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CASE REPORT

Left perisylvian tumor surgery aided by TMS language mapping in a 6-year-old boy: case report

Tizian Rosenstock[1] · Thomas Picht[1] · Heike Schneider[1] · Arend Koch[2] · Ulrich-Wilhelm Thomale[3]

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Abstract

Background Awake surgery to preserve language function in young children is challenging, therefore reliable non-invasive work-up of language functional anatomy is needed to preserve language function at any cost. Furthermore, there are obvious limitations of an awake craniotomy with direct stimulation on a child.

Case report A 6-year-old boy with a low-grade glioma of the left temporal lobe suffering from epileptic seizures underwent surgery, guided by preoperative transcranial magnetic stimulation (TMS) language mapping and consecutive DTI fiber tracking.

Discussion and conclusion We report successful surgery of a language eloquent brain tumor in a young child based on TMS mapping and DTI fiber tracking alone. Surgical treatment of left-sided perisylvian tumors in children is discussed.

Keywords Navigated transcranial magnetic stimulation (nTMS) · Brain tumor surgery · Pilocytic astrocytoma · Diffusion tensor imaging

Introduction

Most of the central nervous system tumors in children are low-grade gliomas (LGG, 30–50%) where pilocytic astrocytoma are the most frequently seen entities [1]. A total resection provides a possibility of a comprehensive cure [2–4]. Malignant transformation of pilocytic astrocytoma does not occur naturally but has been described in a few small case series [5].

The incidence of postoperative aphasia in adults with language eloquent tumors differs greatly in literature (transient aphasia 22.4–70.9%; permanent aphasia 3–9%) [6]. Transcranial magnetic stimulation (TMS) is a useful method for non-invasive mapping of cortical language function in glioma patients [7–9]. The combination of TMS with diffusion tensor imaging (DTI) allows to visualize relevant language-associated white matter tracts [10].

The authors discuss the first case of a 6-year-old boy with a left perisylvian LGG who underwent navigated tumor surgery assisted by rTMS and rTMS-based DTI fiber tracking.

✉ Tizian Rosenstock
tizian.rosenstock@charite.de

[1] Department of Neurosurgery, Charité – Universitäsmedizin Berlin, corporate member of Freie Universität Berlin, and Berlin Institute of Health, Charité University Medicine, Charitéplatz 1, 10117 Berlin, Germany

[2] Department of Neuropathology, Charité – Universitäsmedizin Berlin, corporate member of Freie Universität Berlin, and Berlin Institute of Health, Charité University Medicine, Charitéplatz 1, 10117 Berlin, Germany

[3] Pediatric Neurosurgery, Charité – Universitäsmedizin Berlin, corporate member of Freie Universität Berlin, and Berlin Institute of Health, Charité University Medicine, Augustenburger Platz 1, 13353 Berlin, Germany

Case report

History and examination

A 6-year-old boy presented with progressive epileptic seizures and postictal aphasia. No neurological deficits were seen interictally. Aphasia was scored pre- and postoperatively [8]. A cranial MRI scan demonstrated a heterogenous contrast-enhancing diffuse left temporal thalamic lesion. A previously performed biopsy revealed a low-grade glioma, suggesting the complex form of a dysembryoplastic neuroepithelial tumor (DNT; WHO grade 1). After being offered a subtotal tumor resection, the family sought a 2nd opinion at our hospital. Diffusion tensor imaging (DTI), PET-MRI scan with (18) F-fluoro- ethyl-tyrosine (FET), and a rTMS examination (under regular antiepileptic medication) were performed to evaluate the spatial relationship between tumor and functional tissue.

Neuroimaging studies

The MRI scan revealed a progressive cystic tumor with regional contrast enhancement in the left temporal lobe in comparison to scans performed 3 months ago. 18F-FET-PET-MRI demonstrated increased metabolism within the contrast enhanced regions (Fig. 1).

The rTMS stimulation was well tolerated by the child and no adverse side effects were noted (TMS parameters in Table 1). Language positive spots (at least three errors per stimulation location) were detected near the anterior part of the tumor (Fig. 2).

Subsequently, DTI-based reconstruction of motor and language-related white matter tracts was performed [11]. A combined approach of anatomical and TMS stimulus location-based tractography demonstrated connection of the error-inducing rTMS stimuli to the uncinate (UF) and the arcuate fasciculus (AF), confirming their functional relevance

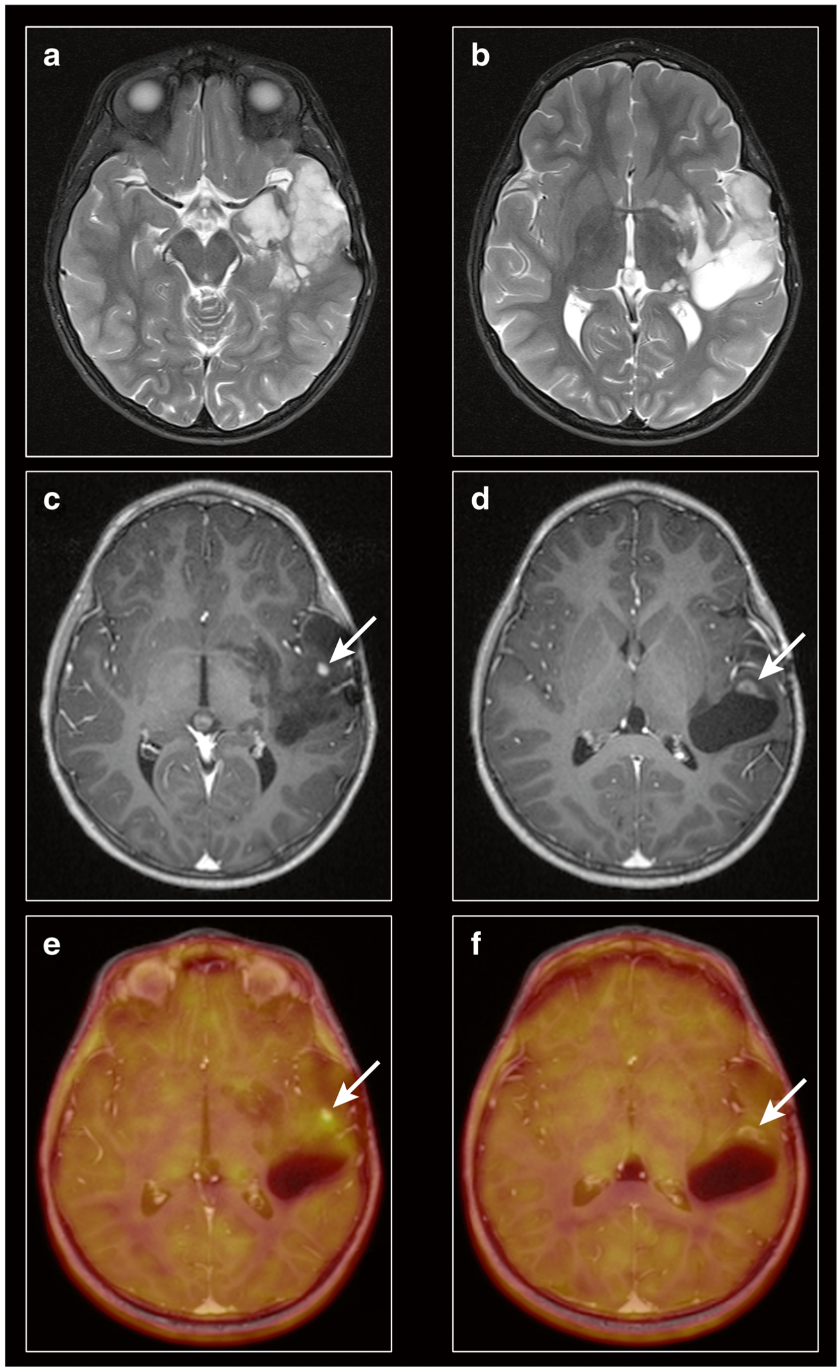


Fig. 1 Axial T2-weighted (**a**, **b**) and T1-weighted post gadolinium (**c**, **d**). MRI studies showing a temporo thalamic T1-hypointense/T2-hyperintense lesion with a cystic mass in the temporal lobe. Contrast enhancement could be detected in the anterior part of the superior temporal gyrus anterior to the cyst (white arrows). A PET-MRI scan with (18)F-fluoro-ethyl-tyrosine (FET) (**e**, **f**) revealed higher utilization of amino acids in the respective regions of MR contrast enhancement (white arrows)

Table 1 rTMS stimulation protocol

Chronology	Description	Remarks
1	-Checking navigation accuracy (< 2 mm) -estimation of the RMT: 51% stimulator output, 95 V/m -motor mapping for the first dorsal interosseous muscle (to identify seed regions for DTI fiber tracking)	-child was kept busy by showing a movie, avoided spontaneous muscle action to ensure sufficient EMG
2	-Baseline: child was exposed to 80 pictures (three times in random order) which were supposed to be named with interpicture interval = 4 s, display time = 1.5 s -58 of 80 pictures were selected for stimulation which were reliably named to avoid false-positive errors	-child cooperated well and showed fun watching and naming pictures
3	-adjustment of stimulation intensity (starting with RMT and decreasing it to level of comfort) -rTMS intensity: 25% stimulator output, median 68 V/m	-possible discomfort was avoided to ensure child's compliance -rTMS was performed using stimulation intensities noticeably lower than RMT level[9]
4	-rTMS was now combined with the naming task of the above-mentioned pictures -picture-to-trigger-interval = 0 ms -stimulation duration = 1 s, -stimulation frequency = 5 Hz -each location was stimulated at least three times in randomized order -simultaneous video recording	-examination was paused to avoid loss of child's concentration -stimulation intensity can be adjusted, when child feels uncomfortable
5	-offline analysis of named pictures under stimulation compared to named pictures without stimulation	-analysis was performed by two experienced researchers

[9] Detailed overview on the used rTMS stimulation protocol following the recommendation of an expert panel. No severe side effect occurred during the rTMS mapping. The stimulation intensities in V/m (= unit of the electric field) were calculated based on a peeling depth of 10 mm. These intensities can vary during the rTMS mapping depending on the coil's rotation and tilt as well as the respective skull thickness. We added recommendations which might help to perform the TMS examination in children. *DTI* diffusion tensor imaging, *RMT* resting motor threshold, *rTMS* repetitive transcranial magnetic stimulation

[10] (Fig. 2). Tumor association with the corticospinal tract could be excluded.

Treatment and postoperative clinical care

After tumor board discussion of the case, decompression of the cyst and resection of the FET-PET positive tumor parts respecting the functional mapping results was proposed to the family. Intraoperatively, the tumor could be identified by functional neuronavigation combined with ultrasound-guided resection (Fig. 3). Overlay of the functional and metabolic information into the microscopic field of view by augmented reality enabled a smooth workflow with decompression of the cyst, resection of the targeted tumor areas while preserving the functional areas of the superior temporal gyrus.

Immediately postoperatively and on follow-up, the child showed no neurological deficits—especially no disturbances in language production or comprehension were noted. A postoperative MRI scan demonstrated decompression of the cyst and resection of the contrast-enhancing tumor parts (Fig. 4). Histological and epigenetic evaluation revealed a low-grade neuroepithelial tumor which clustered with the methylation class family "Pilocytic astrocytoma" (Fig. 5).

Discussion

While intraoperative language mapping and monitoring are considered as gold standard for language preservation, this procedure has specific requirements both in terms of physical and neuropsychological parameters—with the latter making this procedure challenging, if not obsolete in young children, unable to adequately cooperate.

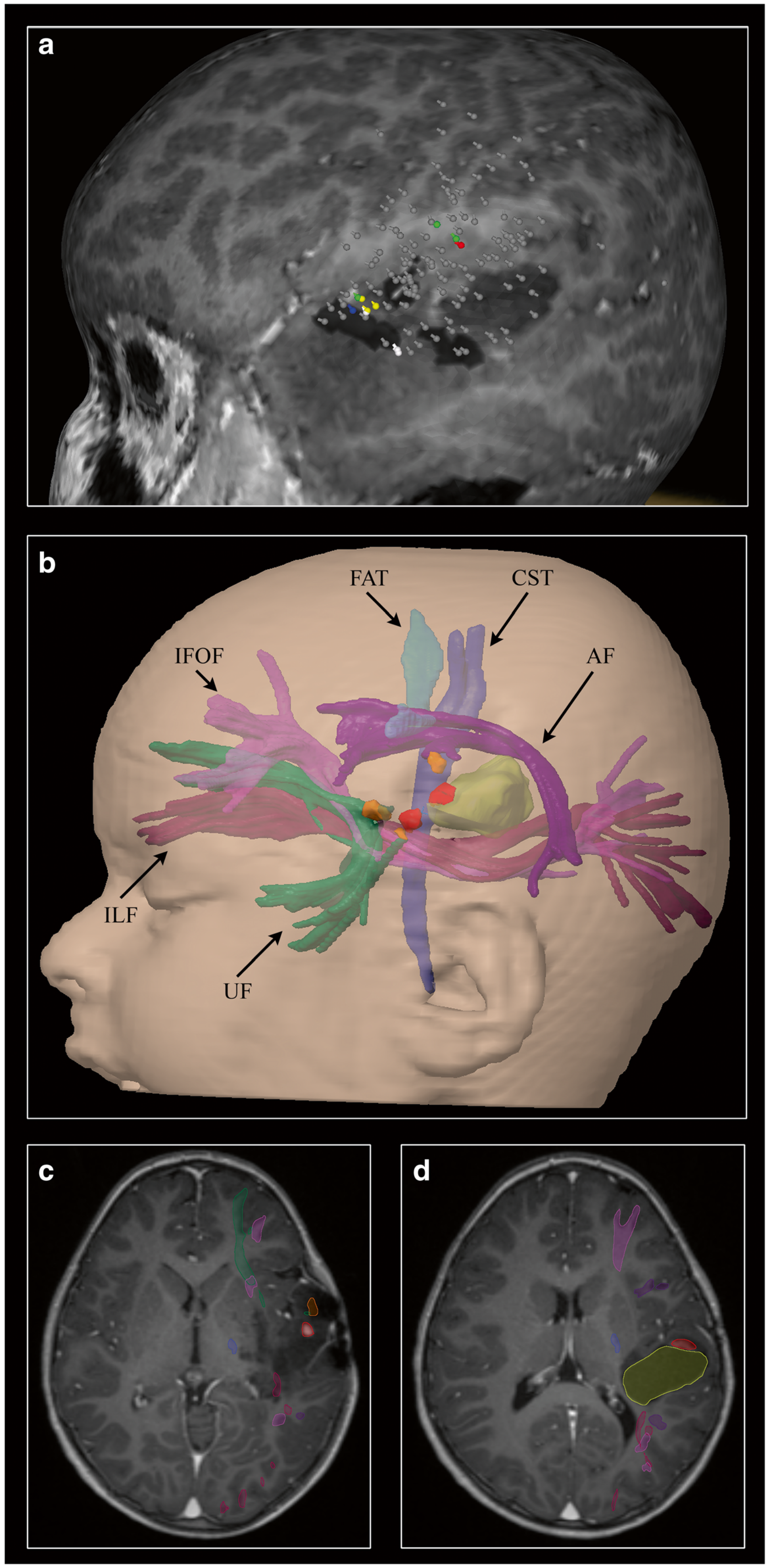


Fig. 2 Visualization of rTMS language mapping and the relevant white matter tracts of the language network. The stimuli on locations are presented within a 3D reconstruction of a T1-weighted MRI scan (**a**) while the color codes represents the characteristics of speech errors (gray = no error, white = no response, blue = semantic error, green = performance error, yellow = phonological error, red = not certainly distinguishable). Stimulation locations where speech errors could be elicited following at least 2 of 3 repetitions were integrated into our DTI-based fiber tracking procedure and displayed in orange (**b**). The contrast agent-enhanced tumor parts are colored in red, the cyst in yellow, the arcuate fasciculus (AF) in purple, the inferior longitudinal fasciculus (ILF) in red, the inferior fronto-occipital fasciculus (IFOF) in pink, the uncinate fasciculus (UF) in green, the frontal aslant tract (FAT) in turquois, and the corticospinal tract (CST) in blue. Connectivity of the rTMS stimuli to the UF and the AF was detected. Detailed analysis in the axial view (**c**, **d**) revealed the spatial relationship between the tumor, the cyst, and the language network

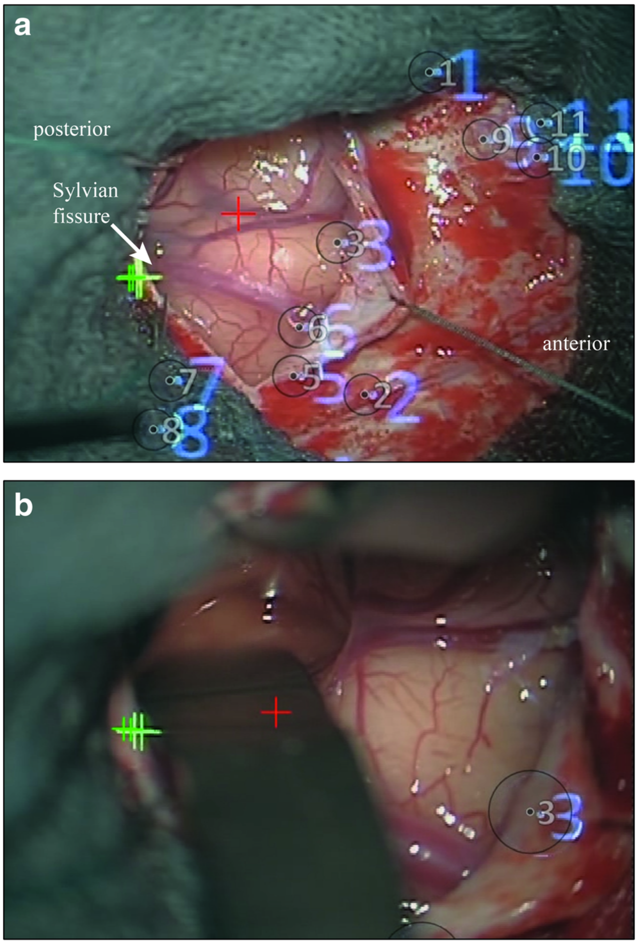


Fig. 3 Intraoperative microscopical view. The chosen location for corticotomy (**a**, red cross) for decompression of the cyst (**b**) respected the rTMS stimulated speech error regions (numbered circles)

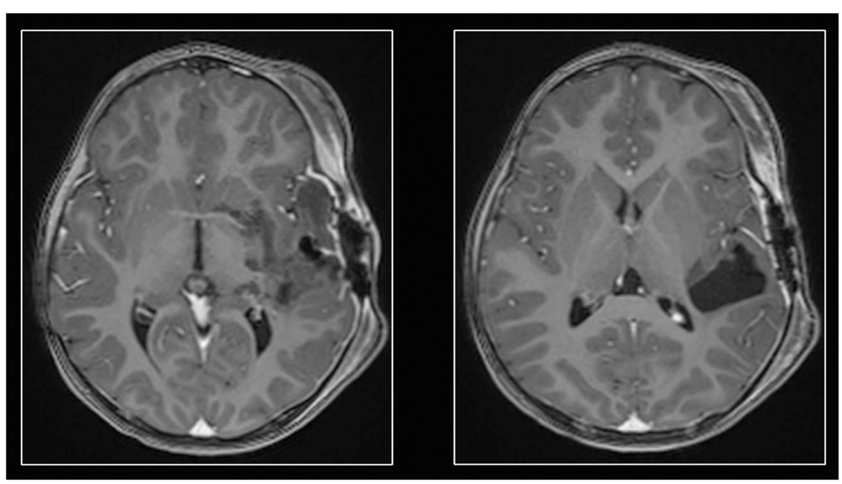
Therefore, preoperative examination methods like rTMS or rTMS-based fiber tracking are needed to increase safety in this vulnerable patient group. In our 6-year-old boy, awake surgery was not an option. Surgery guided by preoperative rTMS language mapping results and rTMS-based fiber tracking was feasible to avoid any new postoperative deficit.

RTMS has been described as safe examination in adults with a high sensitivity (90–100%) and negative predictive value (84–100%) compared with DES while the specificity significantly differs between studies (8–98%) [7, 8, 12–15]. In the present case, reproducible speech errors could be elicited especially in the anterior part of the superior temporal gyrus (Fig. 3a). With stimulation intensities below the resting motor threshold, the child felt comfortable throughout the investigation. While in adults, one out of five patients feels discomfort during rTMS, we strongly recommend adjusting the stimulation intensity to a tolerable level in children to ensure compliance [15].

ROI seeding for the visualization of language-related white matter tracts usually is based on anatomical landmarks [16]. Raffa et al. have recently shown that visualization of the subcortical language network can be improved by implementing rTMS language mapping data as seed regions [10]. In our case, white matter tract delineation could be improved by the use of rTMS stimuli as additional seed regions—especially in the peritumoral area (Fig. 3b). It remains important to point out that the exact clinical relevance of these language tracts has not been validated yet.

The results of the rTMS language mapping and the rTMS-based fiber tracking were discussed with the patient and his parents. A surgical approach under the premise to avoid new functional deficits was agreed on. Therefore, during surgical planning, the targeted tumor resection volume strictly respected the region where language errors were reproducibly induced and connectivity to the UF and AF was identified. This kind of strategy should not only lead to control of the active tumor parts, but also help to diagnose the tumor characteristics by histology and molecular biology, detecting, e.g., malignant transformation with its treatment implications [17].

Fig. 4 Postoperative axial T1-weighted post gadolinium MRI scan showing the initial contrast agent-enhanced tumor parts could be successfully removed and the cyst is decompressed



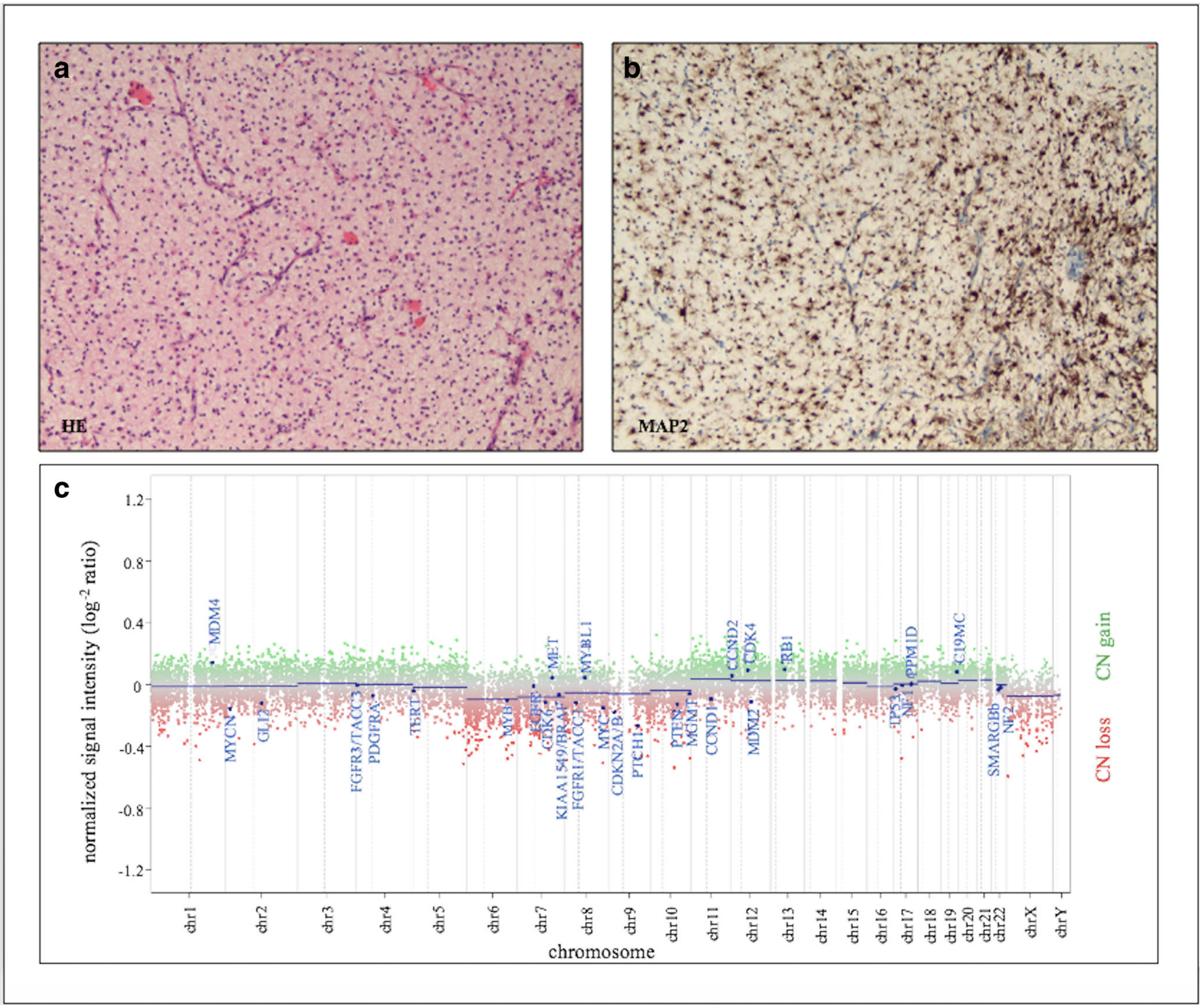


Fig. 5 The H&E stained section reveals an isomorphic neuroepithelial tumor with an oligodendroglial-like growth pattern (**a**). Antigene small cell processes can be detected by antibodies against the MAP2 (**b**). Contrary to the RT-PCR analysis, the copy number variation profile did not detect any typical molecular pattern for a pilocytic astrocytoma like a BRAF/KIAA1549-fusion (arrow) (**c**)

Conclusion

To the best of our knowledge, this is the first case in which brain tumor surgery in a child was assisted successfully by rTMS and rTMS-based DTI fiber tracking data. Repetitive TMS was feasible and identified reproducible language error regions without any adverse side effects. The examination and its results not only helped the surgeon to plan and perform safe surgery, but also improved patient and relatives understanding and their engagement in the treatment planning.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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