NEUROSURGICAL FOCUS

Neurosurg Focus 53 (6):E4, 2022

Neurosurgery for eloquent lesions in children: state-of-the-art rationale and technical implications of perioperative neurophysiology

Sandro M. Krieg, MD, MBA,[1] Denise Bernhard, MD,[2] Sebastian Ille, MD,[1] Bernhard Meyer, MD,[1] Stephanie Combs, MD,[2–4] Alexander Rotenberg, MD, PhD,[5] and Michael C. Frühwald, MD, PhD[6]

[1]Department of Neurosurgery, Klinikum rechts der Isar, School of Medicine, Technische Universität München; [2]Department of Radiation Oncology, Klinikum rechts der Isar, School of Medicine, Technische Universität München; [3]Deutsches Konsortium für Translationale Krebsforschung (DKTK), Partner Sites Munich; [4]Institute of Radiation Medicine (IRM), Department of Radiation Sciences (DRS), Helmholtz Zentrum München (HMGU), Oberschleißheim, Germany; [5]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; and [6]Pediatrics and Adolescent Medicine, Augsburg University Hospital, Augsburg, Germany

OBJECTIVE In adult patients, an increasing group of neurosurgeons specialize entirely in the treatment of highly eloquent tumors, particularly gliomas. In contrast, extensive perioperative neurophysiological workup for pediatric cases has been limited essentially to epilepsy surgery.

METHODS The authors discuss radio-oncological and general oncological considerations based on the current literature and their personal experience.

RESULTS While several functional mapping modalities facilitate preoperative identification of cortically and subcortically located eloquent areas, not all are suited for children. Direct cortical intraoperative stimulation is impractical in many young patients due to the reduced excitability of the immature cortex. Behavioral requirements also limit the utility of functional MRI and magnetoencephalography in children. In contrast, MRI-derived tractography and navigated transcranial magnetic stimulation are available across ages. Herein, the authors review the oncological rationale of function-guided resection in pediatric gliomas including technical implications such as personalized perioperative neurophysiology, surgical strategies, and limitations.

CONCLUSIONS Taken together, these techniques, despite the limitations of some, facilitate the identification of eloquent areas prior to tumor surgery and radiotherapy as well as during follow-up of residual tumors.

https://thejns.org/doi/abs/10.3171/2022.9.FOCUS22316

KEYWORDS glioma; epilepsy surgery; motor; language; preoperative mapping; neurophysiology; neuromonitoring

For brain tumors in adults that are located in motor or language eloquent areas, such as adjacent to the sylvian fissure or central sulcus, a large armamentarium of perioperative techniques improves the extent of resection (EOR) while minimizing morbidity and still maintaining maximum possible progression-free survival (PFS).

Such techniques include not only intraoperative brain mapping by direct cortical stimulation (DCS) but also image guidance, fluorescent dyes, ultrasound, and intraoperative MRI (iMRI). Over the last decade, noninvasive mapping modalities, such as functional MRI (fMRI), tractography, navigated transcranial magnetic stimulation (nTMS), and magnetoencephalography (MEG), have been established as valuable preoperative functional mapping protocols. Because of modern functional mapping capacity, resection of tumors previously judged as unresectable has become a viable option in many cases.[1] Mapping techniques have enabled descriptions of functional reorganization that accompanies brain tumors in adults.[2,3]

While the aforementioned techniques have been repetitively described and are established for adult patients

ABBREVIATIONS DCS = direct cortical stimulation; EOR = extent of resection; fMRI = functional MRI; GBM = glioblastoma; GTR = gross-total resection; HGG = high-grade glioma; iMRI = intraoperative MRI; LGG = low-grade glioma; MEG = magnetoencephalography; MEP = motor evoked potential; nTMS = navigated transcranial magnetic stimulation; PFS = progression-free survival; QOL = quality of life; rs-fMRI = resting-state fMRI; SCS = subcortical stimulation; TCI = transcallosal inhibition; 5-ALA = 5-aminolevulinic acid.

SUBMITTED May 28, 2022. **ACCEPTED** September 22, 2022.
INCLUDE WHEN CITING DOI: 10.3171/2022.9.FOCUS22316.

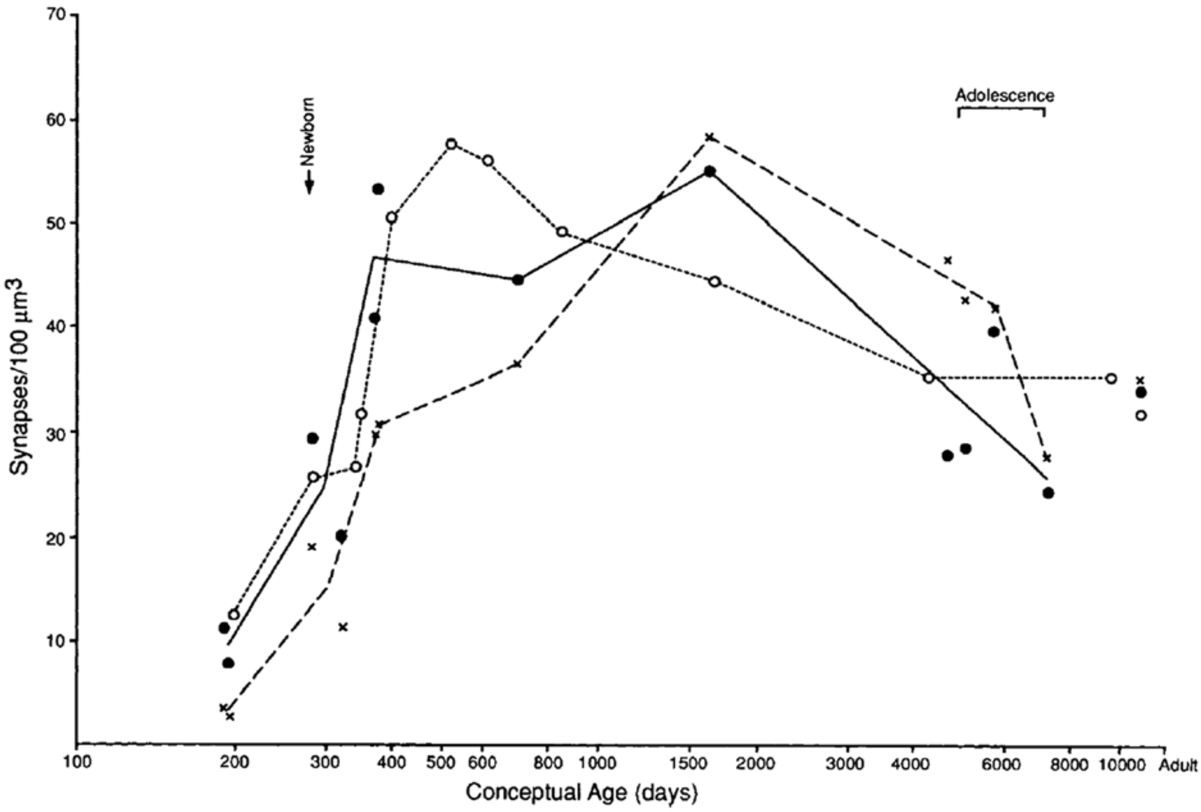

Fig. 2. Mean synaptic density in synapses/100 µm³ in auditory, calcarine, and prefrontal cortex at various ages. Open circles, visual cortex (area 17); filled circles, auditory cortex; x, prefrontal cortex (middle frontal gyrus).

FIG. 1. This figure by Huttenlochner and Dabholkar[57] illustrates the mean synaptic density depending on the respective functional system and age. This demonstrates the chance for synaptic changes and restructure especially in the first years of life. Figure and legend from Huttenlocher PR, Dabholkar AS: Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol.* 1997;387:167-178. © 1997 WILEY-LISS, INC.

with high-grade gliomas (HGGs) and low-grade gliomas (LGGs) as well as arteriovenous and cavernous malformations, they have been poorly studied for supratentorial lesions, such as gliomas, in children.[4]

Development of functional areas of the brain in children and adolescents is highly variable, including the number of synapses depending on developmental stage (Fig. 1).[5] Synaptogenesis has not yet been proven to increase the chance of functional reorganization, but it probably contributes to the much higher rate and degree of functional reorganization in young children.

In children and adolescents affected by CNS tumors, functional anatomy is subject to continuous change and thus an array of interindividual variations.[6] Rapid growth and spread of neurons induces widespread reorganization of the CNS accompanied by an increased vulnerability to exogenous noxae such as radioactive irradiation. While neurogenesis and neuronal migration are primary prenatal events, some GABAergic neuronal migration and especially myelination continue postnatally to a large extent during childhood. The structural variation due to functional reorganization in the developing brain and the decisive nature of gross-total resection (GTR) in terms of prognosis in most, if not all, CNS tumors of childhood necessitate a thorough functional pre- and intraoperative workup.

In this article, we describe the potential of function-guided resection in patients with pediatric LGG and HGG as a personalized multidisciplinary therapeutic approach, including oncological rationale, implications of perioperative neurophysiology, and surgical and radiation oncology strategies, and we present limitations considering the most recent literature and based on our personal experience.

Methods

General Aspects

Modern pediatric neuro-oncology requires consideration of all aspects of the patients' care, including preexisting functional deficits due to the tumor and/or previous treatment. Very similar to adult trials, surgical aspects are frequently not considered, especially when it comes to details such as exact functional anatomy or treatment risks.

Mapping before pediatric tumor surgery allows for a tailored patient consultation and surgical planning based on an assessment of risks to the individual functional anatomy. As opposed to intraoperative mapping, preoperative functional maps can be combined with an estimation of the extent of resection (EOR) and risk stratification prior to tumor surgery and discussed with the patient and therapeutic team.[7] Notably, functional reorganization may facilitate complete tumor resection during the course of the disease.[3,8] Functional assessment at regular intervals should therefore be an integral part of modern pediatric (and adult) neuro-oncology.

Noninvasive functional mapping methods include electrophysiological techniques, such as nTMS and MEG, but also imaging protocols such as fMRI and tractography. Evaluating such data especially for the motor system prior to surgery allows for guidance of intraoperative DCS or subcortical stimulation (SCS) of white matter tracts. As one of the most crucial issues in pediatric electrophysiology, cortical stimulation can be much more difficult not only because of cooperation issues, especially during awake procedures, but also because of lower cortical excitability as a result of incomplete myelination.[9]

Noninvasive Mapping

Functional MRI

While fMRI has its limitations in brain tumor compared with epilepsy surgery, resting-state fMRI (rs-fMRI) might overcome these limitations. A larger series in pediatric patients and proof as a mapping modality for pediatric brain tumor patients are currently lacking.[21] However, a recent series demonstrated that 6 of 20 children were not able to undergo MRI, and thus rs-fMRI without sedation, which reduces the current applicability of this technique considerably[22] (Table 1).

Magnetoencephalography

Comparisons of MEG with invasive intraoperative DCS mapping have been repeatedly applied for motor and language functions, showing analogous results.[12] In children, however, the technique is still limited by the required behavioral cooperation of the patient (Table 1).

Navigated Transcranial Magnetic Stimulation

The combination of transcranial magnetic stimulation with a neuronavigational device and the use of very focal coils allowed for a high-resolution mapping device. For motor mapping, nTMS leads to improved functional and oncological outcomes, reducing not only residual tumor volumes from 42% to 22% but also permanent motor deficits.[15,23] For language, nTMS combined with function-based tractography replaces 2 out of 3 awake procedures in the adult population with comparable outcome in terms of EOR and deficit rates.[16] Thus, pediatric cases per se requiring awake intraoperative mapping and resection may now receive comparable mapping and care by extraoperative mapping even in rather young children.[13,16] In line with our own experience, nTMS was reported to provide reliable data in patients as young as 4 to 6 years of age for language function.[13,14] Mapping functions other than motor and language have been established as well.[24,25]

Apart from exclusive mapping approaches, repetitive nTMS allows for the treatment of postoperative deficits. While this is common clinical practice in patients with depression and chronic pain, several trials have demonstrated its applicability in patients who have experienced stroke. Based on these trials, a recent randomized double-blind trial revealed the efficacy of postoperative repetitive nTMS treatment for surgery-related paresis in patients with glioma.[26] While this was demonstrated in adult patients, the plastic potential of the pediatric brain should be even higher. Chances of nTMS for rehabilitation or even prehabilitation with the induction of functional reorganization will be outlined in the discussion section; currently, there are no reliable data on record (Table 1).

Tractography

Tractography itself does not provide information on specific functions of reconstructed fibers. Thus, function-based tractography is an increasingly used technique. Cortical mapping by MEG, fMRI, or nTMS can provide functional rather than anatomical regions of interest.[7,27] The same is true for language networks.[7] For both motor and language, it allows for preoperative risk assessment based on neurophysiological measures, such as excitability, combined with tumor-to-tract distance.[7,18] Other studies also have proven the excellent specificity and sensitivity of corticospinal tract detection of 93%–95%[19] (Table 1).

Invasive Mapping

Extraoperative Mapping

Especially in epilepsy surgery, extraoperative mapping is part of a state-of-the-art assessment. Individual cases have been reported in children as young as 4 years of age for motor mapping and 5 years of age for language mapping[28] (Table 2).

Intraoperative Mapping

DCS and SCS mapping in unconscious patients are most frequently used to map the motor system. In a series by Berger et al., in pediatric patients with brain tumors, the language cortex and sensorimotor system were safely and reliably mapped.[60] Language especially was reported to be very variable and anatomically unpredictable in children when compared with adults. The largest series reported intraoperative motor evoked potentials (MEPs) in children as young as 3 months but also mentioned the need for high stimulation currents, which impair the resolution and sensitivity of MEP mapping and monitoring[29] (Table 2). Awake surgery is currently mainly indicated for highly eloquent tumors within the left insula, operculum, supramarginal gyrus, angular gyrus, and dorsal superior temporal gyrus to map areas essential for language production and perception. A further advantage is the possibility of monitoring subcortical connections during resection. Depending on the respective function, other neuropsychological functions, such as arithmetic processing, visuospatial attention, categorization, or face recognition, may be examined.

In children with brain tumors, intraoperative awake mapping is only feasible in a subset of patients aged 8 to 10 years and older, mostly because of anesthesia issues and patients' collaboration, but also because of lower ex-

TABLE 1. Summary of noninvasive modalities for cortical and subcortical mapping of functional-anatomical structures

Location	Authors & Year	Modality	Mechanism	Surrogate	Advantages	Disadvantages	Clinical Conclusion
Cortical	Giussani et al., 2010[10] Azad & Duffau, 2020[11]	fMRI	Reduced venous oxygenation levels as a sign of increased cortical activity & oxygen consumption	Yes	Availability	• Low spatial resolution • Cannot differentiate btwn essential & nonessential areas • Oxygen-consuming tumors or malformations may mask neurovascular coupling & impair accuracy	• Unreliable for resection planning in tumors because of inconsistent mapping results • High deficit rates in pediatric & adult series • rs-fMRI might overcome these limitations
	Tarapore et al., 2012[12]	MEG	Measures direct neuronal activation during task performance created by bioelectric currents	No	High temporal resolution	• Low spatial resolution • Limited availability due to highly specialized staff & costs	Comparisons of MEG w/ invasive intraop DCS mapping have been repeatedly applied for motor & language functions, showing analogous results
	Narayana et al., 2021[13] Rosenstock et al., 2019[14] Krieg et al., 2014[15] Ille et al., 2021[16] Lehtinen et al., 2018[17]	nTMS	• The coil-induced magnetic field generates an intracranial electric field that causes depolarization of nearby neurons • Over the primary motor cortex, comparable to DCS it allows elicitation of MEPs • For language mapping, repetitive & therefore functionally inhibitory (= disruptive) nTMS causes a so-called "virtual lesion"	No	High spatial resolution	Current distribution & availability	While language mapping is limited by language capabilities, motor mapping may be performed in children <3 yrs; in line w/ our own experience nTMS was reported to provide reliable data down to 4–6 yrs of age for language functions
Subcortical	Sollmann et al., 2020[7] Rosenstock et al., 2017[18] Bello et al., 2008[19] Sakuma et al., 1991[20]	Tractography	Visualization of the course of subcortical white matter tracts by direction of water diffusion in parallel to white matter fibers	Yes	• Availability • High accuracy if function based	Affected by tumor edema	• For motor & language, it allows for preop risk assessment based on neurophysiological measures, such as excitability, combined w/ tumor-to-tract distance • Other studies also proved the excellent specificity & sensitivity of CST detection of 93–95%

CST = corticospinal tract.

citability of the incompletely myelinated brain by direct electrical stimulation.[30,31]

Intraoperative Monitoring

While all other functions require an awake and responsive patient for monitoring, motor function can be monitored continuously via MEPs by a strip electrode directly placed onto the primary motor cortex and an additional needle electrode at Fpz as the cathodic pole or via transcranial electrical stimulation at C3 and C4 as determined by the 10–20 EEG system. Any decline in amplitude < 50% of the baseline is considered significant if technical problems or anesthesia reasons have been ruled out. For more precise transcranial electrical stimulation results and larger amplitudes, navigated placement of the stimulation electrodes rather than by the 10–20 system should be considered (Table 2).

Anesthesia

For intraoperative neurophysiology, total intravenous anesthesia (propofol, remifentanil) is used, and volatile anesthetics are to be strictly avoided in children as well as adults.[31] For awake surgery, pediatric laryngeal masks can be used. Further special considerations apart from those regularly required for awake surgery (close contact between the anesthesiologist and surgeon, trained team, and neuropsychologist) are not required. However, to address the child's need for a trusted person, a longer and more extensive preoperative preparation together with neuropsychologists and associated disciplines is reasonable.

Illustrative Cases

Case 1

A 7-year-old patient presented with a biopsy-proven right-sided insular pilocytic astrocytoma and another right central lesion (Fig. 2). After nTMS mapping and function-based tractography, resection of the insular lesion and reevaluation of the therapeutic approach of the right-sided lesion were recommended. Surgery resulted in GTR of the insular lesion and a transient paresis of the left upper extremity, which resolved following 6 weeks of rehabilitation. A slight British Medical Research Council grade 4+/5 paresis of the left arm remained. During follow-up, resection of the left central tumor was discussed, but the family decided against this option during consultation, and adjuvant treatment was scheduled.

Case 2

A right parietal lesion was resected in a 5-year-old patient at another hospital that was later diagnosed as an MGMT-negative, H3k27-negative glioblastoma (GBM). After early regrowth of a residual tumor 3 months after surgery, the neurologically completely intact patient was presented for further consultation to our department. MRI revealed a large mass adjacent to the precentral gyrus (Fig. 3A and B). Following functional workup with nTMS mapping and function-based tractography (Fig. 3C and D), resection was recommended because of the location of motor areas in the adjacent gyrus only. Risk assessment concluded a very low chance of surgery-related

TABLE 2. Summary of invasive modalities for cortical and subcortical mapping of functional-anatomical structures

Authors & Year	Modality	Mechanism	Advantages	Disadvantages	Clinical Conclusion
Coppola et al., 2016[4] Behrens et al., 1994[59] Schevon et al., 2007[28]	Extraop grid mapping	In a 1st op approach, grid electrodes are placed on the cortex & either stimulation for functional assessment or seizure detection is performed postop w/ the electrode connections thoroughly draped & diverted btwn electrode placement & resective surgery	Apart from nTMS, extraop mapping is still the only option for electro-physiological stimulation mapping outside the OR	Limited by its cortical nature; allows neither subcortical mapping nor monitoring of system integrity	Cases are reported down to 4 yrs of age for motor & 5 yrs for language
Coppola et al., 2016[4] Roth et al., 2020[29] Taniguchi et al., 1993[58] Trevisi et al., 2016[31]	Intraop DCS & SCS mapping	• DCS mapping in unconscious patients is most frequently done to map the motor cortex • Language mapping requires awake procedures	• Reliable • Largest evidence & experience	• Only available during op • Need for high stimulation currents, which impair the resolution & sensitivity of MEP mapping & monitoring • Language mapping limited to children >8–10 yrs because of awake procedure	Currently, monopolar stimulation in contrast to bipolar stimulation is standard of care; in the pediatric population, only bipolar 50/60-Hz Penfield technique has been well described

OR = operating room.

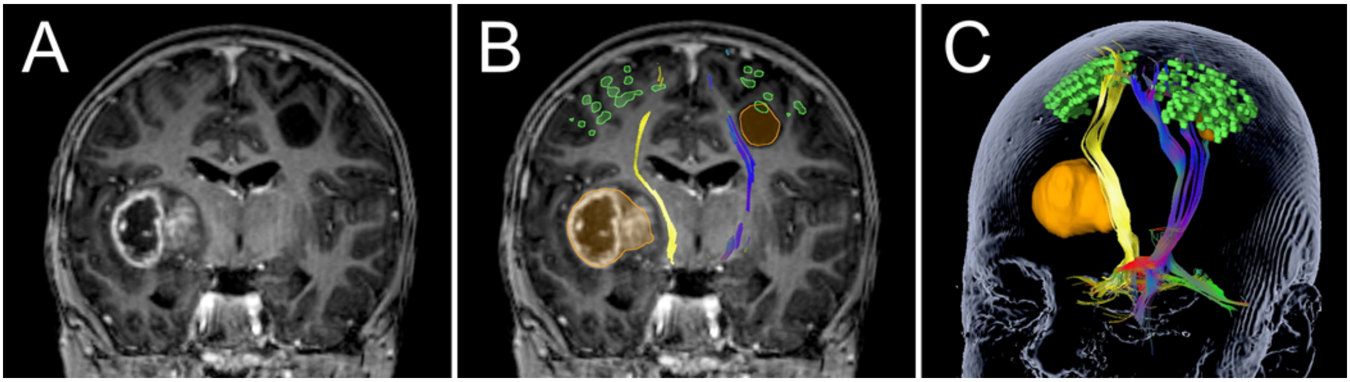

FIG. 2. Case 1. Bilateral pilocytic astrocytoma. **A and B:** Coronal T1-weighted MR images showing the two lesions without any functional data (A), and motor regions (*green*) and the function-based tractography (*yellow* and *blue*) of the corticospinal tract with its relation to the two lesions (*orange*) (B). **C:** Three-dimensional view.

deficits. GTR was then achieved with no functional deterioration, and adjuvant treatment was scheduled within the HIT-HGG trial. The final integrated diagnosis was GBM CNS grade 4, IDH 1 wild type, MYCN amplification, CDKN2A/B deletion.

Discussion

Cases

Both cases clearly demonstrate the options offered by a comprehensive noninvasive preoperative workup. From the treatment team's perspective, proper risk assessment can be done, improving the reliability of patient consultation and selection.[7,18] From the patients' and families' perspectives, such data allow for much improved involvement in decision-making based on reliable functional data, which is otherwise only possible during surgery and invasive DCS mapping. Participation in the evaluation of such data not only helps to improve the consent process but also allows for a tailored function-based surgical therapy in a very personalized way.

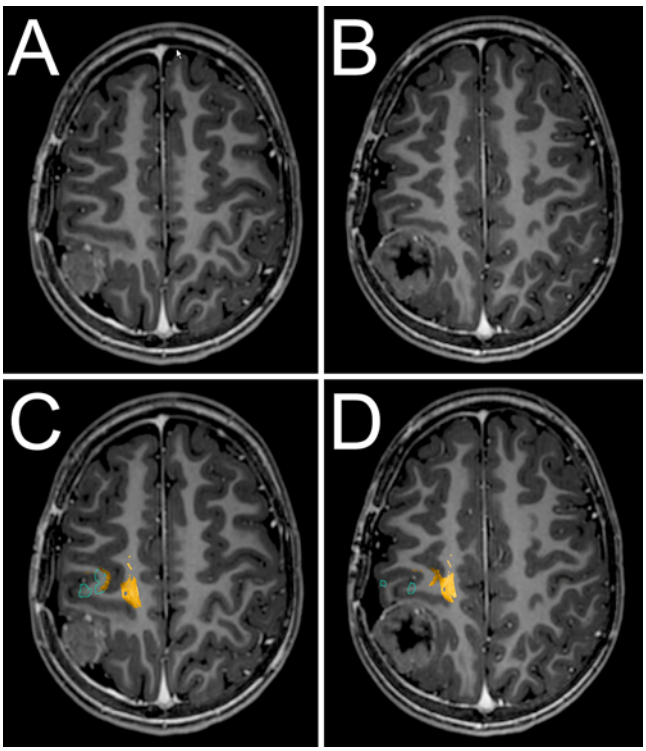

FIG. 3. Case 2. Right parietal GBM. Preoperative axial contrast-enhanced T1-weighted MR images showing the displaced anatomy (**A and B**), and functional data of the motor area (*green*) and function-based tractography (*yellow*) of the corticospinal tract with its relation to the GBM in the same slices (**C and D**).

Implications of Different Functional Anatomy in Children

Cortical and subcortical anatomical maturation proceeds in the developing brain via a series of events (neurogenesis, neuronal migration, synaptogenesis, A and myelination) that overlap in time. While most neurogenesis and neuronal migration is complete at birth, some aspects of these processes as well as synaptic reorganization and myelination continue throughout childhood and into young adulthood.[32,33] This translates into a continuous dynamic remodeling of brain networks, especially for higher-order functions. An optimistic glass-half-full interpretation of such developmental biology is that much of the damage to the pediatric brain can be compensated for quite well, as incomplete brain maturation allows uninjured cortical areas to acquire functions that may be lost during injury. Although stated more precisely, cortical function is relatively diffuse in the developing brain and coalesces to the adult functional map only with maturation. For instance, arm motor cortical representation is bilateral in the neonate and infant and matures to a more contralateral adult organization only in later childhood. Thus, corticospinal tract injury in one hemisphere corresponds to preservation of bilateral motor representation in the contralesional hemisphere.[34] While neuroplasticity is limited mainly by subcortical white matter tract connectivity in adults, this is only partially true in children.

Neuroplasticity

In adult patients affected by gliomas, an increasing number of studies have revealed the potential of tumorinduced functional reorganization. This has been demonstrated for functions with a particular interest in neurosurgery, such as motor and language. Functional anatomy of the motor system has shown a shift in the anteroposterior direction of up to 1 cm or one gyrus during postoperative follow-up investigations.[1,2,8] Language, as a more global network function, exhibits broader patterns, such as wider spread or even partial shifting to the nondominant hemisphere.[3,8] Clinically, the degree of a functional shift to the nondominant hemisphere correlates with a reduced risk of surgery-related aphasia after perisylvian tumor removal.[35] Comparable findings have been observed in the small collection of pediatric cases. Reports have demonstrated that children exhibit not only different cortical patterns of function, such as language, but also altered connectivity profiles.[36]

Apart from the detection of functional reorganization, its induction may open new avenues for pediatric neuro-oncology and especially neurosurgery. As outlined above, repetitive nTMS induces functional reorganization in adult glioma patients.[26] Under physiological conditions, upper-extremity movement is coordinated by both hemispheres and bilateral communication. This avoids mirror movements and enables bilateral coordination. In the damaged brain, transcallosal inhibition (TCI) was shown to aggravate motor recovery by causing pathological overinhibition of the damaged hemisphere by the healthy contralateral motor cortex.[37] Thus, various stroke trials, as well as a recent trial in gliomas, demonstrated improved motor recovery by decreasing TCI via noninvasive downregulation of the contralesional motor cortex.[38] While this has not yet been proven in children affected by glioma, the basic principle of TCI is not different. A randomized trial in pediatric stroke patients has demonstrated the efficacy of contralesional repetitive TMS in the chronic phase using almost the same stimulation protocol as in the current adult glioma trial.[26,39]

Multimodal Surgical Approach

Preoperative Functional Workup

Preoperative functional workup with mapping and function-based tractography is crucial for an optimized function-guided neuro-oncological approach. It allows the treatment team and tumor board to estimate EOR and associated risks of subtotal resection, GTR, or even supramarginal resection.[7,18] It has also been demonstrated that the presence of reliable functional data leads to a considerable translation from planned biopsy toward the decision of tumor resection.[40] In a modern approach, intraoperative neurophysiology starts with presurgical mapping.

Intraoperative Assessment

As prognosis relies in almost any CNS tumor on maximal safe resection, it remains the most important goal regardless of the patient's age. While fluorescent dyes, especially 5-aminolevulinic acid (5-ALA), help to identify tumor tissue of the infiltration zone in HGGs, other measures, such as iMRI, help to update the aforementioned continuous balancing between risk of further resection and oncological impact of tumor remnant. While the beneficial effects of iMRI have been reported repeatedly, its infrastructural difficulties and associated costs still slow down its distribution. Ultrasound, for an intraoperative update of neuronavigation, is another option. Fluorescent dyes have been in neurosurgical use for more than 1 decade, and the evidence for better EOR and survival has been shown in several trials. These dyes usually help in the intraoperative identification of tumor tissue, especially in HGGs. While 5-ALA has been a well-established modality in adult glioma patients for over a decade, its use in children remains off label and its usefulness is currently rare.[41] A multicenter trial evaluating the efficiency of 5-ALA in children is currently recruiting (EuDraCT no. 2014-005669-54).

Supramarginal Resection

The infiltrative nature of gliomas collides with the functional borders within the brain when it comes to optimal treatment. While it is currently clear that the degree of surgical tumor reduction correlates with malignant transformation and PFS, data on the resection far beyond visible tumor borders are not available to date.[42] Yet there is increasing evidence in adult patients that such supramarginal resection improves the course of the disease considerably, leading to better PFS, overall survival, and reduced malignant transformation independently from molecular markers.[43]

Multimodal functional mapping and monitoring allow for a much better definition of resection margins far beyond tumor borders. Looking at the plastic potential of the pediatric brain and the overall oncological potential, supramarginal resection needs to be considered as a valid treatment option. However, pediatric data are currently not available.

Morbidity

Data on surgical morbidity are particularly rare in children and often restricted to tumors of the posterior fossa.[44] The currently largest series refers to ependymomas rather than gliomas. However, sufficient data exist on functional impairments, such as vision, and consecutive negative effects on quality of life (QOL) in children.[45] Long-term data in rather small cohorts of pediatric brain tumor patients have demonstrated the aggravating effects of treatment-related morbidity on QOL during long-term follow-up.[46]

Oncological Impact

Neurosurgery serves several important functions in pediatric neuro-oncology 1) as a potentially lifesaving emergency procedure to alleviate intracranial pressure (e.g., due to hydrocephalus), 2) establishing a tissue diagnosis, and 3) producing an optimal minimal residual disease scenario for adjuvant treatment including chemo- as well as radiotherapy.[47]

EOR has repeatedly been demonstrated to be an important prognostic factor for event-free and overall survival. In a large retrospective evaluation of early mortality in more than 5000 children with gliomas, resection was a significant predictor of positive outcome.[48]

Regarding long-term morbidity, gliomas, especially in eloquent areas of the brain, should under any circum-

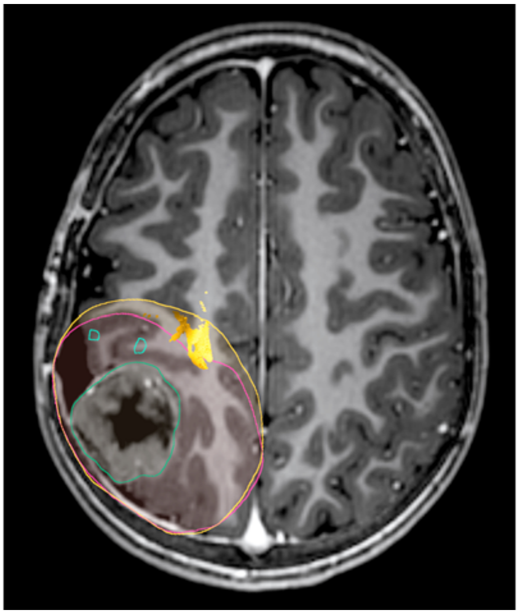

FIG. 4. Case 2. Axial contrast-enhanced MR image showing radiotherapy planning according to the HIT-HGG protocol. While the planning target volume is shown in *yellow*, *red* demonstrates the function-sparing approach as described in earlier works of our group. *Green* indicates motor function.

stances only be operated on by an experienced team with abundant experience in neuromonitoring. Within an interdisciplinary tumor board, the indication for biopsy versus an attempt at a complete resection involving novel pre- and intraoperative techniques must be discussed, weighing factors such as development of the child, eloquent areas of the brain, the ability to resect a majority of the tumor, and the potential of combinatory approaches of radio- and chemotherapy following neurosurgery.

Future Directions

Surgery

Overall, the evidence of various aspects of surgical glioma treatment in children needs to be improved considerably as outlined above and below. Likewise, approaches already established or in incipient clinical studies in adult patients should be assessed for the pediatric population. This starts with fluorescent dyes, such as 5-ALA or fluorescein, and proceeds with intravital confocal microscopy to estimate the extent of tumor infiltration in a real-time manner.

As a handful of groups start to evaluate neuroplasticity and functional reorganization as a new approach in neuro-oncology, the induction and the potential of functional reorganization rather than mere detection could be high potential targets of modern pediatric neuro-oncology research.

Radiation Oncology

With technical improvements of multimodality therapy and new advantages in systemic therapies, survival rates have increased over the last decades. Thus, QOL preservation and neurocognitive functions become even more crucial. The degree of neurotoxicity due to radiotherapy is related to the volume and dose of normal brain tissue exposure. Recent studies, however, have suggested that increased radiotherapy conformality, achieved via intensity-modulated radiation therapy, stereotactic radiosurgery such as Gamma Knife radiosurgery, or proton radiotherapy, may improve neurocognitive function compared with less conformal techniques.[49] The technical developments in radiation oncology have the ability to precisely deliver radiation doses to target volumes while avoiding sensitive organs at risk. Many contouring guidelines for target delineation grow from a historical context rather than being evidence based and are often based on a simple uniform margin with respect to larger anatomical barriers. The target areas of the current glioma guidelines emphasize the presence of edema or areas of T2-weighted/FLAIR hyperintensity, and the irradiation volume is relatively large. However, there is a continuous aim to reduce and optimize pediatric brain target volumes by a better understanding of areas at risk for early recurrence or involvement and patterns of spread. Utilization of these advances requires accurate delineation of avoidance structures. New and noninvasive methods, such as fMRI and tractography, and neurophysiological methods such as nTMS facilitate the identification of eloquent areas prior to radiotherapy and provide the potential to improve and challenge current target volumes (Fig. 4).

A recent report investigating the effects of proton therapy on neurocognition in pediatric patients found that domains of processing speed and visuospatial construction were compromised after less conformal radiotherapy techniques compared with highly conformal proton radiotherapy. While white matter tracts are particularly susceptible to radiation-induced damage, brain surgery was also found to alter white matter functionality.[50] Because of the similar pathophysiological effect on white matter structures independent of the actual cause, the authors concluded that localized damage to white matter tracts impairs overall processing speed to the same extent, irrespective of the treatment approach.[51] Domains dependent on intact white matter structures appear to be especially vulnerable to brain tumor treatment independent of treatment modality. This is also well known from awake surgery and mapping. Even very minor injury to respective tracts can cause severe neuropsychological deficits in contrast to cortical injury, which can be quite considerable without any clinical effect. We hypothesize that the use of advanced neurophysiological testing/mapping can further improve treatment planning and eventually (neurocognitive) outcomes in pediatric patients comparable to those achieved with surgical/perioperative use. Neurophysiological methods such as nTMS could help to improve the balance of tumor control versus normal tissue toxicity or cognition.[52,53] Further trials are warranted to investigate this potential.

Medical Oncology

The advent of targeted treatments holds great promise for the therapy of refractory or unresectable HGG. Recent clinical trials have demonstrated responses to small molecules such as the MEK inhibitors, even in refractory

LGGs.[54] The role of neurosurgery is thus being continuously reevaluated, as previously seemingly untreatable tumors may soon be amenable to operative removal following treatment with novel compounds that reduce the volume of respective lesions in a neoadjuvant setting.[55]

Further Application of Noninvasive Methods

Refinement of noninvasive mapping methods is required to accommodate very young and uncooperative patients (i.e., those unable to tolerate current fMRI, MEG, or nTMS protocols) and to better mimic an anatomical injury (i.e., identifying stimulation parameters that generate a virtual lesion with minimal activation of nearby structures), and prehabilitation. In particular, prehabilitation by preoperative network modulation via repetitive nTMS has high therapeutic potential. Prehabilitation as a strategy to optimize function, or its location in the brain, prior to surgery is undergoing active exploration in adult neuro-oncology. While this approach is more likely to be successful in functions involving larger networks, such as language rather than motor networks, the developing brain seems to present an even more suitable structure for this approach. Especially for motor function, TCI represents a rational prehabilitation target in the pediatric population since its strength was shown to correlate with hand function per se.[56] Given its safety and tolerability in children and its demonstrated capacity to modulate TCI, nTMS is a suitable tool for this endeavor.[26,39]

Research Summary

In contrast to most adjuvant treatment options for pediatric glioma patients, surgical treatment lacks high-quality data and results from multicentric trials. Topics such as induction of functional reorganization, supramarginal resections, fluorescent dyes, and intraoperative radiotherapy of the resection cavity have a considerable potential to avoid morbidity and increase QOL and survival. Current registries and biobanking take neither functional locations nor surgery-related data, such as resection limits or minor residual tumor, into account. In this context, the neuro-oncological team needs to be clearly defined in guidelines.

On another note, enhanced functional pre- and intraoperative evaluation of the child with a CNS tumor should be performed as part of any prospective clinical trial in pediatric neuro-oncology, especially in tumors for which surgery remains the most important factor for prognosis. Putting a focus on these issues is one major objective of this article.

Conclusions

While functional mapping has a great potential for the improvement of EOR and functional outcome, it opens a completely new approach to personalized neuro-oncology for the entire treatment team. Moreover, functional mapping allows strong involvement of patients and their families, especially when it comes to risk assessment of GTR or the planning of supramarginal resections. With such comprehensive approaches, even very young children can undergo extraoperative mapping and resection comparable to the awake intraoperative mapping and resection that is performed in adults. Pediatric neuro-oncology becomes an even more interdisciplinary field with more disciplines and more treatment and diagnostic options but also the need for reliable referrals to such highly specialized centers.

Acknowledgments

This work was funded entirely by institutional grants from the departments of the authors.

References

1. Southwell DG, Birk HS, Han SJ, Li J, Sall JW, Berger MS. Resection of gliomas deemed inoperable by neurosurgeons based on preoperative imaging studies. *J Neurosurg*. 2018; 129(3):567-575.
2. Conway N, Wildschuetz N, Moser T, et al. Cortical plasticity of motor-eloquent areas measured by navigated transcranial magnetic stimulation in patients with glioma. *J Neurosurg*. 2017;127(5):981-991.
3. Traut T, Sardesh N, Bulubas L, et al. MEG imaging of recurrent gliomas reveals functional plasticity of hemispheric language specialization. *Hum Brain Mapp*. 2019;40(4):1082-1092.
4. Coppola A, Tramontano V, Basaldella F, Arcaro C, Squintani G, Sala F. Intra-operative neurophysiological mapping and monitoring during brain tumour surgery in children: an update. *Childs Nerv Syst*. 2016;32(10):1849-1859.
5. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci*. 2003;6(3):309-315.
6. Rivkin MJ. Developmental neuroimaging of children using magnetic resonance techniques. *Ment Retard Dev Disabil Res Rev*. 2000;6(1):68-80.
7. Sollmann N, Zhang H, Fratini A, et al. Risk assessment by presurgical tractography using navigated TMS maps in patients with highly motor- or language-eloquent brain tumors. *Cancers (Basel)*. 2020;12(5):E1264.
8. Ille S, Engel L, Albers L, et al. Functional reorganization of cortical language function in glioma patients—a preliminary study. *Front Oncol*. 2019;9:446.
9. Gallentine WB, Mikati MA. Intraoperative electrocorticography and cortical stimulation in children. *J Clin Neurophysiol*. 2009;26(2):95-108.
10. Giussani C, Roux FE, Ojemann J, Sganzerla EP, Pirillo D, Papagno C. Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. *Neurosurgery*. 2010;66(1):113-120.
11. Azad TD, Duffau H. Limitations of functional neuroimaging for patient selection and surgical planning in glioma surgery. *Neurosurg Focus*. 2020;48(2):E12.
12. Tarapore PE, Tate MC, Findlay AM, et al. Preoperative multimodal motor mapping: a comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation. *J Neurosurg*. 2012;117(2):354-362.
13. Narayana S, Gibbs SK, Fulton SP, et al. Clinical utility of transcranial magnetic stimulation (TMS) in the presurgical evaluation of motor, speech, and language functions in young children with refractory epilepsy or brain tumor: preliminary evidence. *Front Neurol*. 2021;12:650830.
14. Rosenstock T, Picht T, Schneider H, Koch A, Thomale UW. Left perisylvian tumor surgery aided by TMS language mapping in a 6-year-old boy: case report. *Childs Nerv Syst*. 2019; 35(1):175-181.
15. Krieg SM, Sabih J, Bulubasova L, et al. Preoperative motor

mapping by navigated transcranial magnetic brain stimulation improves outcome for motor eloquent lesions. *Neuro Oncol*. 2014;16(9):1274-1282.
16. Ille S, Schroeder A, Albers L, et al. Non-invasive mapping for effective preoperative guidance to approach highly language-eloquent gliomas—a large scale comparative cohort study using a new classification for language eloquence. *Cancers (Basel)*. 2021;13(2):E207.
17. Lehtinen H, Mäkelä JP, Mäkelä T, et al. Language mapping with navigated transcranial magnetic stimulation in pediatric and adult patients undergoing epilepsy surgery: comparison with extraoperative direct cortical stimulation. *Epilepsia Open*. 2018;3(2):224-235.
18. Rosenstock T, Grittner U, Acker G, et al. Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation data. *J Neurosurg*. 2017;126(4):1227-1237.
19. Bello L, Gambini A, Castellano A, et al. Motor and language DTI fiber tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. *Neuroimage*. 2008;39(1):369-382.
20. Sakuma H, Nomura Y, Takeda K, et al. Adult and neonatal human brain: diffusional anisotropy and myelination with diffusion-weighted MR imaging. *Radiology*. 1991;180(1):229-233.
21. Maheshwari M. Pediatric presurgical functional MRI. *Top Magn Reson Imaging*. 2019;28(4):197-204.
22. Roland JL, Griffin N, Hacker CD, et al. Resting-state functional magnetic resonance imaging for surgical planning in pediatric patients: a preliminary experience. *J Neurosurg Pediatr*. 2017;20(6):583-590.
23. Picht T, Frey D, Thieme S, Kliesch S, Vajkoczy P. Presurgical navigated TMS motor cortex mapping improves outcome in glioblastoma surgery: a controlled observational study. *J Neurooncol*. 2016;126(3):535-543.
24. Giglhuber K, Maurer S, Zimmer C, Meyer B, Krieg SM. Mapping visuospatial attention: the greyscales task in combination with repetitive navigated transcranial magnetic stimulation. *BMC Neurosci*. 2018;19(1):40.
25. Schramm S, Sollmann N, Ille S, Meyer B, Krieg SM. Application of navigated transcranial magnetic stimulation to map the supplementary motor area in healthy subjects. *J Clin Neurophysiol*. 2020;37(2):140-149.
26. Ille S, Kelm A, Schroeder A, et al. Navigated repetitive transcranial magnetic stimulation improves the outcome of postsurgical paresis in glioma patients - a randomized, double-blinded trial. *Brain Stimul*. 2021;14(4):780-787.
27. Weiss Lucas C, Tursunova I, Neuschmelting V, et al. Functional MRI vs. navigated TMS to optimize M1 seed volume delineation for DTI tractography. A prospective study in patients with brain tumours adjacent to the corticospinal tract. *Neuroimage Clin*. 2016;13:297-309.
28. Schevon CA, Carlson C, Zaroff CM, et al. Pediatric language mapping: sensitivity of neurostimulation and Wada testing in epilepsy surgery. *Epilepsia*. 2007;48(3):539-545.
29. Roth J, Korn A, Sala F, et al. Intraoperative neurophysiology in pediatric supratentorial surgery: experience with 57 cases. *Childs Nerv Syst*. 2020;36(2):315-324.
30. Talabaev M, Venegas K, Zabrodets G, et al. Result of awake surgery for pediatric eloquent brain area tumors: single-center experience. *Childs Nerv Syst*. 2020;36(11):2667-2673.
31. Trevisi G, Roujeau T, Duffau H. Awake surgery for hemispheric low-grade gliomas: oncological, functional and methodological differences between pediatric and adult populations. *Childs Nerv Syst*. 2016;32(10):1861-1874.
32. Dubois J, Dehaene-Lambertz G, Kulikova S, Poupon C, Hüppi PS, Hertz-Pannier L. The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. *Neuroscience*. 2014;276:48-71.
33. Tau GZ, Peterson BS. Normal development of brain circuits. *Neuropsychopharmacology*. 2010;35(1):147-168.
34. Eyre JA. Corticospinal tract development and its plasticity after perinatal injury. *Neurosci Biobehav Rev*. 2007;31(8):1136-1149.
35. Ille S, Kulchytska N, Sollmann N, et al. Hemispheric language dominance measured by repetitive navigated transcranial magnetic stimulation and postoperative course of language function in brain tumor patients. *Neuropsychologia*. 2016;91:50-60.
36. Orukari IE, Siegel JS, Warrington NM, et al. Altered hemodynamics contribute to local but not remote functional connectivity disruption due to glioma growth. *J Cereb Blood Flow Metab*. 2020;40(1):100-115.
37. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol*. 2004;55(3):400-409.
38. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol*. 2006;5(8):708-712.
39. Kirton A, Chen R, Friefeld S, Gunraj C, Pontigon AM, Deveber G. Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial. *Lancet Neurol*. 2008;7(6):507-513.
40. Picht T, Schulz J, Hanna M, Schmidt S, Suess O, Vajkoczy P. Assessment of the influence of navigated transcranial magnetic stimulation on surgical planning for tumors in or near the motor cortex. *Neurosurgery*. 2012;70(5):1248-1257.
41. Schwake M, Schipmann S, Müther M, Köchling M, Brentrup A, Stummer W. 5-ALA fluorescence-guided surgery in pediatric brain tumors-a systematic review. *Acta Neurochir (Wien)*. 2019;161(6):1099-1108.
42. Molinaro AM, Hervey-Jumper S, Morshed RA, et al. Association of maximal extent of resection of contrast-enhanced and non-contrast-enhanced tumor with survival within molecular subgroups of patients with newly diagnosed glioblastoma. *JAMA Oncol*. 2020;6(4):495-503.
43. Rossi M, Gay L, Ambrogi F, et al. Association of supratotal resection with progression-free survival, malignant transformation, and overall survival in lower-grade gliomas. *Neuro Oncol*. 2021;23(5):812-826.
44. Grønbæk JK, Wibroe M, Toescu S, et al. Postoperative speech impairment and surgical approach to posterior fossa tumours in children: a prospective European multicentre cohort study. *Lancet Child Adolesc Health*. 2021;5(11):814-824.
45. Peragallo JH, Bruce BB, Vasseneix C, et al. Vision-related quality-of-life in pediatric primary brain tumor patients. *J Neurooncol*. 2021;154(3):365-373.
46. Lundar T, Due-Tønnessen BJ, Egge A, et al. Neurosurgical treatment of brain tumors in the first 6 months of life: long-term follow-up of a single consecutive institutional series of 30 patients. *Childs Nerv Syst*. 2015;31(12):2283-2290.
47. Frühwald MC, Rutkowski S. Tumors of the central nervous system in children and adolescents. *Dtsch Arztebl Int*. 2011;108(22):390-397.
48. Zhou X, Niu X, Sun K, Li J, Mao Q, Liu Y. Pediatric glioma outcomes: predictors of early mortality. *World Neurosurg*. 2020;139:e700-e707.
49. Kahalley LS, Douglas Ris M, Mahajan A, et al. Prospective, longitudinal comparison of neurocognitive change in pediatric brain tumor patients treated with proton radiotherapy versus surgery only. *Neuro Oncol*. 2019;21(6):809-818.
50. Law N, Bouffet E, Laughlin S, et al. Cerebello-thalamo-cerebral connections in pediatric brain tumor patients: impact on working memory. *Neuroimage*. 2011;56(4):2238-2248.
51. Weusthof K, Luttich P, Regnery S, et al. Neurocognitive outcomes in pediatric patients following brain irradiation. *Cancers (Basel)*. 2021;13(14):3538.

52. Diehl CD, Schwendner MJ, Sollmann N, et al. Application of presurgical navigated transcranial magnetic stimulation motor mapping for adjuvant radiotherapy planning in patients with high-grade gliomas. *Radiother Oncol*. 2019;138:30-37.
53. Picht T, Schilt S, Frey D, Vajkoczy P, Kufeld M. Integration of navigated brain stimulation data into radiosurgical planning: potential benefits and dangers. *Acta Neurochir (Wien)*. 2014;156(6):1125-1133.
54. Selt F, van Tilburg CM, Bison B, et al. Response to trametinib treatment in progressive pediatric low-grade glioma patients. *J Neurooncol*. 2020;149(3):499-510.
55. van Tilburg CM, Pfaff E, Pajtler KW, et al. The pediatric precision oncology INFORM registry: clinical outcome and benefit for patients with very high-evidence targets. *Cancer Discov*. 2021;11(11):2764-2779.
56. Kurth F, Mayer EA, Toga AW, Thompson PM, Luders E. The right inhibition? Callosal correlates of hand performance in healthy children and adolescents callosal correlates of hand performance. *Hum Brain Mapp*. 2013;34(9):2259-2265.
57. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol*. 1997; 387(2):167-178.
58. Taniguchi M, Cedzich C, Schramm J. Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. *Neurosurgery*. 1993;32(2): 219-226.
59. Behrens E, Zentner J, van Roost D, et al. Subdural and depth electrodes in the presurgical evaluation of epilepsy. *Acta Neurochir (Wien)*. 1994;128(1-4):84-87.
60. Berger MS, Kincaid J, Ojemann, GA, Lettich E. Brain mapping techniques to maximize resection, safety, and seizure control in children with brain tumors. *Neurosurgery*. 1989;25(5):786-792.

Disclosures

Dr. Krieg: consultant for and non–study-related clinical or research support from Brainlab and Ulrich; and speakers bureau for Nexstim, Medtronic, and Zeiss. Dr. Ille: consultant for Brainlab AG and Icotec AG; and honoraria from Nexstim. Dr. Meyer: consultant for Brainlab and Ulrich.

Author Contributions

Conception and design: Krieg, Bernhard, Frühwald. Acquisition of data: Krieg, Bernhard, Frühwald. Analysis and interpretation of data: Krieg, Bernhard, Frühwald. Drafting the article: Krieg, Bernhard, Rotenberg, Frühwald. Critically revising the article: Bernhard, Ille, Rotenberg, Frühwald. Reviewed submitted version of manuscript: Krieg, Ille, Meyer, Combs. Approved the final version of the manuscript on behalf of all authors: Krieg. Administrative/technical/material support: Krieg, Meyer, Combs, Frühwald. Study supervision: Krieg, Rotenberg, Frühwald.

Supplemental Information

Videos

Video Abstract. https://vimeo.com/766175570.

Correspondence

Sandro M. Krieg: Klinikum rechts der Isar, Technische Universität München, Munich, Germany. sandro.krieg@tum.de.