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Anatomical and functional correlates of cortical motor threshold of the dominant hand

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ABSTRACT

Background: Resting Motor threshold (rMT) provides information about cortical motor excitability. Interestingly, the influences of the structural or functional variability of the motor system on the rMT inter-individual variability have been poorly investigated.
Objective/hypothesis: To investigate relationships between rMT and measures of brain structures and function of the motor system. The hypothesis is that cortical excitability not only depends on the primary motor cortex (M1) but also on the integration of information originating from its vicinity such as pre-motor (PMd and SMA) and post-central (S1) cortices.
Methods: We measured brain structures, including grey and white matter properties (cortical volume and fiber coherence respectively), and functional interaction (resting-state functional connectivity-FC) in areas contributing to the corticospinal tract axons, i. e, M1, S1, SMA and PMd in the dominant hemisphere of 21 healthy subjects.
Results: The rMT was inversely correlated with the FC between PMd and M1 ($r = -0.496$, 95% CI: −0.764; −0.081; $p = 0.02$) and the grey matter volume of the dominant hemisphere ($r = -0.463$, 95% CI: −0.746; −0.039; $p = 0.03$). The multiple regression analysis model retained the FC between M1 and PMd (coefficient: -25 ± 9) as well as the grey matter volume of the dominant hemisphere (coefficient: -0.15 ± 0.06) explaining 44% of the variance of the rMT (p: 0.005). When adding age and coil-to-cortex distance, two factors known to influence rMT, the model reached a R2 of 75% (p: 0.0001).
Conclusions: These results underline the major role of the PMd and the cortico-cortical connections toward M1 in the excitation of the corticospinal fibers likely through *trans*-synaptic pathways.

Introduction

The corticospinal tract (CST) is of paramount importance in the motor system given that it enables voluntary movements of distal extremities, and particularly fine motor activities of the hand. CST axons originate from pyramidal cells that arise from large area extending far beyond the primary motor cortex [1]. The advent of imaging techniques such as diffusion tensor imaging (DTI) has greatly advanced understanding of CST anatomy [2] and showed that the primary motor cortex (M1), the primary sensorimotor cortex (S1), the supplementary motor area (SMA) and the dorsal

Abbreviations: rMT, resting motor threshold; M1, primary motor cortex; PMd, dorsal premotor cortex; SMA, supplementary motor area; S1, somatosensory cortex; CST, corticospinal tract; CCD, coil-to-cortex distance; DH, dominant hemisphere; NDH, non-dominant hemisphere; FA, fractional anisotropy; LTP, long-term potentiation; ROI, region-of-interest; TMS, transcranial magnetic stimulation; DTI, diffusion tensor imaging.

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premotor cortex (PMd) contributed to 37%, 32%, 25% and 7% respectively of CST axons in healthy humans [3].

Transcranial magnetic stimulation (TMS) is a common non-invasive technique that enables probing of functional parameters of the CST. When applied over M1, TMS could evoke a series of volleys travelling down the CST and generating motor responses in the contralateral targeted muscle. These volleys are mainly produced by activation of cortico-cortical axons projecting onto corticospinal output neurons but also by direct activation of M1 Betz body cells [4]. Resting Motor threshold (rMT), defined as the lowest intensity at which single pulse TMS elicits a liminal motor response, is a commonly used parameter that provides information about a central core of neurons in M1 [5]. Given that it is modified by drugs that alter membrane excitability but not by drugs that influence synaptic neurotransmission, it is thought that it mostly reflects *trans*-synaptic activation of corticospinal neurons [6].

Inter-individual variability of rMT is well-known [7]. Although several main sources of variability have been identified including psychoactive treatments intake, aging, and the coil-to-cortex distance (CCD) [8,9], a large part of this inter-individual variability remains to be elucidated. Interestingly, the influences of the structural or functional variability of the motor system (including macro to microstructural variations of brain anatomy or inter-individual variations of brain areas functional interactions) on rMT have been poorly investigated so far [10–14]. In addition, given that TMS suffers from a limited spatial resolution due to the large size of the coil employed, it is conceivable that CST excitability, as assessed by rMT, also depends on the integration of information originating from the vicinity of M1 such as premotor and post central cortices. Therefore, the question arises whether and to what extend CST excitability, as measured by rMT, could be more related to neuroanatomical and neurofunctional determinants of the brain. Identifying factors that influence rMT may benefit the interpretation of studies describing altered cortical excitability in various neurological [15,16] and psychiatric diseases [17,18].

In the present study, we investigated relationships between rMT in the dominant hemisphere of healthy subjects and measures of brain structures, including measures of both grey and white matter properties (cortical volume and fiber coherence respectively), functional interaction (resting-state functional connectivity), in areas contributing to the CST axons, i. e, M1, S1, SMA and PMd. Because of this *a priori* on the motor system, we chose a Region-of-Interest (ROI)-based approach for neuroimaging analysis. Identified factors contributing to rMT variability, including aging and CCD, were also considered.

Materials and methods

Population

Twenty-one healthy participants (10 females), aged 22–65 years with mean ± SD: 35 ± 13 (IQR: 27–31) were enrolled in the study. Nineteen subjects were right-handed according to the Edinburgh Handedness Inventory [19]. Data is derived from a parallel study (Core protocol: NCT 02284087; all data presented in this report was collected before the intervention stage of this study).

Inclusion criteria were (i) no history of neurological or psychiatric disorders, (ii) Mini-Mental State Examination score greater or equal to 27, (iii) age older than 18 years, (iv) no contraindications for MRI or TMS and, (v) no use of psychoactive medication or recreational drugs. The study was approved by the appropriate legal and ethical authority (CPP Ile de France VI–Pitié-Salpêtrière, Paris, France) and was conducted according to the guidelines of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all participants.

MRI

Image acquisition

MRI of the whole brain was performed at 3T (Magnetom VERIO, Siemens, Erlangen, Germany) with a 32-channel head coil. The MR protocol included anatomical three-dimensional (3D) T1-weighted MPRAGE images (TR = 2.3 s; TE = 4.18 ms; flip angle = 9°; TI = 900 ms; voxel size = 1 × 1 × 1 mm^3; 176 slices), and a multiband spin-echo echo-planar diffusion tensor imaging acquired with reversed phase-encode blips (TR = 4 s, TE = 87 ms, voxel size = 2 × 2 × 2 mm^3, 60 slices, 60 gradient AP-encoded directions with a b-value of 1500 s/mm^2 and 60 PA-encoded directions, with 11 non-diffusion-weighted volumes for each). For the resting state functional MRI (rsfMRI), subjects were instructed to close their eyes, thinking of nothing at all and not moving. BOLD contrast images were acquired using an echo-planar pulse sequence (TR = 2460 ms; TE = 30 ms; flip angle = 90°; voxel size = 3 × 3 × 3 mm^3; 200 vol).

Quantification of fractional anisotropy abnormalities in the sensorimotor system

The diffusion image processing was carried out using the FSL software (version 3.3; http://www.fmrib.ox.ac.uk/fsl). Diffusion images were corrected for eddy current distortions Moreover, as data were collected with reversed phase-encode blips resulting in pairs of images with distortions going in opposite directions, we used a second correction method implemented in FSL [20] to combine the image into a single corrected one [21]. Then, Fractional Anisotropy (FA) maps were generated using FDT (FMRIB's Diffusion Toolbox) [22]. MRIs from left-handers were flipped along the median line, in order to have the “dominant hemisphere” as the left hemisphere.

Regions-of-interest (ROIs) were delineated on two contiguous slices of the FA map of each subject in the native space by interactive manual outlining using fslview (fsl.fmrib.ox.ac.uk/fsl/fslview/). M1, PMd and SMA were delineated as described previously by Newton et al. [23]. S1 was defined posteriorly and contiguously to M1 [24]. The regions defined for a single subject are shown rendered on their FA map in Fig. 1. FA values were then extracted from each ROI with a threshold of 0.15, to remove voxels from the grey matter (and keep a measure of the white matter microstructure). FA_{DH}M1 is the FA value in the dominant hemisphere for M1 (or PMd, or S1 or SMA) and FA_{NDH}-M1 is the FA value in the homologous region in the non-dominant hemisphere.

Additionally, we extracted the FA values of the entire corticospinal tract (CST) in the dominant (DH) and non-dominant (NDH) hemisphere using a template [25] available in BCBtoolkit [26] that was denormalized and resliced on each individual FA map.

Resting state fMRI connectivity in regions of interest

Anatomical images were segmented using SPM12 (SPM, http://www.fil.ion.ucl.ac.uk/spm) into CSF, grey and white matter maps and were then normalized in MNI space.

The functional images were pre-processed using SPM12. The functional images were slice-time corrected, realigned to the first volume of the sequence and then normalized to the symmetrical SPM T1-weighted template in the MNI space using the transformation matrix from the anatomical images after coregistration. The functional images were smoothed using an isotropic 8-mm full width at half-maximum Gaussian kernel. The Conn Toolbox [27] was used to remove spurious components such as rapid and slow head movements, physiological activity (breathing and heartbeat) in order to achieve structured noise reduction and improve any subsequent detection and analysis of signal fluctuations related to