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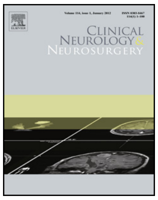

Correlating subcortical interhemispheric connectivity and cortical hemispheric dominance in brain tumor patients: A repetitive navigated transcranial magnetic stimulation study

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ABSTRACT

Objective: The present study aims to investigate the relationship between transcallosal interhemispheric connectivity (IC) and hemispheric language lateralization by using a novel approach including repetitive navigated transcranial magnetic stimulation (rTMS), hemispheric dominance ratio (HDR) calculation, and rTMS-based diffusion tensor imaging fiber tracking (DTI FT).

Methods: 31 patients with left-sided perisylvian brain lesions underwent diffusion tensor imaging (DTI) and rTMS language mapping. Cortical language-positive rTMS spots were used to calculate HDRs (HDR: quotient of the left-sided divided by right-sided naming error rates for corresponding left- and right-sided cortical regions) and to create regions of interest (ROIs) for DTI FT. Then, fibers connecting the rTMS-based ROIs of both hemispheres were tracked, and the correlation of IC to HDRs was calculated via Spearman's rank correlation coefficient (r_s).

Results: Fibers connecting rTMS-based ROIs of both hemispheres were detected in 12 patients (38.7%). Within the patients in which IC was detected, the mean number of subcortical IC fibers ± standard deviation (SD) was 138.0 ± 346.5 (median: 7.5; range: 1–1,217 fibers). Regarding r_s for the correlation of HDRs and fiber numbers of patients that showed IC, only moderate correlation was revealed.

Conclusion: Our approach might be beneficial and technically feasible for further investigation of the relationship between IC and language lateralization. However, only moderate correlation was revealed in the present study.

Abbreviations: aHDR, anterior hemispheric dominance ratio; CC, corpus callosum; CPS, cortical parcellation system; CST, corticospinal tract; DTI, diffusion tensor imaging; DTI FT, diffusion tensor imaging fiber tracking; DCS, direct cortical stimulation; ER, error rate; FA, fractional anisotropy; FACT, fiber assignment by continuous tracking; fMRI, functional magnetic resonance imaging; HDR, hemispheric dominance ratio; IC, interhemispheric connectivity; IAT, intracarotid amobarbital test; MRI, magnetic resonance imaging; pHDR, posterior hemispheric dominance ratio; PTI, picture-to-trigger-interval; RMT, resting motor threshold; ROI, region of interest; r_s, Spearman's rank correlation coefficient; rTMS, repetitive navigated transcranial magnetic stimulation; SD, standard deviation; TMS, transcranial magnetic stimulation.

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1. Introduction

So far, the distinct anatomo-functional relationship between interhemispheric connectivity (IC), predominantly mediated by the corpus callosum (CC), and the degree of language lateralization has only been investigated infrequently in the human brain [1–4]. In this context, it is supposed that the CC is of particular importance for hemispheric language development and specialization [5–7]. Furthermore, it has been assumed that the degree of language lateralization might be closely related to the transcallosal IC between the left and right hemisphere [7,8]. However, only few studies in healthy and neurologically diseased humans have systematically investigated the potential relationship between IC characteristics and language lateralization, leading to partially contradictory results [1–4,9–12]. Besides common neuroimaging modalities like functional magnetic resonance imaging (fMRI), for instance, repetitive navigated transcranial magnetic stimulation (rTMS) can be used for cortical mapping of language-related areas by eliciting different kinds of language errors when applied with high frequency during a cognitive task like object naming, for example [13–17], and previous studies have already successfully employed rTMS for evaluating language lateralization and plasticity [18,19]. In this context, the so-called hemispheric dominance ratio (HDR), which is basically defined as the quotient of the left-sided divided by the right-sided naming error rate (ER) for corresponding left- and right-sided cortical regions, was introduced, and this ratio can be taken for the determination of the degree of hemispheric language lateralization [19].

Since rTMS mapping itself primarily provides language mapping at the cortical level, subcortical language-related structures could be detected by combining this technique with diffusion tensor imaging fiber tracking (DTI FT). However, only one recent case report has demonstrated the feasibility of cortical rTMS language maps for DTI FT of subcortical fiber tracts related to language subfunctions so far [20]. Therefore, the correlation of the HDR with rTMS-based DTI FT for detection of subcortical language-related fiber pathways represents a novel and potentially beneficial approach for investigation of the transcallosal IC—language lateralization relationship. Thus, the present study hypothesizes that transcallosal IC revealed by rTMS-based DTI FT correlates with hemispheric language dominance as the parameter for tumor-induced language shift to the non-dominant hemisphere. Hence, a novel multimodal approach consisting of rTMS for cortical language mapping, rTMS-based DTI FT for evaluation of subcortical language-related IC fiber bundles, and HDR calculation for assessment of hemispheric dominance is presented.

2. Materials and methods

2.1. Patients

A total number of 31 right-handed patients suffering from different kinds of brain lesions affecting perisylvian cortical areas of the left hemisphere were enrolled in the present investigation. Exclusion criteria were age <18 years and general rTMS exclusion criteria, such as the presence of a cochlear implant, deep brain stimulation electrodes, or cardiac pacemaker, for example. The study cohort consisted of 10 female (32.3%) and 21 male (67.7%) subjects. The median age was 38 years (range: 20–63 years). Two patients suffered from astrocytoma WHO grade I (6.5%), and 9 patients were diagnosed with astrocytoma WHO grade II (29.0%). Regarding high-grade gliomas, 4 patients suffered from astrocytoma WHO grade III (12.9%), whereas 11 subjects suffered from glioblastoma WHO grade IV (35.5%). Another 5 patients were diagnosed with arteriovenous malformation (16.1%).

2.2. Neuroimaging

A 3 Tesla magnetic resonance imaging (MRI) scanner (Achieva 3T, Philips Medical Systems, The Netherlands B.V.), in combination with an eight-channel phased-array head coil, was used for preoperative anatomical imaging. The scanning protocol included a T2-weighted FLAIR (TR/TE: 12,000/140 ms, voxel size: $0.9 \times 0.9 \times 4\,\text{mm}^3$, acquisition time: 3 min) and a three-dimensional T1-weighted gradient echo sequence (TR/TE: 9/4 ms, $1\,\text{mm}^3$ isovoxel covering the whole head, acquisition time: 6 min 58 s) with and without contrast enhancement. Furthermore, diffusion tensor imaging (DTI) sequences with six (TR/TE 7571/55 ms, spatial resolution of $2 \times 2 \times 2\,\text{mm}^3$, b-values of 0 and 800, acquisition time: 2 min 15 s) orthogonal diffusion directions were acquired for later DTI FT.

2.3. Repetitive navigated transcranial magnetic stimulation

2.3.1. Experimental setup and protocol

In the present study, the eXimia NBS system (version 3.2.2 or 4.3, Nexstim Oy, Helsinki, Finland) was used for cortical rTMS language mapping of both hemispheres during object naming prior to surgery. Every patient underwent two baseline trials (object naming without simultaneous rTMS) before stimulation, and only the objects that were named correctly and without hesitation were displayed during mapping. The general rTMS language mapping procedure has already been repeatedly outlined in various publications [13–15,17,18,21,22]. Furthermore, all mappings were performed according to a stimulation protocol that has been frequently used in past studies of different research groups [14,15,17,21]. Accordingly, rTMS pulses were applied time-locked to the objects displayed on a screen in front of the patient (display time: 700 ms, inter-picture-interval: 2500 ms), and the picture-to-trigger interval (PTI) was 300 ms in the first 9 patients and 0 ms in the remaining 22 patients. In general, evidence for both PTIs can be found in recent literature [23–26], but we decided to switch to a PTI of 0 ms referring to the benefits of 0 ms for rTMS language mapping shown in a recent publication [22]. Baseline and stimulation performances of each patient were video-recorded for analysis of naming performance during object naming [14].

2.3.2. rTMS data analysis

All stimulation videos were systematically searched for naming errors by comparing them to the corresponding baseline recordings as described in previous studies [13–15,22]. Then, the registered naming errors were classified as no-response errors, performance errors, neologisms, phonological paraphasias, or semantic paraphasias [27]. After video analysis, we transferred all left- and right-hemispheric cortical rTMS spots at which naming errors of the above-mentioned error types were elicited (language-positive spots) to an external BrainLAB iPlan Net server (version 3.0.1, BrainLab AG, Feldkirchen, Germany) via the DICOM standard for later DTI FT.

Furthermore, we used the cortical parcellation system (CPS) for anatomy-related data analysis [15,18,19,27–29]. ERs were calculated by dividing the number of induced naming errors by the number of applied rTMS trains for each error