Language pathway tracking: comparing nTMS-based DTI fiber tracking with a cubic ROIs-based protocol

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OBJECTIVE Diffusion tensor imaging (DTI) fiber tracking (FT) has been widely used in glioma surgery in recent years. It can provide helpful information about subcortical structures, especially in patients with eloquent space-occupying lesions. This study compared the newly developed navigated transcranial magnetic stimulation (nTMS)-based DTI FT of language pathways with the most reproducible protocol for language pathway tractography, using cubic regions of interest (ROIs) for the arcuate fascicle.

METHODS Thirty-seven patients with left-sided perisylvian lesions underwent language mapping by repetitive nTMS. DTI FT was performed using the cubic ROIs–based protocol and the authors’ nTMS-based DTI FT approach. The same minimal fiber length and fractional anisotropy were chosen (50 mm and 0.2, respectively). Both protocols were performed with standard clinical tractography software.

RESULTS Both methods visualized language-related fiber tracts (i.e., corticonuclear tract, arcuate fascicle, uncinate fascicle, superior longitudinal fascicle, inferior longitudinal fascicle, arcuate fibers, commissural fibers, corticohalamic fibers, and frontooccipital fascicle) in all 37 patients. Using the cubic ROIs-based protocol, 39.9% of these language-related fiber tracts were detected in the examined patients, as opposed to 76.0% when performing nTMS-based DTI FT. For specifically tracking the arcuate fascicle, however, the cubic ROIs-based approach showed better results (97.3% vs 75.7% with nTMS-based DTI FT).

CONCLUSIONS The cubic ROIs-based protocol was designed for arcuate fascicle tractography, and this study shows that it is still useful for this intention. However, superior results were obtained using the nTMS-based DTI FT for visualization of other language-related fiber tracts.

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KEY WORDS cortical mapping; fiber tracking; language; navigated transcranial magnetic stimulation; space-occupying lesions; subcortical; surgical technique
Yet, the importance of eloquent subcortical structures, the role of subcortical plastic reorganization, and the ongoing shift toward a more hodotopical perspective, describing the language process as an interaction of corticosubcortical subnetworks, cannot be ignored.\(^{9,12,14,18,21,35}\)

Diffusion tensor imaging (DTI) fiber tracking (FT), in particular, has become a frequently used technique in modern neurosurgery, both in the clinical routine and for neuroscientific research purposes. DTI FT can be based on either functional data (provided by functional MRI [fMRI], nTMS, and so on) or anatomical landmarks. One of the most reproducible language-related, anatomically based DTI FT protocols uses 3 cubic seed regions of interest (ROIs), placed according to anatomical landmarks, for visualization of the arcuate fascicle (AF) in patients with space-occupying lesions.\(^{44}\)

Previous studies of nTMS-based DTI FT of the corticospinal tract (CST) have provided promising feasibility data.\(^{10,16,19,49}\) and initial studies with successful repetitive nTMS (rTMS)-based DTI FT of language-related subcortical fiber tracts have been completed.\(^{59}\) Therefore, this study investigated the feasibility and application of rTMS-based DTI FT for language-related subcortical fiber tracts in patients with left-sided perisylvian lesions, and compared rTMS-based DTI FT with a cubic ROIs-based DTI FT protocol to further investigate the benefits and potential limitations of function-based DTI FT with respect to language-related fiber tracts.

**Methods**

**Ethics Approval**

In conformity with the Declaration of Helsinki, the experimental protocol used in this study was certified by the local ethical committee of the Technical University of Munich. All enrolled patients gave their written informed consent to this study before language mapping by rTMS was performed.

**Study Design**

The study was designed to be prospective and nonrandomized.

**Patients**

From May 2011 to August 2014, 37 patients underwent preoperative language mapping by rTMS. Inclusion criteria were left-sided perisylvian lesion, age older than 18 years, and written informed consent. The general rTMS exclusion criteria (e.g., having a cochlear implant or cardiac pacemaker) were applied.

**Preoperative MRI and DTI**

All enrolled patients received preoperative MRI with additional DTI sequences in 6–15 diffusion directions. The navigational MR images were acquired on a 3-T MR scanner (Achieva 3T, Philips Medical System) with an 8-channel phased-array head coil. Our standard protocol included a T2-weighted FLAIR sequence (TR/TE 12,000/140 msec; inversion time of 2500 msec; 30 slices with 1-mm gap; voxel size 0.9 × 0.9 × 4 mm; 3-minute acquisition time), an intravenous contrast administration of gadopentetate dimeglumine, 0.1 mmol/kg body weight (Magnograf, Marotrastr GmbH), and a 3D gradient echo sequence (TR/TE 9/4 msec; 1-mm\(^3\) isovoxel covering the whole skull; 418-second acquisition time). DTI sequences were acquired with a single-shot spin echo planar imaging (TR/TE = 7571/55 msec) with \(b\) values of 0 and 800, and 6 orthogonal diffusion directions or in some cases 15 directions. Parallel imaging techniques were used (sensitivity encoding factor 2), and 2 averages of 73 contiguous 2-mm slices with a matrix of 112\(^2\)–112 mm scanning the whole skull were taken in 135 seconds. The DTI sequences were subsequently added to a matrix of 224\(^2\)–224 mm; the voxel size was 0.88\(^\circ\)–0.88\(^\circ\)–2 mm\(^3\). Motion artifacts of the DTI data were adjusted using the installed software on the scanner.

For navigational MRI, a 3D fast-field echo sequence was chosen, with a TR/TE of 9/4 msec and a flip angle of 8\(^\circ\). The complete head was covered in an isotropic resolution of 1 mm\(^3\), using a sense factor of 1.5 and a turbo factor of 164. The resulting 3D data set was transferred (via DICOM standard) to the rTMS system (eXimia, Nexstim) and to the BrainLAB iPlanNet Cranial 3.0 tractography software.

**Language Mapping by rTMS**

All enrolled patients underwent language mapping using nTMS eXimia NBS version 3.2.2 and Nexstim NBS 4.3 with a NEXSPEECH module (Nexstim). A standardized, previously published protocol was used.\(^{28,32,42}\) Subsequently, the resting motor threshold (RMT) of every patient was retrieved while performing motor mapping of the cortical representation of the contralateral abductor pollicis brevis muscle.\(^{20}\) The obtained RMT was used afterward as a basic value for language mapping by rTMS; an object naming task, containing 131 colored pictures of common objects, was then performed.\(^{28,32,42}\)

First, 2 baseline trials (object naming without simultaneous rTMS) were carried out. The patient was asked to identify 131 pictures of common objects in his or her native language. Each object was displayed for 700 msec (display time), and the interpuncture interval was set to 2.5 seconds. These settings were not changed for subsequent language mapping. All objects that could not be named quickly and fluently in the baseline trials were discarded and thus excluded from the stimulation trials. The correct, pronounced responses were video recorded and used in the subsequent language mapping.\(^{28,43}\)

During the actual language mapping, rTMS pulses were applied and time-locked to the randomly displayed objects. The picture-to-trigger interval (the time between the presentation of an object on the screen and the onset of the rTMS pulse) was set to 300 msec for the first 15 patients and then changed according to our current protocol to 0 msec for the following 22 patients. Even though there is evidence for both picture-to-trigger intervals,\(^{17,32,36,50}\) we decided to adapt our protocol to 0 msec, according to a recent publication that described the potential benefits of immediate stimulation onset.\(^{23}\) The mapping intensity and frequency were individually determined using our standard protocol.\(^{31,40,42}\)

During language mapping by rTMS, the stimulation coil was placed tangential to the patient’s skull, with
the electrical field in strict anteroposterior orientation to achieve maximum field induction. The magnetic coil was moved between 2 displayed objects (the interpicture interval) in approximately 10-mm steps. The induced electrical field strength varied between 55 and 80 V/m. Naming performance under stimulation was video recorded, as in the prior baseline trials.

For post hoc analysis, the baseline and the stimulation recordings were analyzed, compared, and systematically searched for naming errors by the same person who performed the language mapping. Language errors were categorized as no-response errors, performance errors, neologisms, phonological paraphasias, or semantic paraphasias. Since hesitations errors were not objectified by latency recordings in our study, they were discarded. Errors due to direct muscle stimulation, noncompliance, or pain were not taken into account.

**DTI FT**

Since one of our intentions in this study was to evaluate the feasibility of DTI FT using language-related areas mapped by rTMS as the ROI, we chose a deterministic algorithm. Moreover, since another leading goal was the acquisition of data for direct clinical use in the treatment plan of patients with brain tumor, we used a common deterministic tractography software for neurosurgical applications (iPlanNet 3.0, BrainLAB AG).

Language-positive stimulation spots were then imported and integrated into the deterministic tractography software using the DICOM standard. Via autosegmentation, the integrated spots were turned into individual objects and fused with DTI sequences, and the navigational T1-weighted, contrast-enhanced MRI. A 5-mm margin was added to the language-positive spots, which were then used as an ROI for the following DTI FT.

For anatomically based DTI FT, according to the cubic ROIs-based protocol, 3 cubic seed ROIs were placed along the opercular part of the inferior frontal gyrus, the inferior part of precentral gyrus, supramarginal gyrus, and the superior and medial temporal gyrus (Fig. 1). DTI FT was then performed using a minimum fiber length (MFL) of 50 mm and fractional anisotropy (FA) of 0.2; in case of poor results due to brain edema, the FA was changed to 0.15 (Fig. 2). Subsequently, the DTI FT results were analyzed and searched for visualizations of language-related fiber tracts known to be related to language processing: corticonuclear tract; arcuate fascicle; uncinate fascicle; superior longitudinal fascicle (SLF); inferior longitudinal fascicle; arcuate fibers (ArF); commissural fibers; corticothalamic fibers; frontooccipital fascicle.

Although the AF is part of the SLF, we chose to analyze them separately in this study, because impairment of the AF is highly associated with the presence of conduction aphasia. Therefore, the AF plays a major role in the surgical resection of the perisylvian space-occupying lesions of the left hemisphere. The AF was defined as the part of the SLF connecting to the angular gyrus and the superior temporal gyrus.

Additionally, DTI FT was performed using 5 MFL and FA settings, which, according to a previous study, delivered the best results in visualization of language-related subcortical fibers (Negwer et al., unpublished data) (Fig. 3): MFL 70 mm, FA 0.2; MFL 80 mm, FA 0.15; MFL 90 mm, FA 0.15; MFL 100 mm, FA 0.1; and MFL 100 mm, FA 0.15. Furthermore, the number of visualized fibers for each performed DTI FT was noted.

**Statistical Analysis**

Mean values ± the standard deviation (SD), medians, minimum and maximum values, fibers per tract ratios,
percentages of visualized language pathways, and subject-related characteristics were determined by using the GraphPad Prism software version 6.04 (GraphPad Software).

To evaluate variations between groups, the number of visualized fibers divided by the number of visualized fiber tracts (fibers/tract ratio) and the percentage of visualized language tracts out of the 9 above-outlined subcortical

FIG. 2. Example of DTI FT using the cubic ROIs-based protocol and the nTMS-based protocol. Images show DTI FT performed on the same patient using the cubic ROIs-based protocol (A) and the nTMS-based DTI FT protocol (B). MFL and FA were set to 50 mm and 0.2, respectively, in both cases. Figure is available in color online only.

FIG. 3. Percentages of visualization for every individual subcortical language tract analyzed for the 5 most optimal nTMS-based DTI FT settings (MFL 70 mm, FA 0.2; MFL 80, FA 0.15; MFL 90 mm, FA 0.15; MFL 100 mm, FA 0.15; and MFL 100 mm, FA 0.1) for comparison with the cubic ROIs-based protocol. The 2 gray bars in each graph represent the results of the cubic ROIs-based protocol and the most optimal setting for nTMS-based DTI FT (MFL 100 mm; FA 0.1). CF = commissural fibers; CNT = corticonuclear tract; CIF = corticothalamic fibers; FoF = fronto-occipital fascicle; ILF = inferior longitudinal fascicle.
language tracts (percentage of tracts) were used. The fibers/tract ratio illustrates the fiber density; it is an index of DTI FT's visual portrayal and, thus, its specificity. The percentage of visualized subcortical language tracts was calculated to indicate the visualization sensitivity of the different language-related tracts via DTI FT. Additionally, Fisher's exact test was applied, measuring differences between the groups (Fig. 4). For all statistical calculations, \( p < 0.05 \) was determined to be statistically significant.

Results

Subject and Mapping Characteristics

We enrolled 37 patients with left-sided perisylvian lesions (Table 1). Twenty-three patients were male (62.2%), and 14 were female (37.8%). Five patients (13.5%) had intracerebral vascular lesions (arteriovenous malformation, cavernoma, or hemangioblastoma), 2 had World Health Organization (WHO) Grade I astrocytoma (5.4%), 9 had WHO Grade II astrocytoma or oligoastrocytoma (24.3%), 5 had WHO Grade III astrocytoma or oligoastrocytoma (13.5%), and 16 had WHO Grade IV glioblastoma (43.3%). The median age was 39 years (range 19–65 years). Most patients had no preoperative language disorder (\( n = 23; 62\% \)), 7 patients (19%) had mild aphasia, and 6 (16%) had moderate aphasia. There was only 1 case (3%) of severe aphasia among the cohort (Table 1). To categorize the patient's aphasia, we used the previously published aphasia grading scale.\(^{35,41}\)

Cortical language mapping by rTMS was well tolerated overall, and there were no adverse events reported during stimulation. The intensity during stimulation was 103.0% ± 9.0% RMT (range 80%–120% RMT), and the mean RMT was 33.2% ± 7.9% (range 21%–58%). Twenty-two patients (59.5%) received rTMS with 5 pulses of 5 Hz, 8 subjects (21.6%) received 5 pulses of 7 Hz, and 7 patients (18.9%) received 7 pulses of 7 Hz.

DTI FT

Both protocols could be applied in every enrolled patient, and DTI FT was technically possible in all cases. Compared with the nTMS-based DTI FT, the cubic ROIs-based protocol had a better visualization of the AF (97.3% vs 75.7%; \( p < 0.05 \)) and of the SLF, although the latter was without statistical relevance (Table 2 and Fig. 4). For the other 7 subcortical language tracts, the nTMS-based protocol had superior results, which were statistically significant (\( p < 0.05 \)) for all of the language-related fiber tracts (Fig. 4). In particular, the shorter language tracts, such as ArFs or the uncinate fascicle (UF), were visualized more effectively using the nTMS-based approach (\( p < 0.001 \)). The UF was not detectable with the cubic ROIs-based protocol in any case (Table 2 and Fig. 4).

The fibers/tract ratio using nTMS-based DTI FT was 236 ± 73; it was 286 ± 9 using the cubic ROIs-based protocol (Table 2). These 2 values are comparable and both within the range we previously defined as ideal for a clear DTI FT result (fibers/tract 0–500; Negwer et al., unpublished data).

In addition, we performed nTMS-based DTI FT using the 5 most optimal settings and analyzed the respective percentage of visualization for the 9 subcortical language tracts (Fig. 3).

Discussion

Besides demonstrating the reliable application of nTMS-based DTI FT for language pathways, the main goal of our study was to compare this new function-based approach to one of the best-known protocols for anatomically based DTI FT for subcortical language pathways.\(^{44}\)

At this point, we want to emphasize that the cubic ROIs-based protocol was developed especially for SLF/AF DTI FT, so the direct comparison with our nTMS-based approach is imperfect on some points. The cubic ROIs-based

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**FIG. 4.** Percentages of successful visualized language-related fiber tracts. The bar graph compares the visualized percentages of the 9 examined language-related fiber tracts using the cubic ROIs-based protocol (gray) and the nTMS-based protocol (white). A \( p \) value < 0.05 was determined as statistically significant.
protocol was never meant for DTI FT of language-related subcortical fiber tracts aside from SLF/AF, so its application for other language-related fiber tracts should be considered experimental. However, this protocol is one of the first anatomically based approaches for tractography of language-related white-matter tracts, and it has provided steady results, so an analysis of these 2 methods is certainly a subject of interest for scientific and clinical purposes.

As mentioned, there are 2 ways to place ROIs for the purpose of DTI FT. Function-based DTI FT, as the name suggests, uses functional data that can be provided by different examinations (fMRI, magnetoencephalography, nTMS), and anatomically based DTI FT relies on ROI seeding, using predefined anatomical landmarks. The biggest disadvantage of anatomically based DTI FT is that anatomy may be altered by the tumor mass and/or the surrounding edema; thus, even for a trained examiner, precise ROI seeding might be cumbersome.27,30,33 Moreover, the results depend on the examiner’s expertise and experience, so there is a high interobserver variability,8,47 whereas a previous study analyzing interobserver differences in the application of anatomically and nTMS-based DTI FT for the CST showed significantly less interobserver variability for nTMS-based DTI FT.19

However, function-based DTI FT has its own limitations, which mainly depend on the reliability and accuracy of the chosen modality. For example, fMRI data, in particular the blood oxygenation-dependent signal, may be altered by tumor surrounding edemas and by changed oxygen levels, leading to inaccurate results.4,42

After providing promising and reliable data in previous studies, nTMS gained importance in neuroscience research and modern neurosurgery, showing good correlation with DCS results, and certainly still represents the gold standard for the detection of language-related brain areas.22,32,46 Furthermore, the results of the application of nTMS-based DTI FT of the CST were promising and could be confirmed by intraoperative subcortical stimulation.10,16,19,49 Recent reports analyzing nTMS-based DTI FT for language-related tracts also showed convincing results that correlated with clinical status.39 Thus, nTMS-

### TABLE 1. Patient characteristics

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<th>Case No.</th>
<th>Sex</th>
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<td>2</td>
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<td>30</td>
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<td>62</td>
<td>GBM</td>
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<td>46</td>
<td>GBM</td>
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### TABLE 2. Percentages of individually visualized fiber tracts, mean fibers per tract ratios, and mean percentages of all visualized tracts, by protocol*

<table>
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<th>Tract</th>
<th>nTMS-Based Protocol (%)</th>
<th>Cubic ROIs-Based Protocol (%)</th>
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<tr>
<td>ArF</td>
<td>100</td>
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<td>CF</td>
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<td>FoF</td>
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<td>39.9</td>
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<tr>
<td>Fibers/tract ratio</td>
<td>236 ± 73</td>
<td>286 ± 9</td>
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* Aphasia grade: 0 = no aphasia; 1 = mild aphasia; 2 = moderate aphasia; 3 = severe aphasia; A = predominantly motor impairment; B = predominantly sensory impairment.

AF = arcuate fascicle; ArF = arcuate fibers; CF = commissural fibers; CNT = corticocerebellar tract; CIF = corticothalamic fibers; FoF = fronto-occipital fascicle; ILF = inferior longitudinal fascicle; SLF = superior longitudinal fascicle; UF = uncinate fascicle.

* Minimum fiber length 50 mm, fractional anisotropy 0.2.
based DTI FT has the potential to become a helpful tool for preoperative planning and intraoperative application in modern neurosurgery.

In this study, the results of the nTMS-based DTI FT protocol showed overall superior results to those of the anatomically based approach using cubic ROIs. The AF was more reliably visualized using the cubic ROIs-based protocol than using our nTMS-based DTI FT. However, if the results of our nTMS-based protocol are further analyzed using the 5 most optimal settings mentioned, the successful visualization of the AF was possible in up to 97.3% of the enrolled cohort (range 67.2%–97.3%) (Fig. 3). Therefore, this particular advantage of the cubic ROIs-based protocol can be discarded. Visualization of the SLF, using the cubic ROIs-based protocol, showed slightly better results, but these were without statistical significance (97.3% cubic ROIs-based protocol vs 89.2% nTMS-based protocol; p = 0.36) (Table 2 and Fig. 4). When using an MFL of 100 mm and FA of 0.1 (1 of the 5 most optimal settings), the visualization increased to 100% for the nTMS-based approach (Fig. 3). To better compare the obtained results, we used the same MFL and FA settings as in the cubic ROIs-based protocol (MFL 50 mm; FA 0.2); these, however, do not correspond with the optimal settings for nTMS-based DTI FT for language-related subcortical fiber tracts (Negwer et al., unpublished data). Nevertheless, even with this suboptimal combination, our new protocol showed superior results. The cubic ROIs-based protocol did not allow constant visualization of the other analyzed subcortical fiber tracts, the UF was not detectable in any of the patients, and the ArF were only detectable in 5.4% of the patients (Table 2 and Fig. 4). The cubic ROIs were placed using anatomical landmarks along the expected fiber course of the AF/SLF, so the DTI FT of other subcortical fiber tracts in different anatomical regions was suboptimal, and sometimes impossible, as expected.

Reviewing the results, DTI FT, especially of the AF/SLF, is feasible and successful using the cubic ROIs-based protocol, keeping in mind that it was designed for this purpose. However, by using the 5 most optimal parameters, we achieved an improved visualization of the different subcortical fiber tracts using nTMS-based DTI FT compared with using the predefined settings (MFL 50; FA 0.2) of the ROIs-based protocol14 (Fig. 3). The best results were seen using MFL of 100 mm and FA of 0.1, so this setting is recommended for optimal results.

From our point of view, it is essential to analyze the individual subcortical language pathways and their interrelations to further investigate language function and potential subcortical plasticity. For this purpose, our protocol seems to be an applicable tool, as it focuses on many subcortical fiber bundles and not just the major subcortical fiber tracts, such as the AF/SLF, with high percentage of visualization.

Limitations

One major limitation of this technique is the challenge of reconstructing crossing fibers because the technique inhibits the identification of a voxel’s primary eigenvector, thus impeding FT.2,18,25 Furthermore, DTI FT, especially in patients with space-occupying lesions, can provide false-negative and other inaccurate results in regions close to the lesion or edema, because of low anisotropy.2,19

As mentioned, previous studies have analyzed DTI FT using intraoperative subcortical stimulations and have provided promising results.1,24,26,29 Furthermore, nTMS-based DTI FT of the CST could be validated using subcortical stimulation, encouraging new approaches in this field.10

In our study, we enhanced the TMS-positive spots by a rim of 5 mm because, rather than considering cortical language located in 1 spot, we prefer the theory of a language-positive area on the cortical surface. Certainly this approach is experimental, and it remains unclear in which dimension the enlargement affects the following DTI FT.

In this study, the nTMS-based protocol showed better results, especially in tracking a multitude of language-relevant white-matter tracts, as opposed to the anatomical-based approach. These results do not ensure the superiority of the protocol, because what is certainly more important than a higher number of tracked fibers is the question of their functionality.

Until now, there have been no studies examining the correlation of nTMS-based DTI FT for subcortical language tracts, so it remains unclear whether the provided results can be objectified by subcortical stimulation. Thus, this should be the next step in future studies.

Conclusions

This study demonstrates the feasibility of nTMS-based DTI FT and its superiority to the cubic ROIs-based DTI FT approach, with the exception of AF. These results are encouraging and could further accelerate the spread of nTMS-based DTI FT, which is a reasonable and standardized approach for the visualization of language-related white-matter tracts.

Besides its scientific applications, nTMS-based DTI FT also seems to be feasible for clinical use, especially for preoperative planning in patients with brain tumor. However, these results need to be validated by intraoperative subcortical stimulation in future studies prior to routine clinical use.

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**Disclosure**

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Conception and design: Krieg. Acquisition of data: Negwer, Sollmann, Ille, Hauck, Maurer, Kirschke. Analysis and interpretation of data: Negwer. Drafting the article: Krieg, Negwer. Critically revising the article: Krieg, Kirschke. Reviewed submitted version of manuscript: Krieg, Sollmann, Ille, Hauck, Maurer, Ringel, Meyer. Approved the final version of the manuscript on behalf of all authors: Krieg. Statistical analysis: Krieg, Negwer. Administrative/technical/material support: Krieg, Ringel, Meyer. Study supervision: Krieg, Ringel, Meyer.

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