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The relationship between TMS measures of functional properties and DTI measures of microstructure of the corticospinal tract

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Background

Recently, a link between resting motor threshold (RMT) and local tissue microstructure, as indexed by fractional anisotropy (FA), was demonstrated in large parts of white matter. However, regions showing such correlations were generally found outside of the corticospinal tract (CST). Therefore, the question arises whether other electrophysiologic measurements could be more locally related to microstructural properties of the CST. In this study, we explored the relationship between such measurements and regional FA in a group of healthy volunteers.

Objective/Hypothesis

We hypothesized that RMT might be more related to an overall susceptibility of white matter to TMS, whereas other electrophysiologic markers might be more specifically related to properties of the CST only.

Methods

Thirty-seven subjects were included. We studied RMT, active motor threshold (AMT), intensity to evoke a motor-evoked potential (MEP) of 1 mV (S1mV), MEP input-output curve (IO-curve), and central motor conduction time (CMCT) using transcranial magnetic stimulation, and FA of the corticospinal tract using diffusion tensor magnetic resonance imaging. We performed voxel-wise and TBSS correlation analysis between these electrophysiologic measurements and FA. In addition, we tested for significant correlation between these parameters and mean diffusivity (MD).

Results

On voxel-wise analysis, we did not detect significant correlations between any electrophysiologic parameter (RMT, AMT, S1mV, IO curve slope, CMCT) and FA. With TBSS, we detected correlations between FA and bilateral AMT, as well as left-hemispheric S1mV, but these correlations were found in locations unlikely to contribute to motor pathways.

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Conclusions
Although a relationship between structure and function has been shown in many other regions of the brain, it seems to be much more challenging to demonstrate such a relationship in the CST of healthy subjects.

Keywords corticospinal tract; transcranial magnetic stimulation; motor threshold; central motor conduction time; diffusion tensor imaging

The relationship between anatomy and function in the human brain has drawn scientists' attention for many decades. The corticospinal tract (CST) is a main focus of such research because of its obvious importance, but also because motor responses are readily accessible for measurements. Transcranial magnetic stimulation (TMS)[1] is a noninvasive technique that enables probing of functional parameters of the CST in the living human brain. By applying short magnetic transients of great magnitude, a small current is induced in cortex and adjacent white matter.

When exciting primary motor area (M1), volleys of excitation descend the CST and generate motor responses. In M1, TMS generates these volleys mainly by indirect excitation of M1 Betz cells via cortico-cortical axons,[2,3] rather than direct stimulation of these cell bodies. The resting motor threshold (RMT) is a parameter of the excitability of M1, that is, the minimum stimulation intensity needed to elicit a predefined, small motor response.[4] There is variability of RMT across subjects, and it is a matter of debate which properties of study subjects exert an influence on RMT. Straight-forward geometric issues aside, for example, the inverse relationship between coil-to-cortex distance (CCD) and RMT,[5,6] one such property under discussion is local tissue microstructure, and recent advances in diffusion magnetic resonance imaging (MRI) allow now for its semi-quantitative assessment.[7-9]

The most commonly used measure to assess tissue properties with diffusion MRI is fractional anisotropy (FA), a cumulative measure of the amount of "directionality" of free water diffusion in a given volume element. This directionality is a consequence of white matter fibers hindering perpendicular diffusion more strongly than diffusion along fibers, leading to anisotropic diffusion profiles. Similarly, mean diffusivity (MD) is a quantitative measure of the amount of free water diffusion, which is hindered by the presence of diffusion barriers in the tissue.

As summative measures, no single property of white matter explains FA and MD variability in the human brain. Rather, axon density, the degree of myelination, and axon diameter have been shown to take influence on both measures.[9]

Recent research suggested a link between RMT and FA that is spread around much of the white matter of the human brain.[10] However, there was no local correlation between FA and RMT in the posterior part of the internal capsule, where the CST descends.

Therefore, the question arises whether other electrophysiologic measures of corticospinal excitability and function could be more locally related to microstructural properties of the CST. In particular, we hypothesized that whereas RMT is likely more related to local axonal excitability of cortico-cortical fibers projecting onto corticospinal neurons,[11] other measures such as the motor-evoked potential (MEP) input-output curve (IO-curve) or the central motor conduction time (CMCT) are likely more specifically related to properties of the CST.[12]

In the study presented here, we explore the relationship between such TMS measures and regional measures of diffusivity, using voxel-wise statistical analysis and tract-based spatial statistics (TBSS) in a group of healthy volunteers.

Material and methods

Subjects

Thirty-seven healthy, right-handed subjects (21 females), aged 23 to 75 years (mean age, 42.7 ± 14.6 years) participated in the study. All subjects were healthy without history of neurologic or psychiatric disease. All subjects were right handed with a lateralization index >0.7 according to the Edinburgh Handedness inventory.[13]

Because age constitutes a strong confound with respect to diffusivity measures[14] and electrophysiologic measures of CST function,[15] we also performed an additional analysis on a subgroup limited to younger subjects with a narrower age range (n = 18, mean age, 30.2 ± 5.3 years).

All subjects gave written informed consent. The experiments conformed to the declaration of Helsinki and were approved by the ethics committee of the University Hospital Frankfurt.

Electromyography-recording

Surface electromyography (EMG) was recorded from the first dorsal interosseous muscle (FDI) of both hands using Ag-AgCl electrodes in a belly-tendon montage. The EMG was amplified and band-pass filtered (20-2.000 Hz) (Counterpoint Electromyograph, Dantec Electronics, Skovlunde, Denmark), digitized at a sampling rate of