Assessing the Integrity of Corticospinal Pathways From Primary and Secondary Cortical Motor Areas After Stroke

Robert Schulz, MD; Chang-Hyun Park, PhD; Marie-Hélène Boudrias, PhD; Christian Gerloff, MD; Friedhelm C. Hummel, MD*; Nick S. Ward, MD*

Background and Purpose—Aside from the primary motor cortex, the corticospinal tract (CST) also receives fibers from dorsal and ventral premotor cortices and supplementary motor area, all of which might potentially contribute to motor function after stroke. We sought to quantify the microstructural integrity of CST originating from the hand representations in these 4 motor cortices separately and examined how these values related to hand motor impairment.

Methods—Probabilistic tractography from functional MRI-defined cortical sites demonstrated continuous CST originating from hand representations within each motor area in a group of healthy subjects. Microstructural integrity for each tract was calculated using fractional anisotropy at the level of the posterior limb of the internal capsule in a group of patients with chronic stroke.

Results—Fractional anisotropy was reduced in all 4 CSTs in the affected hemisphere. Grip strength correlated with the integrity of the CSTs originating from primary motor and dorsal premotor cortices, whereas, in a multiple regression model, the latter improved the ability of primary motor cortex CST to explain variability in grip strength.

Conclusion—Handgrip critically depends on the CST originating in primary motor cortex but microstructural integrity of CST originating from premotor cortices appears to play a role in supporting motor function after stroke. (Stroke. 2012; 43:2248-2251.)

Key Words: corticospinal | diffusion | M1 | motor | premotor | recovery | stroke

Motor function after stroke critically depends on corticospinal tract (CST) integrity. Diffusion tensor imaging has addressed this structure–function relationship for the degree of damage to CST fibers originating from the primary motor cortex (M1). Although M1 contributes the majority of the fibers to the CST, significant contributions also arise from secondary motor areas such as the dorsal (PMd) and ventral (PMv) premotor cortex and the supplementary motor area (SMA).1,2 There is still limited knowledge to what extent these non-M1 contributions to the CST might be important for motor performance after stroke.3 We used diffusion tensor imaging (1) to quantify the microstructural integrity of CST originating from functionally defined M1, PMd, PMv, and SMA separately in a group of patients with chronic stroke; and (2) to examine the extent to which tract-specific integrity contributes to motor impairment.

Materials and Methods
Thirteen right-handed patients with chronic stroke with a range of upper limb weakness (assessed by the ratio of affected/unaffected hand grip strength) underwent brain MRI. In 9 age-matched healthy volunteers, we performed probabilistic tractography to reconstruct common CST originating from functional MRI-defined upper limb representations4 in each of M1, PMd, PMv, and SMA to the pontomedullary junction. At the level of the internal capsule, these common tracts were further analyzed: (1) a center-of-gravity analysis was performed to infer tract-specific topography of the CST within the posterior limb of the internal capsule (PLIC); (2) the microstructural integrity of the 4 tracts (fractional anisotropy [FA]) was calculated as proportional FA values (affected/unaffected hemisphere); and (3) correlation and multiple regression analysis were conducted to assess how well tract-specific FA could account for variability in grip strength in the patient group. Additionally, a voxelwise whole-brain analysis identified areas in which white matter tract damage correlated with grip strength. Results are presented as mean±SEM. Statistical significance was assumed at $P<0.05$, Bonferroni-corrected (online-only Data Supplement).

Results

Topological Organization of CST Based on Probabilistic Tractography
Probable CSTs from handgrip related cortical seed areas M1, PMd, PMv, and SMA were obtained in healthy subjects (Figure 1A). Fibers originating from M1 and PMd formed
separate white matter bundles leaving the hand-knob and the adjacent precentral gyrus, which then enter the corona radiata. Within PLIC (Figure 1B), the M1 tract resides at a posterior and lateral location with some overlap with the PMd tract, which is located more anteriorly. PMv and SMA trajectories were located more anteriorly compared with the one from M1 (online-only Data Supplement). Converging at lower z-values, all fiber bundles could be followed continuously to the target zone at the pontomedullary junction (Figure 1A, z = −44).

The CST originating from M1, PMd, PMv, and SMA connecting grip-related cortical seed areas and caudal pontine target zone. A, CST originating from M1, PMd, PMv, and SMA connecting grip-related cortical seed areas and caudal pontine target zone. B, Topographical CST distribution within PLIC with M1 located posteriorly, PMd, PMv, and SMA following in a posteroanterior direction. Framed voxels indicate the center of each CST. Binarized CSTs common to the group overlaid on a MNI-FA template. Axial slices at given z-values. CST indicates corticospinal tract; M1, primary motor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; SMA, supplementary motor area; PLIC, posterior limb of the internal capsule; MNI, Montreal Neurological Institute; FA, fractional anisotropy.

Figure 1. A, CST originating from M1, PMd, PMv, and SMA connecting grip-related cortical seed areas and caudal pontine target zone. B, Topographical CST distribution within PLIC with M1 located posteriorly, PMd, PMv, and SMA following in a posteroanterior direction. Framed voxels indicate the center of each CST. Binarized CSTs common to the group overlaid on a MNI-FA template. Axial slices at given z-values. CST indicates corticospinal tract; M1, primary motor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; SMA, supplementary motor area; PLIC, posterior limb of the internal capsule; MNI, Montreal Neurological Institute; FA, fractional anisotropy.

Tract-Specific White Matter Integrity and Motor Impairment
In patients with stroke (see Figure 2A for lesion locations), proportional FA values (microstructural integrity) were non-specifically reduced for all 4 tracts in the affected hemispheres (Figure 2B). The integrity of the CST originating from M1 and PMd showed positive correlations with grip strength (Figure 2C). Age and time since stroke did not correlate with impairment. To estimate the extent to which each CST predicts motor impairment, we performed a multiple regression analysis. The winning model included the M1 and also the PMd tract-specific proportional FA (Table). PMv and SMA tract-specific FA did not improve this model.

Voxelwise Correlation Analysis of White-Matter Tract FA
Grip strength depends on fiber tracts more posteriorly located within PLIC originating from M1 and PMd. To verify this functional topography in an unbiased way, we performed a whole brain voxelwise analysis. In fact, handgrip specifically depends on the integrity of the posterior parts of PLIC at superior and inferior levels and the posterior corona radiata (Figure 2D). Given distinct CST PLIC topography and a particular functional impact of the more posterior tracts, we combined both independent approaches. Indeed, the overlap between tract-based spatial statistics-derived clusters and the ipsilesional motor tracts (corrected for side of the infarct) was largest for M1 with 88% followed by 67% for PMd, 40% for PMv, and 36% for SMA, respectively.

Discussion
Aside from M1,5 secondary motor areas such as PMd, PMv, and SMA2,3 also contribute fibers to the CST which might be relevant for motor function after stroke. Here, we sought to investigate this tract-specific structure–function relationship focusing on 2 novel aspects.

First, previous studies used the whole of a particular cortical region as seed regions for CST reconstruction. We used functional MRI-defined hand representations in each cortical region to calculate continuous tracts with a consistent anteroposterior topography within PLIC.6 In fact, without any formal proof of superiority, a post hoc analysis suggested that our approach might be beneficial in predicting grip strength with CST integrity data (online-only Data Supplement). Second, the degree of damage to each CST has been previ-
ously inferred from its spatial overlap with the stroke lesion.2,3 Here we report reduced tract-specific FA within PLIC reflecting damaged white matter microstructure due to the infarction itself and consequent Wallerian degeneration of the CSTs remote from the lesion at least in some patients. As shown for M1, the latter occurs in the acute and chronic stage and correlates with persistent motor impairment5 and functional gains during therapy.7

We show that grip strength after stroke most strongly relates to the integrity of the CST originating from the hand representation of M1 and that CSTs from premotor regions such as PMd appear to play a supporting role. Likewise,
compared with CSTs from PMv and SMA, these tracts also predicted treatment gains under therapy best. However, considering the small number of subjects, technical limitations (online-only Data Supplement) and the heterogeneous locations of the stroke lesions, caution is advised when inferring tract-specific functional meaning for handgrip after stroke. For instance, pontine lesions in 3 patients may affect the FA measures within PLIC. Also, we cannot exclude that lesions to the basal ganglia may influence motor function irrespective of CST integrity. However, because the majority of variance in grip strength is explained by the microstructural status of the CST in the internal capsule, we assume that such infarctions might not explain everything. Larger studies applying more powerful regression analyses are needed to answer how CSTs originating in primary and secondary motor areas are related and where they functionally dissociate themselves from each other.

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Disclosures
None.

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| Table. Multiple Regression Results of Tract-Specific FA and Grip Strength |
|---|---|---|---|---|
| Model | Included Variable | Model Summary R | Corrected R² | ANOVA F | P Value |
| | | | | B Value | Beta | P Value |
| 1 | M1 | 0.871 | 0.736 | 34.5 | <0.001 |
| 2* | M1 | 2.761 | 1.717 | 0.001 |
| +PMd | 0.921 | 0.817 | 27.9 | <0.001 |

FA indicates fractional anisotropy; ANOVA, analysis of variance; M1, primary motor cortex; PMd, dorsal premotor cortex.

*Winning model.
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脳卒中後の一次および二次皮質運動野からの皮質脊髄路の健全性の評価

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脳卒中後の一次および二次皮質運動野からの皮質脊髄路路（CST）は、一次運動野のほかに、脳卒中における運動障害の原因である。脳卒中後の運動機能の復帰性がある。我々は、これら4つの運動野における手の領域から脳卒中後のCSTの微細構造の健全性の変化を評価した。これらの検査手の運動障害の原因であるかを評価した。

方法：機能的MRIで明確にされた皮質部位からの確率的トラクトグラフィ（probabilistic tractography）により、健康な被験者のグループにおいて、各運動野内手の領域から脳卒中後のCSTの微細構造の健全性を評価した。CSTの微細構造の健全性を、慢性期脳卒中患者のグループを対象に、内包後肢のレベルで異方性度（fractional anisotropy）を用いて評価した。

結果：異方性度は、4つのCSTすべてにおいて患側半球で低かった。握力は一次運動野および脳卒中後のCSTの健全性と関連していた。一方、重心モデルにおいて、握力は握力の変動を説明する一次運動野CSTの能力を向上させた。

結論：握力は一次運動野に影響するCSTに影響をもたらすが、脳卒中後の運動機能の補助では運動前野に影響するCSTの微細構造の健全性が役割を果たしているようである。

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