was used for linear mixed effects modeling with repeated measures, fit by restricted maximum likelihood (REML) including *Group* as between- and *Tract* and *Hemisphere* as within-factors (CST of the affected and unaffected hemisphere: CST_a, CST_u; aMF of the affected and unaffected hemisphere: aMF_a, aMF_u). *Age* was included as

Table 1
Clinical data.

ID	Age	Gender	Side	Location	*Dom*	TAS	Grip force			UEFM	MO
							aff.	unaff.	Ratio		
1	35	M	R	CR	0	94	2.2	17.0	0.13	42	− 0.11
2	54	M	R	CR, SC	0	112	0.0	32.0	0.00	30	− 0.79
3	63	M	L	CR	1	88	1.1	25.0	0.04	21	− 1.04
4	60	M	R	F, P, T	0	100	0.0	39.0	0.00	46	− 0.21
5	60	M	R	SC	0	113	0.0	27.0	0.00	14	− 1.38
6	79	F	R	CR, SC	0	103	0.7	13.0	0.05	37	− 0.44
7	48	F	R	CR, SC	0	98	0.1	21.0	0.01	41	− 0.38
8	53	F	R	TH	0	87	21.7	18.7	1.16	60	2.17
9	75	M	R	SC	0	90	2.0	18.0	0.11	58	0.23
10	66	M	R	CR	0	88	2.7	27.3	0.10	55	0.12
11	65	F	R	SC	0	80	14.0	15.7	0.89	66	2.39
12	66	M	L	F, P, CR, SC	1	115	10.0	29.0	0.34	66	0.53
13	55	M	L	SC	1	98	9.7	14.0	0.69	62	2.25
14	67	F	L	T, PI, CR, SC	1	91	0.0	6.0	0.00	4	− 1.74
15	55	F	R	CR	0	99	2.0	22.0	0.09	45	− 0.24
16	54	M	R	SC	0	94	19.0	28.0	0.68	57	2.06
17	47	F	L	SC	0	115	2.0	18.0	0.11	59	0.27
18	55	M	L	F, CI	1	105	25.0	35.0	0.71	43	1.55
19	37	F	L	SC	1	112	12.0	20.0	0.60	60	2.17
20	62	M	L	PI	1	92	0.0	28.0	0.00	20	− 1.16
21	52	M	L	SC	1	97	7.0	35.0	0.20	55	0.12
22	52	F	R	CR	0	96	1.0	10.0	0.10	34	− 0.65
23	35	F	R	PI	1	101	0.0	32.0	0.00	14	− 1.38
24	68	M	R	SC	0	94	8.0	46.0	0.17	58	0.23
25	42	F	L	PI	1	110	0.0	9.5	0.00	20	− 1.16
26	45	F	R	CR	0	104	0.5	6.6	0.08	47	− 0.17
27	69	F	L	SC	1	109	0.0	25.0	0.00	40	− 0.43
28	67	F	R	CR	0	98	0.0	32.0	0.00	18	− 1.23
29	52	F	R	CR	0	85	0.0	62.0	0.00	16	− 1.31
30	40	M	R	PI	0	89	20.0	35.0	0.57	50	1.01
31	58	F	L	CR	1	104	0.0	10.4	0.00	4	− 1.74
32	64	M	L	CR	1	92	5.0	36.7	0.14	24	− 0.76
33	40	M	L	F, CI	0	87	29.0	44.0	0.66	57	1.43
34	67	M	R	CR	1	105	0.0	26.5	0.00	17	− 1.27
35	77	M	R	CR	0	117	12.0	16.0	0.75	55	1.52
36	70	F	R	S1	0	129	0.3	1.3	0.23	55	0.55
37	80	F	L	CR	1	99	0.5	8.7	0.06	54	0.19
38	67	M	L	CR, SC	1	112	0.0	20.3	0.00	4	− 1.74
39	73	F	L	SC	1	81	0.1	0.6	0.21	55	0.52

Clinical characteristics are given for each patient. M male, F female. R right, L left. Stroke locations are given: BG Basal ganglia, CR Corona radiata, F Frontal lobe, IC Internal capsule, P Parietal lobe, SC Striatocapsular, T Temporal cortex, TH Thalamus, PI Peri-insula, CI Cingulate cortex, S1 Primary sensory cortex. *Dom* indicates whether the dominant hemisphere was affected (1) or not affected (0). TAS Time as days after stroke. Grip force summarizes whole-hand grip force as absolute values in kg for the affected (aff.) and unaffected (unaff.) hand and the proportional values of the ratio affected/unaffected hand. UEFM Fugl-Meyer score of the upper extremity. MO composite motor output score.

an additional covariate to account for the broad range of age in the stroke patients and the group difference as well. Controls' hemispheres were pseudo-randomly assigned to be affected or unaffected according to the distribution of lesions to the dominant and non-dominant hemispheres in the stroke patients (Schulz et al., 2012). Estimated means are given for all tracts with 95% confidence intervals (CI). For pairwise comparisons, *t*-tests were used based on Satterthwaite approximations to degrees of freedom, subsequent false discovery rate correction was used to account for multiple post-hoc pairwise comparisons to detect FA differences between the groups (Benjamini and Yekutieli, 2001). Multiple linear regression models were fitted using R's *lm* for the absolute CST and aMF FA values and residual motor output in the stroke patients (MO, log-transformed after data translation to a minimum of 1, for the sake of a normal distribution). *Age* and the information whether the dominant or non-dominant hemisphere was lesioned (*Dom*) were included as additional variables to adjust the target effects in agreement with recent reports (Schulz et al., 2015a, 2015b). Estimated coefficients are given with 95% CI. Behavioural scores values are given as mean ± standard deviation (SD). Statistical significance was assumed at $p < 0.05$.

3. Results

3.1. Probabilistic tractography and tract-related FA

Probable trajectories of CST and aMF were successfully obtained in the healthy participants. Fig. 1 shows the group averages of the tracts with excellent spatial reproducibility across the participants. Given a significant *Group* ∗ *Tract* ∗ *Hemisphere* interaction ($t = -8.201$, 189 degrees of freedom, $p < 0.0001$), post-hoc comparisons revealed that tract-related white matter integrity of both CST and aMF was significantly affected by the stroke (Fig. 2). For stroke patients, estimated mean FA values were 0.47 (95% CI 0.45–0.48) for CST_a and 0.61 (95% CI 0.59–0.62, $p < 0.0001$) for CST_u. Mean FA values for aMF_a and aMF_u in the stroke patients were 0.59 (95% CI 0.58–0.61) and 0.63 (95% CI 0.61–0.64, $p = 0.0025$), respectively. Pair-wise group comparisons revealed significantly lower mean CST_a FA in stroke patients compared to healthy controls (0.65, 95% CI 0.64–0.67, $p < 0.0001$). For CST_u there was no significant group difference. Likewise, also for aMF, there were no significant group differences: Controls' mean FA for aMF_a was 0.61 (95% CI 0.59–0.63) and for aMF_u 0.62 (95% CI 0.61–0.64).

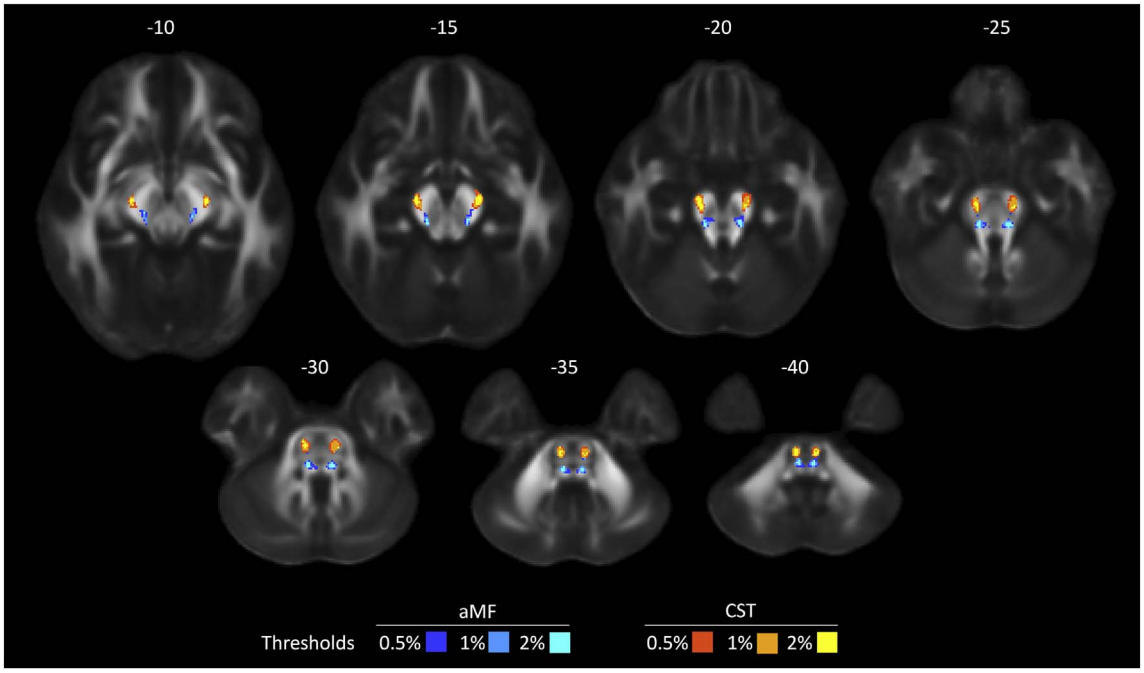

Fig. 1. Group averaged trajectory map for corticofugal motor connections.Probable courses of the fiber tracts for the corticospinal tract (CST) and alternate motor fibers (aMF) as derived from probabilistic tractography in 26 healthy controls presented on axial slices in MNI standard space.Note that microstructural integrity was calculated as fractional anisotropy (FA) for each threshold at the level of the mesencephalon between z = − 20 and z = − 25 (MNI). FA values were then averaged across all 3 thresholds.

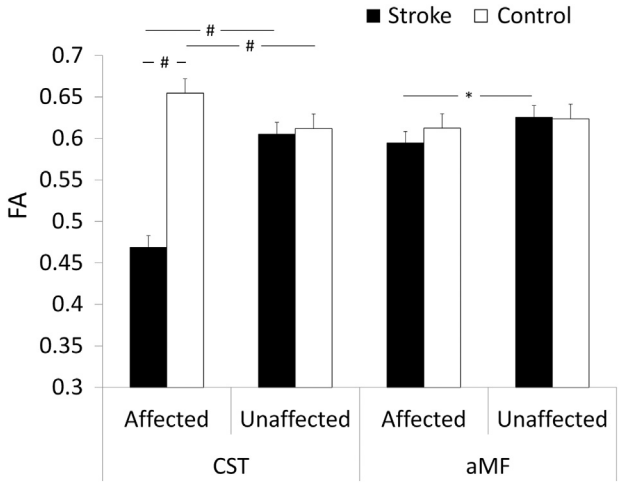

Fig. 2. Tract-related white matter integrity of corticofugal pathways after stroke.Estimated means of tract-related fractional anisotropy (FA) as a measure of structural integrity with 95% confidence intervals. * $p < 0.001$, # $p < 0.0001$ (corrected for age and multiple comparisons).

3.2. Contribution of CST and aMF for residual motor function after stroke

The initial regression model included CST and aMF FA values of the affected and unaffected hemispheres. After stepwise elimination of non-significant tracts (CST_u and aMF_u, $p > 0.38$), the final model included a significant positive influence of CST_a FA (3.93, 95% CI 2.21–5.66, $p < 0.0001$, Fig. 3) and a negative influence of aMF_a FA (− 4.43, 95% CI − 7.21–1.64, $p = 0.003$, Fig. 3) on MO (overall model multiple $R^2 = 0.49$, $F[4,34] = 8.295$, $p < 0.0001$). Explained variance (difference in R^2) was 25.5% for CST_a and 15.5% for aMF_a, respectively. The factors *Age* and *Dom* did not exert significant influences but were kept as control variables. Significant multi-collinearity between CST_a and aMF_a, which would lead to inaccurate estimation of variances, was excluded by means of the analysis of cross-correlation (Pearson's $R = 0.20$, $p = 0.22$) and the variation inflation factors (VIF = 1.06 for CST_a and VIF = 1.09 for aMF_a). To address our hypothesis whether CST_a FA might influence the contribution of aMF_a FA, we added an interaction term CST_a *X* aMF_a to this model. However, this term did not further improve it ($p = 0.882$) and was omitted again. Two separate univariate models (similarly corrected for *Age* and *Dom*) were subsequently tested which included CST_a or aMF_a alone, respectively. While the former confirmed a significant positive influence of CST_a on MO (3.46, 95% CI 1.55–5.38, $p < 0.0001$), the latter showed that aMF_a significantly lost functional relevance when considered solely (− 3.35, 95% CI − 6.80–0.10, $p = 0.056$).

In addition to the present combined modeling of CST_a and aMF_a testing for *statistical* interactions between these fiber tracts, an additional post-hoc analysis was conducted to explore the influence of aMF_a to MO in a more *neuro-anatomic* approach: Two separate models were re-estimated for (a) patients with low damage to the CST and (b) patients with high damage to the CST. These models confirmed the absence of the significant interaction between CST_a and aMF_a (see Supplementary Online Material).

4. Discussion

The main finding of the present study was that CST_a and aMF_a significantly contributed to residual motor output in late subacute stroke patients. Specifically, the structural state of aMF_a explained variance in motor output in addition to the established, well-known influence of the CST_a. However, a direct interaction between CST_a and aMF_a that influences their individual functional role, i.e. whether the amount of damage to the CST_a might influence the functional relevance of aMF_a, was not detected. This suggests that the importance of both corticofugal pathways for residual motor output in the late subacute stage after stroke might be synergistic but independent in nature.

The present data is well in line with a variety of reports showing that a stroke leads to the disruption of the CST_a and that its residual structural state critically influences residual motor output (Lindenberg et al., 2010; Rüber et al., 2012; Schaechter et al., 2009; Schulz et al., 2015b), for a comprehensive review please see Koch and colleagues (Koch et al., 2016). It has already been suggested that these remote

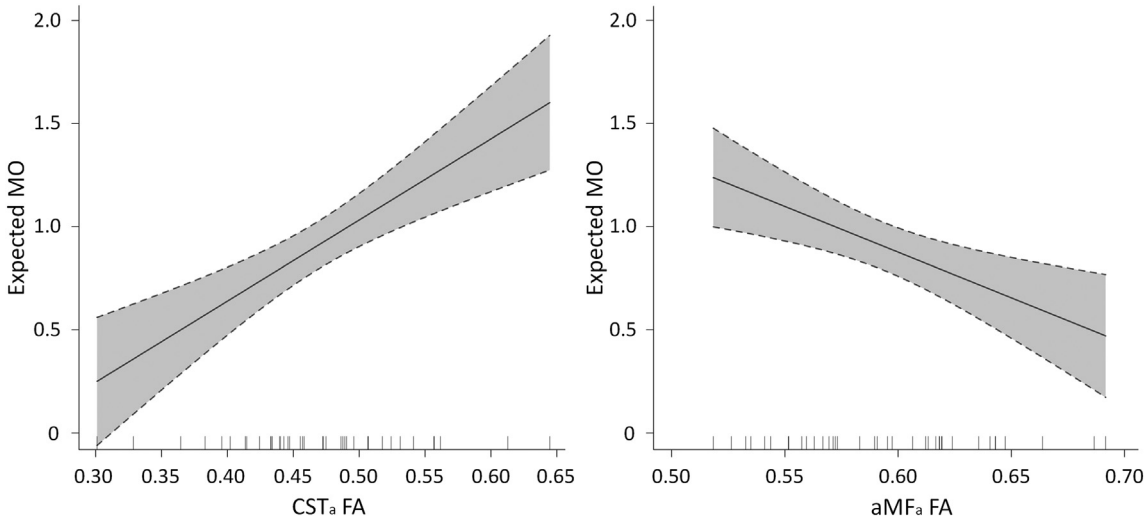

Fig. 3. Structure-function relationship for CST and aMF white matter integrity after stroke.Effect plots for the significant correlation between the tract-related mean FA of the CST and aMF of the affected hemisphere (CST_a: coefficient = 3.93, 95% CI 2.21–5.66, $p < 0.0001$, aMF_a: coefficient = −4.43, 95% CI −7.21–1.64, $p = 0.003$) and the expected residual motor output (MO) after stroke (dimensionless, log-transformed, see Statistics). Plot shows the estimated means (solid lines) with 95% confidence intervals (dotted lines). The rug plots indicate the actually measured tract-related FA values for CST_a and aMF_a.

lesion effects might also lower white matter integrity of aMF_a comprising cortico-rubro-spinal and cortico-reticulo-spinal fibers due to Wallerian degeneration (Lindenberg et al., 2012; Schaechter et al., 2009), particularly originating from M1 (Rüber et al., 2012). In agreement, the patients of the present study also showed significantly reduced FA of aMF_a compared to aMF_u, although differences of tract-related FA were marginal in the present data, when contrasted with CST or healthy controls. This might indicate that – already in the late subacute stage after stroke – mono-synaptic CST fibers might be more prone to degenerative white matter processes (e.g., Wallerian degeneration) than multi-synaptic ones, like the aMF (Lemon, 2008). Previous univariate voxel-wise analyses have found significant correlations between motor function and regional FA along the aMF tract (Rüber et al., 2012; Takenobu et al., 2014). Other reports have not detected such associations between aMF-related white matter integrity and behaviour (Schaechter et al., 2009). The present multivariate approach showed that aMF_a FA was associated with residual motor output, most strongly when the positive relationship of the CST_a was taken into account. Statistical consideration of aMF_a alone revealed a clearly reduced, functional relevance for motor function, a finding well in line with another trial on chronic stroke patients (Schaechter et al., 2009). To some extent, this might argue for a limited influence of aMF to residual motor function compared to that of the CST, a finding which could not be inferred, even though plausible, from previous univariate analyses.

Studies have already reported an association between aMF and residual motor functioning (Rüber et al., 2012) or a relevant role for functional gains under therapy (Lindenberg et al., 2012) positive in nature. In contrast, our model suggests a negative association between mesencephalic aMF_a FA and residual motor output. This finding may be explained as follows: Higher FA has been widely related to better white matter microstructure, both in areas with coherent, densely packed parallel fibers such as in the internal capsule or the corpus callosum, but also in subcortical regions with more complex fiber orientations. It has been associated with superior performance in healthy participants and patients with neurological disease. Along this consideration, FA reduction, as in the present analysis both for CST_a and aMF_a, would be best interpreted as remote lesion effects and Wallerian degeneration of descending fiber tracts. Why should a degenerated aMF_a exhibit an inverse relationship to behaviour in contrast to other white matter tracts such as the CST? In fact, FA depends of various microscopic factors such as axonal coherence, fiber density and thickness or myelinisation (Beaulieu, 2002). Its interpretation is neither straightforward nor completely understood, particularly in white matter with more complex microstructure (e.g., crossing fibers with multiple fiber orientations per voxel). Therefore, lower FA might be alternatively related to adaptive plastic reorganizational processes after stroke, e.g., axonal sprouting, synapto-genesis or changes in myelinisation and could therefore also associate with better outcome. This argumentation might lead to the speculation that CST_a and aMF_a might undergo differential changes at the microscopic level in response to a stroke, i.e., a strong Wallerian effect particularly on the CST leading to a reduced FA, while notable reorganizational processes, in addition to Wallerian processes, might drive the FA reduction in aMF. Notably, also other studies have reported negative associations between FA and behaviour (Roberts et al., 2013). This special aMF characteristic in the context of structural imaging after stroke is further emphasized by an interesting finding in post-acute (Yeo and Jang, 2010), subacute (Takenobu et al., 2014) and chronic stroke patients (Rüber et al., 2012). It has been shown that white matter directly in the red nucleus or its vicinity gradually increased after stroke while FA decreases are normally anticipated in numerous brain regions (Schaechter et al., 2009). Univariate analyses have reported rather inconsistent results showing both positive (Takenobu et al., 2014) and negative (Rüber et al., 2012) associations of this FA increment with motor function. Also these studies have speculated about plastic remodeling with synaptic reorganization of aMF to compensate for CST injury (Buffon et al., 2005). To investigate this further, a post-hoc analysis of the final model including CST_a and aMF_a (corrected for *Age* and *Dom*) was conducted to examine the influence of two other established diffusion metrics which are axial/parallel (AD) and radial/perpendicular (RD) diffusivity. These metrics have been suggested to reflect axonal injury or processes of myelination, respectively (Alexander et al., 2011; Basser and Pierpaoli, 1996; Pierpaoli et al., 2001). However, two separate models based on AD or RD values for CST_a and aMF_a, respectively, did not provide additional information: For AD, there was a similar significant positive influence of CST_a ($p = 0.04$) and a negative influence of aMF_a ($p = 0.03$). For RD, there was a strong negative influence for residual motor function for CST_a ($p = 0.003$) and at least a positive trend for aMF_a ($p = 0.07$). Given that FA values have been suggested to share information of AD and RD on one hand, and the present post-hoc AD/RD models were inferior when compared with the primary FA model (multiple $R^2 = 0.30$) on the other, reasonable additional conclusions cannot be drawn. Hence, the precise nature of aMF alterations after stroke and

their potential role for motor recovery still remains relatively vague. It might also depend from stroke severity, location or the stage of recovery. Longitudinal studies and other imaging techniques such as magnetization transfer ratio for the quantification of myelinisation might be helpful to investigate this further (Lin et al., 2015).

Nevertheless, all of these human imaging data and previous non-human primate data suggest that aMF might support motor outcome in patients with CST damage (Belhaj-Saïf and Cheney, 2000; Kinoshita et al., 2012; Lawrence and Kuypers, 1968a, 1968b; Zaaimi et al., 2012). More recently, an interesting concept has been proposed that aMF_u might contribute to motor function negatively to positively depending from CST_a white matter integrity (Bradnam et al., 2013). This would lead the way towards an interrelationship between both corticofugal pathways: Could the CST influence the functional relevance of aMF regarding recovery after stroke? However, such cross-network interactions have not been addressed so far. The present combined analysis now shows that the influence of aMF_a is detectable in late subacute stroke patients and appears independent from the level of damage to the CST_a, an interaction was not present. AMF_u was not found to be significantly correlated with motor output. Thus, at this point, our structural data cannot corroborate the suggested functional concept by Bradnam and colleagues (Bradnam et al., 2013). Whether it really holds true has to be evaluated by future longitudinal studies from the acute to the chronic stage after stroke using the present methodology.

Some limitations are worth to consider. First, late subacute stroke patients were included in the present study. Whether the present findings are also evident in the acute stage and chronic phases of recovery has to be investigated in upcoming studies. Longitudinal studies would be needed to answer the question how the contribution of aMF to motor function might change over time. Moreover, we need to understand better the contribution of the lesion itself and the influence of patient-specific brain anatomy as an individual prerequisite for motor recovery. Second, in this analysis we used common tract averages derived from healthy controls to estimate tract-related FA for CST and aMF in each stroke patient. These trajectories might differ to individual brain anatomy. In this context, the aMF template has most likely covered a broad range of alternate motor fibers passing this area, including more lateral rubro-spinal and more medial reticulo-spinal, vestibulo-spinal and tecto-spinal pathways (Naidich et al., 2009). Indeed, there are open controversies to what extent the former is evolutionally regressed in humans (Onodera and Hicks, 2010) and whether the reticulo-spinal pathways might be more important (Baker, 2011; Bradnam et al., 2013; Kinoshita et al., 2012; Zaaimi et al., 2012). The current spatial resolution of the brain imaging limits the analysis of these distinct tracts of aMF. Future studies with improved resolution will have to address this further. Third, the CST and aMF were investigated based on clear hypotheses. Other cortico-subcortical tracts, e.g., between motor cortex and basal ganglia, or cortico-cerebellar connections might influence the present models. Finally, the present results and interpretation were inferred from rather simple statistical modeling looking for additive and interactive influences of CST and aMF for residual motor function in stroke patients. This simplified exploratory approach might be susceptible for unknown confounders or epiphenomena and does not prove causality. Hence, the actual neurophysiologic relationships might be overestimated. However, other means, such as virtual lesion approaches for cortical areas, are not available at the moment to address the present question. Future multimodal studies are needed to confirm or correct the present findings.

5. Interpretation

In summary, the present data show that the structural states of the CST and also – to a smaller degree – of the aMF correlate with residual motor output in late subacute stroke patients. The absence of a significant interaction between both tracts, a novel finding which could not be assessed by the previous analyses, suggests that both corticofugal pathways act synergistically but largely independently. Future work is needed to shed further light on CST and aMF relevance in the context of other structural and functional network parameters and clinical measures, such as the presence of upper limb spasticity or synergistic proximal movements.

Conflict of interests

Nothing to declare.

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Appendix A. Supplementary data

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