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Feasibility of nTMS-based DTI fiber tracking of language pathways in neurosurgical patients using a fractional anisotropy threshold

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HIGHLIGHTS

- nTMS maps can be used for DTI FT of subcortical language pathways.
- Language pathways are detectable with nTMS spots as ROI.
- 25% and 50% FAT allow for most favorable DTI FT of language pathways.

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ABSTRACT

Background: Navigated transcranial magnetic stimulation (nTMS) provides language maps in brain tumor patients. Yet, corresponding data on the visualization of language-related subcortical pathways is lacking. Therefore, this study evaluates the feasibility of nTMS-based diffusion tensor imaging fiber tracking (DTI FT) for subcortical language pathways by a fractional anisotropy (FA) protocol.
New method: DTI FT was performed in 37 patients suffering from left-sided perisylvian brain lesions based on nTMS data exclusively, using the FA-based protocol originally established for the corticospinal tract (CST) by Frey et al. (2012): minimum fiber length was 110 mm and the highest individual FA value leading to visualization of white matter tracts was determined as the FA threshold (FAT). Then, deterministic DTI FT using an FA value of 100%, 75%, 50%, and 25% of the individual FAT (with 25% as an additional setting to the original protocol) was performed.
Results: Our approach visualized 9 language-related subcortical white matter pathways. By using 100% FAT, the mean percentage of visualized tracts was 13.5%, whereas DTI FT performed with 75%, 50%, and 25% FAT detected 30.6%, 61.3%, and 93.7% of language-related fiber tracts, respectively.
Comparison with existing methods: nTMS language mapping alone is not able to visualize subcortical language-related pathways.

Abbreviations: 3-D, three-dimensional; AAT, Aachen Aphasia Test; ANOVA, analysis of variance; AVM, arteriovenous malformation; CST, corticospinal tract; DT, display time; DTI, diffusion tensor imaging; DTI FT, diffusion tensor imaging fiber tracking; DCS, direct cortical stimulation; FA, fractional anisotropy; FACT, fiber assignment by continuous tracking; FAT, fractional anisotropy threshold; fMRI, functional magnetic resonance imaging; GBM, glioblastoma multiforme; HARDI, high angular resolution diffusion imaging; IPI, inter-picture-interval; MEG, magnetoencephalography; MRI, magnetic resonance imaging; nTMS, navigated transcranial magnetic stimulation; PDD, principal diffusion direction; PTI, picture-to-trigger-interval; RMT, resting motor threshold; ROI, region of interest; rTMS, repetitive navigated transcranial magnetic stimulation; SD, standard deviation.

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Conclusions: This study shows that nTMS language maps are feasible for DTI FT of language-related pathways within the scope of a FAT-based protocol. Although this approach is novel and might be helpful during scientific neuroimaging and tumor resection, intraoperative validation is needed to go beyond the level of feasibility.

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1. Introduction

The principles of diffusion tensor imaging (DTI) were initially described in the early nineties (Basser et al., 1994; Douek et al., 1991; Moseley et al., 1990). Since then, this magnetic resonance imaging (MRI) method has gained increasing importance for the detection and visualization of subcortical white matter fibers in the living human brain within the scope of DTI fiber tracking (DTI FT). Technically, DTI is based on measuring the diffusivity of water molecules in the brain tissue. Since the main diffusion direction of water molecules is typically oriented parallel to subcortical white matter fiber bundles, the information about diffusion directions allows for fiber reconstruction using a certain tractography algorithm (Catani et al., 2002). Concerning so-called deterministic tractography, only one single diffusion direction per voxel is followed to reconstruct fiber tracts, which can then be integrated into three-dimensional (3-D) anatomic MRI sequences for the simultaneous visualization of subcortical white matter tracts and "conventional" anatomical information.

Roughly all tractography algorithms require the placement (=seeding) of one or more regions of interest (ROIs) into the brain tissue. Conventionally, ROIs are manually created according to anatomical landmarks, but they can also be seeded with respect to individual functional data derived from magnetoencephalography (MEG), functional MRI (fMRI), or navigated transcranial magnetic stimulation (nTMS). So far, a very limited number of studies have used nTMS maps for ROI placement, and the feasibility of this approach has primarily been demonstrated for DTI FT of subcortical motor pathways, such as the corticospinal tract (CST) (Conti et al., 2014; Forster et al., 2015; Frey et al., 2012; Krieg et al., 2012; Weiss et al., 2015). Only one single case report has demonstrated that DTI FT based on nTMS language data could be technically feasible to detect specific language-related tracts in general, and might be furthermore helpful during surgery since it proved to be in good accordance with subcortical stimulation during tumor removal (Sollmann et al., 2015a).

Therefore, the present study investigates the feasibility of nTMS language mapping for ROI seeding and DTI FT of subcortical language pathways in 37 patients with left-sided brain tumors. In this context, a modified fractional anisotropy (FA) based protocol was used to assess feasibility and to evaluate the most suitable parameters for optimal visualization of subcortical language pathways (arcuate fibers, commissural fibers, arcuate fascicle, corticonuclear tract, corticothalamic fibers, superior longitudinal fascicle, inferior longitudinal fascicle, uncinate fascicle, and frontooccipital fascicle).

2. Materials and methods

2.1. Ethics

Written informed consent was obtained from all patients, and the experimental protocol was approved by our local institutional review board (registration number: 2793/10) in accordance with the Declaration of Helsinki.

2.2. Patients

In total, 37 patients who presented with left-sided perisylvian brain lesions in our neurosurgical department were enrolled in the present study. The inclusion criteria were left-sided perisylvian tumor location, age above 18 years, and written informed consent. Exclusion criteria were age under 18 years, other severe neurological diseases, and general nTMS exclusion criteria (e.g., the presence of a cochlear implant, deep brain stimulation electrodes, or cardiac pacemaker).

All patients underwent MRI and repetitive nTMS (rTMS) for the mapping of cortical language-related spots prior to surgery. Furthermore, each patient underwent a thorough clinical examination according to a standardized protocol including coordination, sensory function, muscle strength, and cranial nerve function, which was performed by an experienced medical doctor. The examination protocol was established in 2006 as clinical routine in our department. Furthermore, the individual preoperative language status of each patient was evaluated by a trained neuropsychologist. In this context, the Aachen Apasia Test (AAT) was used (Huber et al., 1984), and, in addition to the AAT, four previously established deficit grades were reported (Krieg et al., 2014a; Sollmann et al., 2015b):

1) No deficit.
2) Mild deficit: undisrupted conversational speech and/or speech comprehension, adequate communication ability to slight amnesic aphasia.
3) Medium deficit: slight impairment of conversational speech and/or speech comprehension, adequate communication ability.
4) Severe deficit: clear impairment of conversational speech and/or speech comprehension, disrupted communication ability.

The aim of the present study was then to evaluate the feasibility of language-related cortical areas mapped by nTMS as ROI for DTI FT in the context of the protocol described by Frey et al. (2012).

2.3. Magnetic resonance imaging

All imaging was performed on the same magnetic resonance scanner (Achieva 3T, Philips Medical Systems, The Netherlands B.V.) through the use of an eight-channel phased-array head coil. Our scanning protocol consisted of a T2-weighted FLAIR (TR/TE: 12,000/140 ms, voxel size: $0.9 \times 0.9 \times 4\,mm^3$, acquisition time: 3 min) and a 3-D T1-weighted gradient echo sequence (TR/TE: 9/4 ms, 1 mm^3 isovoxel covering the whole head, acquisition time: 6 min 58 s) with and without intravenous contrast administration (gadopentetate dimeglumine; Magnograf, Marotrast GmbH). Additionally, DTI sequences (TR/TE 7,571/55 ms) with 6 orthogonal diffusion directions were performed in each patient with *b*-values of 0 and 800. Using parallel imaging (sensitivity encoding factor 2), 2 averages of 73 contiguous 2-mm slices with a matrix of 112°–112 mm covering the whole brain were acquired within 2 min 15 s. Subsequently, all DTI data were interpolated to a matrix of 224°–224, which resulted in a voxel size of 0.88°–0.88°–2 mm^3.

The contrast-enhanced 3-D gradient echo sequences of each patient were then exported to the Nexstim eXimia NBS system

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