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White matter integrity of premotor–motor connections is associated with motor output in chronic stroke patients

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ABSTRACT

Corticocortical functional interactions between the primary motor cortex (M1) and secondary motor areas, such as the dorsal (PMd) and ventral (PMv) premotor cortices and the supplementary motor area (SMA) are relevant for residual motor output after subcortical stroke. We hypothesized that the microstructural integrity of the underlying white matter tracts also plays a role in preserved motor output. Using diffusion-tensor imaging we aimed at (i) reconstructing individual probable intrahemispheric connections between M1 and the three secondary areas (PMd, PMv, SMA) and (ii) examining the extent to which the tract-related microstructural integrity correlates with residual motor output. The microstructural integrity of the tract connecting ipsilesional M1 and PMd was significantly associated with motor output ($R = 0.78$, $P = 0.02$). The present results support the view that ipsilesional secondary motor areas such as the PMd might support M1 via corticocortical connections to generate motor output after stroke.

1. Introduction

Functional imaging studies (Grefkes et al., 2008; Rehme et al., 2012; Ward et al., 2003a, 2003b) and electrophysiological experiments (Johansen-Berg et al., 2002a; Fridman et al., 2004) have revealed that corticocortical interactions between the primary motor cortex (M1) and secondary motor areas, such as the dorsal (PMd) and ventral (PMv) premotor cortices and the supplementary motor area (SMA) are particularly relevant for motor recovery and residual motor output after subcortical stroke. Connectivity analyses have demonstrated less effective communication between premotor areas and M1 in the affected hemisphere in the early stage after stroke. Subsequent reinstatement of effective coupling was associated with functional improvement (Rehme et al., 2011). Interventional studies have revealed that ipsilesional premotor areas might take over functions that are not controlled by these areas in healthy individuals (Fridman et al., 2004; Ward, 2011).

As the structural integrity of the underlying corticocortical pathways of the motor network is an important basis for neuronal information throughput and relevant for behavior (Schulz et al., 2014), we questioned whether the microstructural integrity of corticocortical white matter tracts might also contribute to motor output after stroke. At the corticospinal level, it has been already shown that the motor output critically relies on the integrity of the corticofugal fibers (Werring et al., 2000; Schaechter et al., 2009; Sterr et al., 2010; Zhu et al., 2010). Tracing (Catsman-Berrevoets and Kuypers, 1976; Dum and Strick, 1991; He et al., 1993; He et al., 1995; Dum and Strick, 1996) and structural imaging studies (Newton et al., 2006; Schulz et al., 2012) have shown that contributions to corticospinal fibers arise not only from M1 but also from secondary motor areas, such as PMd, PMv or SMA. Partly, the integrity of these corticofugal pathways has predicted additional variance in motor output (Newton et al., 2006; Schulz et al., 2012) and treatment gains in chronic stroke patients (Riley et al., 2011).

We hypothesized that such a structure–behavior relationship might also hold true for the structural integrity of specific corticocortical pathways between the primary motor cortex and these three secondary motor areas and motor outcome which has not been investigated so far. Using diffusion-tensor imaging we aimed at (i) reconstructing probable intrahemispheric connections between M1 and both PMd, PMv and SMA and (ii) examining the extent to which tract-related microstructural integrity correlates with preserved motor output in patients with subcortical stroke.

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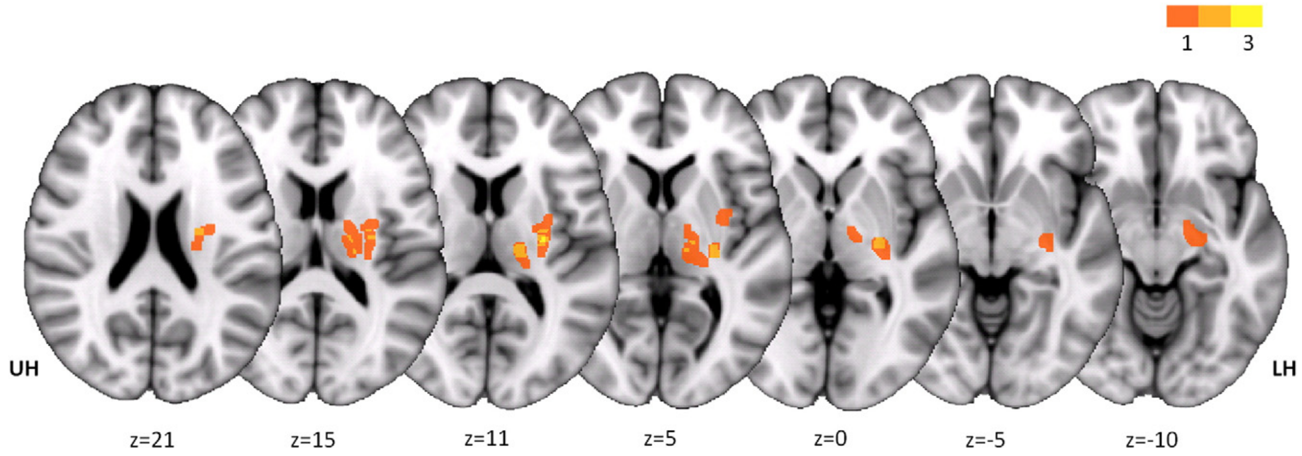

Fig. 1. Lesion locations. Subcortical strokes are overlaid on axial MNI T1 slices (z-values in Montreal Neurological Institute (MNI) standard space). Brains with right-sided lesions were flipped over the mid-sagittal plane. Color bar indicates the number of subjects in which voxels are considered part of the lesion. UH unaffected hemisphere, LH lesioned hemisphere.

2. Participants and methods

2.1. Participants and clinical data

Ten right-handed patients (mean age 62.4 years, range 30–76, 6 males) with first-ever subcortical strokes (5 in the dominant hemisphere, see Fig. 1 for lesion location and Table 1 for clinical data) in the chronic stage of recovery were recruited from a larger study population of a longitudinal study, focusing on longitudinal changes in intracortical inhibition (Liuzzi et al., 2014). Initial motor deficit included weakness of at least the small hand muscles between 3 and 4 on the Medical Research Council Scale (MRC). In a cross-sectional design (11.6 ± 0.6 months after stroke), the patients were re-evaluated on grip strength, pinch strength and finger tapping speed. For the former assessments, the mean value (in kg) of three consecutive measurements separated by approximately 30 s of rest was calculated. For the latter, patients were seated in front of an electronic keyboard in an upright position with the forearm lying on a table. They were instructed to press a specific key with the paretic index finger as quickly as possible for a total of 10 s. This task was repeated three times with an approximately thirty second rest in between repetitions. Finger tapping was defined as the mean number of taps in the three repetitions. The three behavioral scores were expressed as the ratio (affected hand/unaffected hand, Table 1). Based on them, one composite motor output score (MO) was calculated applying a factor analysis with principal component extraction. Explaining 78.6% of the behavioral variance, this score was used for further analyses (Table 1). Patients gave written informed consent according to the Declaration of Helsinki. The study was approved by the local ethics committee.

Table 1
Clinical data. Age (in years) and sex (M male, F female), stroke location, affected hemisphere (R right, L left). Time in months after stroke. Relative grip and pinch force and finger tapping (FT) speed (ratio affected/unaffected hand, dimensionless) merged to one composite motor output score (MO). PLIC posterior limb of the internal capsule, CR corona radiata, TC thalamocapsular, LC lenticocapsular.

Patient	Age	Sex	Stroke	Hemisphere	Time	Grip	Pinch	FT	MO
1	69	F	PLIC	R	10.1	0.55	0.77	0.76	−1.89
2	68	F	CR	R	8.6	0.73	0.82	0.90	−0.99
3	67	M	PLIC	L	8.8	1.51	1.42	1.44	3.30
4	65	M	CR	L	12.9	0.93	1.02	0.97	0.02
5	30	F	TC	L	12.4	1.17	0.91	0.92	0.18
6	47	M	LC	R	11.6	0.96	0.79	0.87	−0.64
7	60	M	CR, LC	R	13.3	0.88	0.85	0.77	−1.00
8	76	F	TC	R	13.6	0.65	1.24	0.67	−1.02
9	69	F	TC, PLIC	L	12.7	1.10	1.56	1.13	1.80
10	70	M	PLIC	L	11.7	1.03	0.96	1.01	0.23

2.2. Brain imaging

A 3 T Trio Siemens MRI scanner (Erlangen, Germany) was used to acquire both diffusion- and T1-weighted images in the stroke patients and a group of nine healthy, age- and gender-matched controls (mean age 65.1 years, range 60–71, Student's T-test $P = 0.58$; 3 males, Fisher's exact $P = 0.37$). Probabilistic tractography was carried out using the FSL 4.1 software package (http://www.fmrib.ox.ac.uk/fsl) to reconstruct probable intrahemispheric pathways connecting hand representations of M1 and PMd, PMv and SMA. Individual tracts were used to calculate tract-related and subject-specific mean fractional anisotropy (FA), a surrogate parameter for white matter integrity. FA values were calculated for both the affected and unaffected hemispheres, and proportional FA values (affected/unaffected hemisphere, Schulz et al., 2012) were used for correlation and multiple regression analyses with MO. For imaging details see the online-only data supplement.

2.3. Statistics

One-way and repeated measures (RM) analyses of variance (ANOVA) were used for between and within group comparisons (GROUP) with within-factors TRACT and, for tract volumes and absolute FA values, HEMISPHERE. For group comparisons, four of the control participants were randomly selected and assigned to right (R) versus left (L) tract-related FA proportionality, while L/R proportionality was calculated for the other five. Accordingly, right or left hemispheric absolute FA/tract volumes values were compared with the lesioned (LH) or unaffected hemisphere (UH) in the stroke patients to account for hand dominance. Partial correlation analysis of proportional tract-related FA values and MO were used to infer tract-related structure–behavior relationship. Multiple linear regression analysis was conducted in a stepwise fashion, inclusion/exclusion was determined by F probability of $P < 0.05$ for inclusion and $P > 0.1$ for exclusion. Statistical significance was assumed at P-values ≤ 0.05. All results are given as mean ± standard error of the mean (SEM). Statistical analysis was conducted using SPSS 19 software (IBM Corp., NY, US).

3. Results

3.1. Clinical and behavioral data

Clinical and behavioral data are listed in Table 1. For locations of subcortical strokes please see Fig. 1.

A one-way ANOVA revealed a significant effect of the side of the lesion (dominant or non-dominant hemisphere) on MO. Regardless of the initial deficit or amount of recovery over the past year, which was not