Modern preoperative imaging and functional mapping in patients with intracranial glioma

Moderne präoperative Bildgebung und funktionelle Kartierung bei Patienten mit intrakraniellen Gliomen

Authors

Nico Sollmann[1, 2, 3, 4], Haosu Zhang[5], Christopher Kloth[1], Claus Zimmer[2, 3], Benedikt Wiestler[2, 6], Johannes Rosskopf[1, 7], Kornelia Kreiser[1, 8], Bernd Schmitz[1, 7], Meinrad Beer[1], Sandro M. Krieg[3, 5]

Affiliations

1 Department of Diagnostic and Interventional Radiology, University Hospital Ulm, Ulm, Germany
2 Department of Diagnostic and Interventional Neuroradiology, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, München, Germany
3 TUM-Neuroimaging Center, Klinikum rechts der Isar, Technical University of Munich, München, Germany
4 Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, United States
5 Department of Neurosurgery, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, München, Germany
6 TranslaTUM – Central Institute for Translational Cancer Research, Klinikum rechts der Isar, Technical University of Munich, München, Germany
7 Section of Neuroradiology, Bezirkskrankenhaus Günzburg, Günzburg, Germany
8 Department of Radiology and Neuroradiology, Universitäts- und Rehabilitationskliniken Ulm, Ulm, Germany

Key words

glioma, preoperative mapping, functional mapping, magnetic resonance imaging, navigated transcranial magnetic stimulation, tractography

received 23.07.2021
accepted 18.04.2023
published online 24.05.2023

Bibliography

Fortschr Röntgenstr 2023; 195: 989–1000
DOI 10.1055/a-2083-8717
ISSN 1438-9029

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Dr. Nico Sollmann
Department of Diagnostic and Interventional Radiology, University Hospital Ulm, Albert-Einstein-Allee 23, 89081 Ulm, Germany
Tel.: +49/7 31/5 00-6 10 01
nico.sollmann@tum.de

Zusätzliches Material finden Sie unter https://doi.org/10.1055/a-2083-8717

ABSTRACT

Magnetic resonance imaging (MRI) in therapy-naïve intracranial glioma is paramount for neuro-oncological diagnostics, and it provides images that are helpful for surgery planning and intraoperative guidance during tumor resection, including assessment of the involvement of functionally eloquent brain structures. This study reviews emerging MRI techniques to depict structural information, diffusion characteristics, perfusion alterations, and metabolism changes for advanced neuro-oncological imaging. In addition, it reflects current methods to map brain function close to a tumor, including functional MRI and navigated transcranial magnetic stimulation with derived function-based tractography of subcortical white matter pathways. We conclude that modern preoperative MRI in neuro-oncology offers a multitude of possibilities tailored to clinical needs, and advancements in scanner technology (e. g., parallel imaging for acceleration of acquisitions) make multi-sequence protocols increasingly feasible. Specifically, advanced MRI using a multi-sequence protocol enables noninvasive, image-based tumor grading and phenotyping in patients with glioma. Furthermore, the add-on use of preoperatively acquired MRI data in combination with functional mapping and tractography facilitates risk stratification and helps to avoid perioperative functional decline by providing individual information about the spatial location of functionally eloquent tissue in relation to the tumor mass.

Key Points:

- Advanced preoperative MRI allows for image-based tumor grading and phenotyping in glioma.
- Multi-sequence MRI protocols nowadays make it possible to assess various tumor characteristics (incl. perfusion, diffusion, and metabolism).
- Presurgical MRI in glioma is increasingly combined with functional mapping to identify and enclose individual functional areas.

- Advancements in scanner technology (e. g., parallel imaging) facilitate increasing application of dedicated multi-sequence imaging protocols.

Citation Format

- Sollmann N, Zhang H, Kloth C et al. Modern preoperative imaging and functional mapping in patients with intracranial glioma. Fortschr Röntgenstr 2023; 195: 989–1000

ZUSAMMENFASSUNG

Der Magnetresonanztomografie (MRT) bei unbehandelten intrakraniellen Gliomen kommt entscheidende Bedeutung im Rahmen der neuroonkologischen Diagnostik zu, während die MRT-Bildgebung zum Zeitpunkt vor einer neurochirurgischen Tumorresektion zudem Bilddaten liefert, welche die chirurgische Planung und das intraoperative Vorgehen unterstützen können und insbesondere Rückschlüsse auf eine mögliche Beteiligung funktionell eloquenter Strukturen zulassen. Die vorliegende Arbeit stellt aktuell aufkommende MRT-basierte Techniken vor, welche eine Darstellung von strukturellen und diffusionsbasierten Charakteristika sowie Perfusionsveränderungen und Alterationen des Metabolismus im neuroonkologischen Zusammenhang ermöglichen. Darüber hinaus stellt sie fortschrittliche Methoden zur Kartierung von Gehirnfunktionen in Nachbarschaft eines Tumors vor unter Einbezug der funktionellen MRT sowie der navigierten transkraniellen Magnetstimulation und funktionsbasierten Traktografie von subkortikalen Faserbahnen der weißen Substanz. Zusammenfassend eröffnet die moderne präoperative MRT-Bildgebung in der Neuroonkologie eine wachsende Bandbreite an Möglichkeiten gemäß der individuellen klinischen Anforderungen, wobei Weiterentwicklungen im Bereich der Scanner-Technologie (z. B. parallele Bildgebung zur Beschleunigung der Bildakquisition) auch Protokolle mit einer zunehmenden Anzahl von Sequenzen möglich machen. Im Speziellen erlaubt eine fortschrittliche MRT-Bildgebung mittels multisequenzieller Protokolle eine nichtinvasive, bildbasierte Tumorklassifikation und Phänotypisierung bei Patienten mit Gliomen. Des Weiteren ermöglicht die zusätzliche Verwendung präoperativer MRT-Bildgebung in Kombination mit funktioneller Kartierung und Traktografie eine Risikostratifizierung und hilft bei der Vermeidung perioperativer funktioneller Defizite, da individuelle Informationen über die räumliche Lokalisation funktionell eloquenter Strukturen in Relation zum Tumor bereitgestellt werden können.

Kernaussagen:

- Moderne präoperative MRT-Bildgebung ermöglicht eine bildgestützte Tumorklassifikation und Phänotypisierung bei Gliomen.
- Bildgebungsprotokolle mit vielfältigen Sequenzen können heutzutage eine Darstellung verschiedenster Tumorcharakteristika gewährleisten (inkl. Perfusion, Diffusion sowie Metabolismus).
- Präoperative MRT-Bildgebung bei Gliomen wird zunehmend mit funktioneller Kartierung zur Identifikation und Abgrenzung individueller funktioneller Areale kombiniert.
- Weiterentwicklungen der Scanner-Technologie (z. B. parallele Bildgebung) können zu einer weiter verbreiteten Anwendung spezifischer multisequenzieller Bildgebungsprotokolle beitragen.

Introduction

Gliomas represent the most common malignant entity of neoplasms of the central nervous system (CNS), accounting for approximately 50 % of all malignant brain tumors [1, 2]. According to the 2021 World Health Organization (WHO) classification of tumors of the CNS, gliomas can be categorized into different entities according to combined histological and molecular grading [3]. High-grade astrocytoma and glioblastoma are particularly common high-grade tumors (WHO grades 3 and 4) and have extraordinarily poor prognoses (5-year survival rates below 30 %) [1, 2]. Therapy in most cases includes neurosurgical tumor resection and extended focal irradiation, as well as adjuvant chemotherapy [4–6].

During the course of disease, cranial magnetic resonance imaging (MRI) is paramount for the diagnosis, prognosis estimation, and treatment response assessment and monitoring. Specifically, initial imaging prior to tumor resection allows not only assessment of the distinct location of tumor growth and involved structures but also image-based tumor grading and phenotyping [7, 8]. Furthermore, preoperative MRI provides images crucial for neurosurgical tumor resection planning and guidance, which can include the assessment of the involvement of functionally eloquent brain structures using additional techniques such as functional MRI (fMRI) and tractography of subcortical white matter (WM) pathways [9, 10]. Lately, navigated transcranial magnetic stimulation (nTMS) has found its way into the armamentarium of the preoperative workup of patients with glioma, providing image-based functional mapping data with the major goal of sparing functionally eloquent brain tissue from harm during resection [11, 12]. Functional data derived from fMRI or nTMS mapping can also be effectively combined with diffusion-weighted MRI to establish function-based tractography of major WM bundles, such as the corticospinal tract (CST) or arcuate fascicle (AF) [12, 13].

Against this background, the purpose of this narrative review article is to provide an overview of advanced preoperative MRI and functional mapping. Specifically, we review applications such as diffusion-weighted imaging including fiber tractography, magnetic resonance spectroscopy (MRS), perfusion imaging, contrast-enhanced T1-weighted imaging, fMRI, and nTMS. Relevant studies were identified by PubMed search (http://www.ncbi.nlm.nih.gov/pubmed; **Supplementary Table**).

Advanced Preoperative Imaging

Overview of methods

Conventional structural MRI defines the standard approach in neuro-oncological imaging, including axial fluid-attenuated inversion recovery (FLAIR), axial diffusion-weighted imaging, axial T2-weighted, and three-dimensional (3D) T1-weighted sequences before and after the administration of contrast agents using a 1.5-Tesla MRI system at minimum [14, 15]. This approach is commonly supplemented by further advanced sequences, depending on technical feasibility, time constraints, and individual needs with respect to interdisciplinary clinical requirements: diffusion tensor imaging (DTI) or specific high-resolution iso-volumetric 3D imaging may be added for dedicated neurosurgical needs or radiosurgical planning [14, 16, 17].

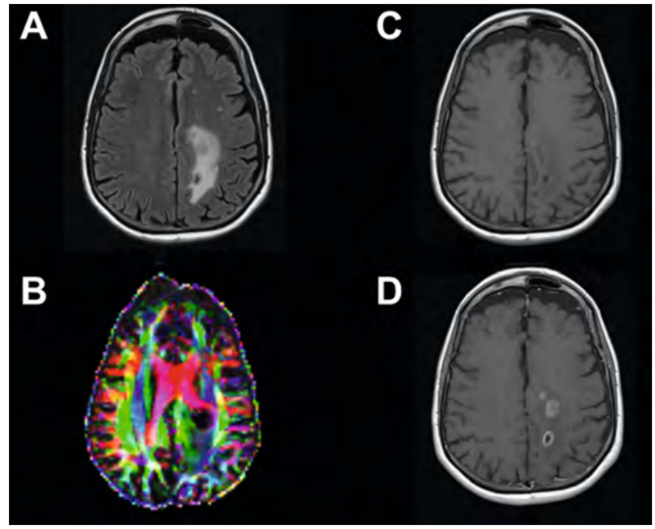
Diffusion-weighted imaging

Diffusion-weighted imaging in neuro-oncology covers a broad spectrum of different sequences and approaches. Most commonly, the DTI technique is used during the clinical routine, which investigates the shape of diffusion considering direction (eigenvectors) as well as diffusivity (eigenvalues) and allows extraction of scalar measures such as the fractional anisotropy (FA), either for specific regions of interest (ROIs) or the whole brain [18, 19]. Commonly, maximal and/or mean FA values are significantly higher in high-grade glioma compared to low-grade glioma, with a pattern of infiltration and disruption of fibers being more characteristic for high-grade tumors [20–22]. Specifically, cutoff values of 0.129 (mean FA) and 0.219 (maximal FA) have been proposed to distinguish between low- and high-grade glioma, with a resulting specificity of 69.2 %/76.9 % and sensitivity of 93.3 %/100 % [21]. Additionally, studies used the FA to discriminate between tumors according to the isocitrate dehydrogenase (IDH) mutation status, which has become a relevant diagnostic marker since mutation correlates to less aggressive biologic behavior and better clinical outcome compared to the wild-type status [23]. Maximal FA and the ratio of maximal FA (maximal FA divided by the contralateral normal FA) were significantly different between oligodendroglial tumors with IDH mutations and those without mutations (area under the curve [AUC]: 0.79 and 0.82) [24, 25]. Furthermore, DTI-derived parameters, in particular mean diffusivity and FA, can visualize tumor cell densities and infiltration [26, 27]. This relevant information is, however, overlaid by free-water contamination, which is particularly relevant for the peritumoral edematous region. Thus, several strategies have been developed to disentangle and bias-correct the "true" diffusion signal, which could increase the diagnostic value of DTI-derived metrics [28–30].

Besides its role for tumor grading, the DTI technique can be used to visualize the spatial course of WM pathways, which can appear unaffected, deviated, infiltrated, or destroyed (entire or partial disintegrity) due to the tumor mass as depicted in color-coded FA maps (► **Fig. 1**) [31]. Yet, most notably, the DTI technique has been used to conduct fiber tractography to delineate specific subcortical WM pathways prior to tumor resection.

It needs to be emphasized that although widely used in the clinical routine, the DTI method has relevant drawbacks because a single tensor can only resolve a single fiber direction within an imaging voxel, while the vast majority of WM voxels may be constituted of more than a single fiber [32–34]. Hence, novel methods have been developed lately, which may partially compensate for the drawbacks of DTI and could provide information beyond a simple diffusion scalar by emphasizing the importance of more complex 3D patterns of diffusion within the brain. Diffusion kurtosis imaging (DKI) is an approach to provide a more accurate model of diffusion and to capture non-Gaussian diffusion patterns as representative markers for tissue heterogeneity [35]. For glioma grading, it has been shown that DKI-derived mean, radial, and axial kurtosis were significantly higher in high-grade than in low-grade gliomas, probably as a result of a higher degree of tissue complexity in high-grade glioma, while conventional diffusion parameters (e.g., FA and MD) were not significantly different between grades [36]. Moreover, neurite orientation dispersion and density imaging (NODDI) is a technique for estimating the microstructural complexity of dendrites and axons [37]. In glioma, NODDI for evaluation of the T2-hyperintense region around contrast-enhancing tumor parts might facilitate differentiation between the region infiltrated by the tumor and edematous or normal tissue [38]. For the peritumoral region, it has also been proposed that metrics derived from NODDI could be helpful for differentiating between metastatic lesions and glioma [39].

A promising approach particularly for the purpose of fiber tracking is high angular resolution diffusion imaging (HARDI), which excels in detecting the orientational distribution of water diffusion and, thus, could also resolve complex fiber configura-



► **Fig. 1** Diffusion tensor imaging (DTI). Axial fluid-attenuated inversion recovery (FLAIR) **A**, DTI-derived fractional anisotropy (FA) color map **B**, and T1-weighted images before **C** and after **D** administration of a gadolinium-based contrast agent. Conventional structural sequences are indicative of a left-hemispheric high-grade glioma affecting the precentral, postcentral, and superior and middle frontal gyrus, which affects the spatial architecture of subcortical white matter (WM) pathways according to the color-coded FA map. Specifically, tracts are deviated and partially destroyed due to tumor growth when compared to the contralateral unaffected hemisphere.

tions [40, 41]. Exemplarily, one study using both DTI- and HARDI-based tractography has demonstrated that the HARDI-based approach displayed more compact fiber bundles and more neuroanatomically plausible fibers in the vicinity of the tumor and within the peritumoral region, which were not tracked using DTI [42]. Furthermore, HARDI q-ball tractography (using residual bootstrap) enables prediction of long-term language deficits following tumor resection [43]. Another novel approach is multi-level fiber tracking (MLFT) as an attempt to add branches to reconstructed WM pathways that do not reach a predefined target region [44]. Specifically, based on a conventional diffusion-weighted MRI sequence, MLFT has been shown to provide CST reconstructions with higher radial extent, thus enabling delineation of CST fanning with a wider angular range [44]. While such advanced methods have not yet been broadly implemented in the clinical routine, they may have the potential to considerably improve diffusion-weighted MRI including tractography.

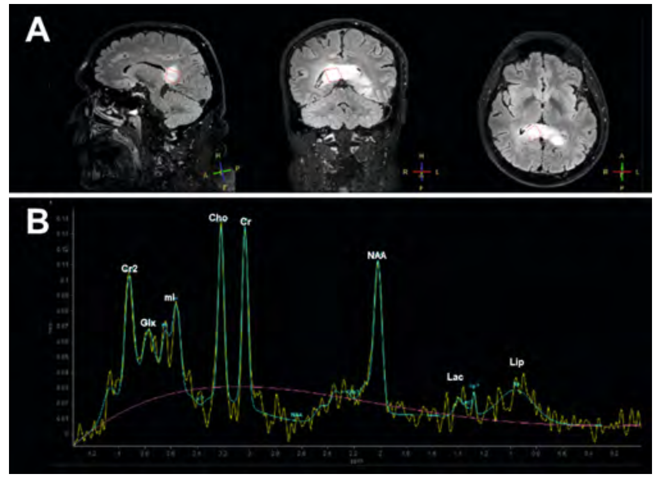
Magnetic resonance spectroscopy

The application of MRS allows for noninvasive metabolic quantification by means of a spectrum of peaks that represent metabolite intensities resonating at different frequencies, which is often referred to as "virtual biopsy" [45, 46]. Proton MRS is commonly used in the clinical setting and is derived from one or more voxels of interest placed within the tumor volume or surrounding tissue (▶ **Fig. 2**) [45, 46].

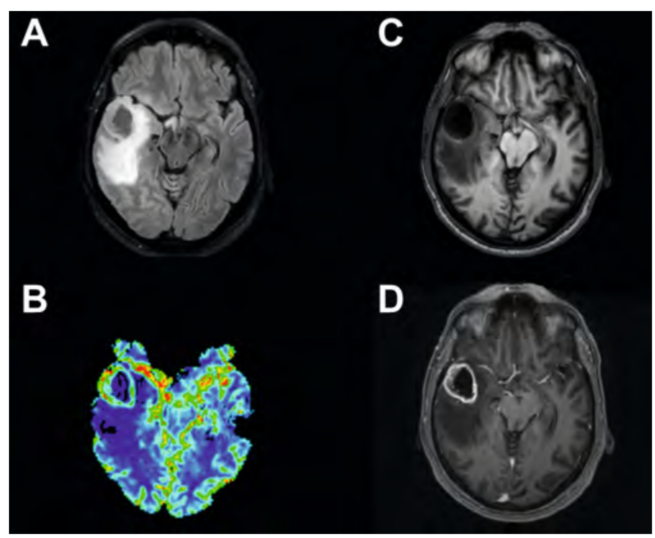
An early study proposed that MRS has potential in the diagnosis of low- vs. high-grade tumors and high-grade tumors vs. metastases when used as part of a multi-sequence MRI protocol [47]. Another study investigated the added value of MRS, showing that MRS data improved low- and high-grade tumor prediction when compared to conventional MRI alone (AUC low-grade tumors: 0.93 vs. 0.81; AUC high-grade tumors: 0.93 vs. 0.85 for MRI with MRS vs. conventional MRI alone) [48]. In this context, relatively increased total choline (Cho) and decreased total N-acetylaspartate (NAA) are diagnostic characteristics indicative of brain tumors [45, 49]. Beyond tumor grading, MRS has also been shown to be able to identify subtypes of glioma with IDH mutations, and the prominent signal at 1.3 ppm that stems from lipids of cytoplasmic droplets associated with necrosis or hypoxia has been shown to correlate with higher tumor aggressiveness or poor survival [50, 51].

Perfusion imaging

Several techniques are available for measuring perfusion, including dynamic susceptibility contrast (DSC) imaging and arterial spin labeling (ASL) [52–54]. In the clinical setting, DSC imaging is the most common option. It requires a bolus of contrast agent passing through the capillary bed of the brain, causing measurable susceptibility-induced signal loss on T2*-weighted imaging (▶ **Fig. 3**) [55]. A fundamentally different technique is ASL, which does not need the application of any contrast media, but instead makes use of the labeling of arterial blood that flows to the brain [55]. Common parameters that can be extracted from DSC perfusion are relative cerebral blood flow (CBF), relative cerebral blood



▶ **Fig. 2** Proton magnetic resonance spectroscopy (MRS). Placement of the voxel of interest for MRS in sagittal, coronal, and axial view of the fluid-attenuated inversion recovery (FLAIR) sequence **A**, together with the obtained spectrum of metabolites (Cr2/Cr: creatine, Glx: glutamate and glutamine, mI: myo-inositol, Cho: choline; NAA: N-acetylaspartate; Lac: lactate; Lip: lipids). The spectrum is indicative of a brain tumor with slightly increased Cho (at ~3.22 ppm) and decreased NAA (at ~2.02 ppm) compared to reference values known for healthy brain tissue.



▶ **Fig. 3** Dynamic susceptibility contrast (DSC) perfusion. Axial fluid-attenuated inversion recovery (FLAIR) **A**, color-coded map for relative cerebral blood volume (CBV) derived from DSC imaging **B**, and T1-weighted images before **C** and after **D** administration of a gadolinium-based contrast agent. Conventional structural sequences are indicative of a right-hemispheric high-grade glioma of the temporal lobe, with increased relative CBV at the contrast-enhancing tumor borders and decreased relative CBV in the necrotic tumor core according to DSC perfusion.

volume (CBV), and mean transit time, while ASL measurements may be mostly restricted to CBF [54, 55].

Notably, there is a strong correlation between the glioma grade and DSC-derived relative CBV, with high-grade tumors typically presenting with markedly higher relative CBV than low-grade tumors or normal-appearing WM [56–58]. In view of earlier work showing that increased relative CBV indeed correlates with neoangiogenesis, these results corroborate the potential of perfusion imaging to visualize this central oncogenic process in high-grade gliomas [59–61]. Furthermore, relative CBV was shown to be increased up to about one year before contrast enhancement is visualized on T1-weighted sequences for low-grade gliomas that undergo a malignant transformation [62]. Yet, a very common challenge to relative CBV quantification from DSC perfusion is that the presence of a leaky blood-brain barrier can confound measurements, which needs to be corrected for [63]. A multitude of methods are available to address leakage correction, yet no universally accepted approach has been revealed [63, 64]. Nevertheless, in the clinical routine, most tools for the analysis of DSC perfusion data nowadays incorporate correction steps to mitigate bias due to leakage.

Regarding ASL-derived CBF, both maximum CBF and maximum relative CBF have shown to be significantly higher in high-grade than low-grade gliomas (AUC maximum CBF: 0.83; AUC maximum relative CBF: 0.86) [65]. Furthermore, ASL-derived CBF maps allowed stratification of survival in the case of glioblastoma and could be used to differentiate gliomas with respect to IDH mutation status [66, 67]. It has recently been suggested that ASL perfusion may predict malignant progression within one year among patients with glioma WHO grade II [68]. In essence, the advantages of ASL are that CBF quantification is not affected by leakage effects, and it does not require administration of a contrast agent. In light of ongoing debates regarding gadolinium depositions from contrast media within the brain, this characteristic could be regarded as being of special interest [69]. Yet, ASL imaging typically has a lower signal-to-noise ratio than DSC perfusion, and the relevance of contrast media-free imaging is relativized in most cases since contrast agents are applied anyway for later T1-weighted imaging to evaluate contrast enhancement of brain tumors.

Contrast-enhanced T1-weighted imaging

Imaging with T1-weighted sequences before and after the administration of a contrast agent is an integral part of an imaging protocol in neuro-oncology. The T1 relaxation time is shortened by gadolinium-based contrast agents, which increase tissue contrast by accentuating areas where leakage into interstitial tissue is present due to blood-brain barrier disruption, with resulting parenchymal enhancement being positively correlated to the tumor grade with few exceptions [70, 71]. Most commonly, turbo field echo (TFE) imaging before and after contrast administration is used to assess tumor-related contrast enhancement and spread, but recent studies have suggested improved depiction of intracranial contrast-enhancing pathology with advanced sequences [72, 73]. Specifically, T1-weighted black-blood sequences may better delineate therapy-naïve high-grade gliomas with higher contrast-to-noise ratios when compared to established TFE sequences, which was also confirmed for intraoperative MRI during tumor removal where assessment of the extent of tumor resection could be accelerated [73, 74].

Advanced image analysis

With advancements in scanner technology, a multi-sequence protocol including imaging for diffusion, perfusion, metabolism, and function in addition to conventional structural sequences (i. e., T1- and T2-weighted and FLAIR sequences) can become feasible in most patients within a reasonable scan time, which is partly due to the introduction of different image acquisition acceleration techniques for clinical routine MRI [75–78]. The rich information on tumor biology contained herein reflects many key cellular and oncogenic aspects, including cellularity, proliferation, neoangiogenesis, and invasion, with the opportunity to extract and define quantitative MRI-based biomarkers for neuro-oncological imaging [7]. While glioma genotyping based on tissue probes as gathered from biopsy or tumor resection remains the reference standard, genotype predictions by advanced MRI could support clinical decision-making and individual patient management that is tailored to the distinct tumor characteristics [7]. Leveraging the rich information from multi-sequence MRI for training multi-parametric models to infer tumor biology is therefore an active field of research, both at initial diagnosis and along the disease course [79–81].

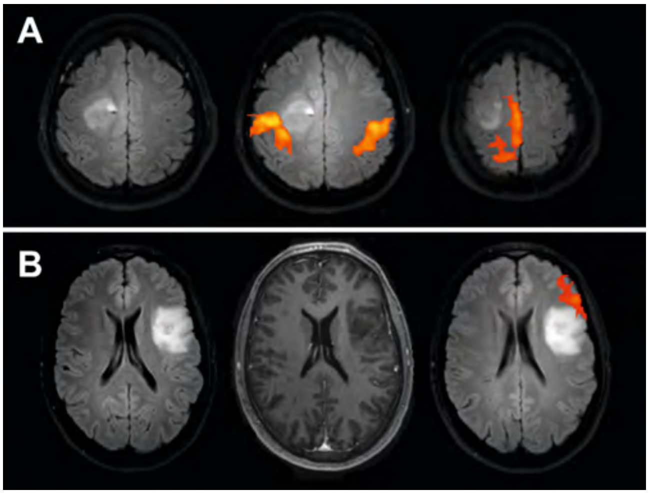
Mapping of Brain Function

Overview of methods

For the preoperative workup of patients, functional mapping is of high importance in addition to structural MRI when the tumor is supposed to affect functionally eloquent brain structures (e. g., the hand knob as the center of primary motor function or the left-hemispheric opercular and triangular parts of the inferior frontal gyrus harboring the Broca's area). Major techniques used for this purpose are fMRI, magnetoencephalography (MEG), and nTMS. While MEG is rather expensive and not widely available in most countries, fMRI is the standard approach in many centers. More recently, nTMS has been made available for preoperative functional mapping [11, 12].

Functional magnetic resonance imaging

Methodologically, fMRI indirectly measures neuronal activation by making use of the deoxyhemoglobin-to-oxyhemoglobin ratio as a contrast mechanism, which is referred to as the blood oxygenation level-dependent (BOLD) signal that can be used to map function within the brain when combined with a task (e. g., finger tapping task to detect motor function within the brain) (▶ **Fig. 4**) [82–85]. While task-based fMRI is the most common technique for presurgical functional mapping among patients with brain tumors, resting-state fMRI, which measures spontaneous low-frequency fluctuations in the BOLD signal between regions to detect functional networks, has also been applied recently [85–87]. Regarding preoperative motor mapping by task-based fMRI, most studies demonstrated that task-based fMRI is an adequate method to localize motor function, and it could facilitate surgical planning and decrease the time needed for intraoperative mapping using direct electrical stimulation (DES) [88–90]. Specifically, the sensitivity and specificity of



▶ **Fig. 4** Functional magnetic resonance imaging (fMRI). Task-based fMRI with derived activation maps in axial view to localize motor function **A** and language function **B**. A finger-tapping task and toe-movement task were used to localize motor function, which was located lateral to the tumor for upper extremity motor representation (middle image, **A**) and medial to the tumor for lower extremity motor representation (right image, **A**). Specifically, motor activation maps primarily overlapped with the precentral gyrus bilaterally as well as with parts of the superior frontal gyrus of the right hemisphere (middle and right image, **A**). A picture-naming task was used to localize language function, which was located anterior to the tumor (right image, **B**). Specifically, left-hemispheric fronto-temporal parts of the language network overlapped with the language activation map (right image, **B**).

task-based fMRI for the delineation of motor function have been reported to range from 71 % to 100 % and 68 % to 100 %, respectively [88–90]. Yet, the specificity and sensitivity for the preoperative localization of language function using task-based fMRI showed higher variability, with sensitivity ranging from 59 % to 100 % and specificity ranging from 0 % to 97 % compared to DES [88, 91, 92]. The variability regarding sensitivity and specificity across studies may be related to a variety of factors, including differences in the language tasks that are used, the MRI hardware, and the software including analysis paradigms [85, 93]. For instance, an appealing option to tackle issues related to fMRI data alignment, which is a prerequisite for comparing features such as brain activity at corresponding locations across patients, can be based on global functional connectivity patterns, which facilitates matching of functionally corresponding areas in a more accurate fashion than conventionally used anatomical alignment [94]. Furthermore, nonrigid image registration algorithms may overcome limitations regarding alignment for longitudinal studies and particularly for registering presurgical to intraoperative datasets including the registration of fMRI to anatomical sequences [95]. A longitudinal design may be chosen in particular to track down plastic reorganization of the brain in response to the presence and growth patterns of glioma by means of changes in the fMRI signal and connectivity profiles over time, which could relate to measurable reallocation of motor or language areas [96–98].

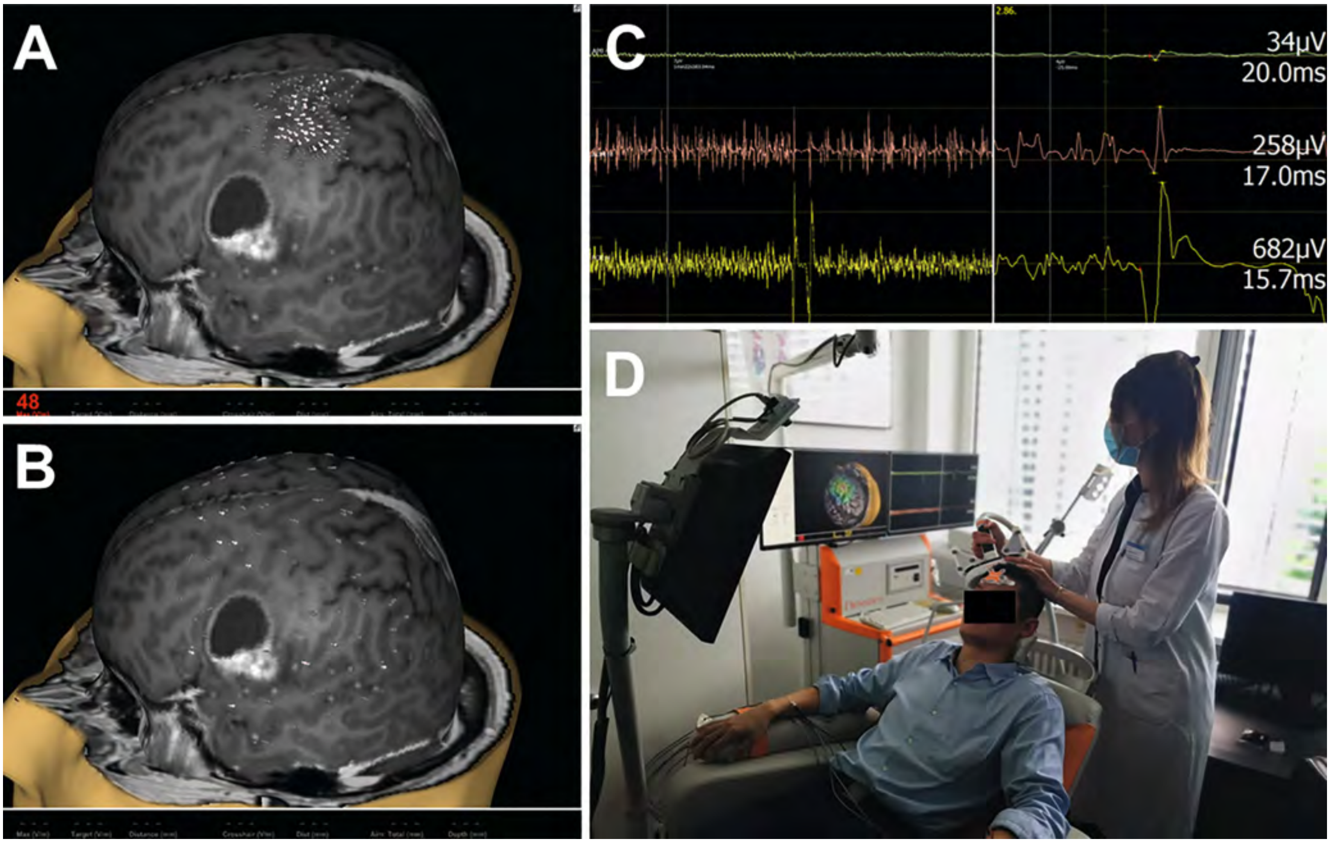
A main criticism regarding fMRI is that tumor vasculature can lose the ability to autoregulate, which – together with tumor-related compressive effects on venules and larger veins and arteriovenous shunting – can render BOLD signal evaluations imprecise and, thus, impacts the accuracy of findings, particularly for patients with high-grade glioma [99–101]. Due to this neurovascular uncoupling, task-based fMRI can be considered more accurate and useful in low-grade compared to high-grade gliomas [100, 102, 103]. Another issue is that fMRI activation maps could show false-positive results by outlining a region larger than the actual functionally eloquent area when correlated to DES, which could negatively influence the extent of tumor resection [104].

Navigated transcranial magnetic stimulation

Functional mapping using magnetic stimulator devices is based on the principle of electro-magnetic induction [105–107]. Brief high-current pulses are produced by a magnetic coil, which is placed above the scalp [105–107]. A transient electric field is then induced perpendicular to the magnetic field, which is capable of causing neuronal activation with different extents and effects, depending on factors such as stimulation intensity, pulse shape, and frequency [105–107]. The fundamental difference between nTMS and other techniques is that when a physiological response is evoked by stimulation of a cortical area, that specific cortical area is causally related to the response since a so-called "virtual lesion" is induced by nTMS [12, 106]. Furthermore, it is believed that responses to nTMS are not biased due to tumor characteristics (e. g., related to increased perfusion), making the technique potentially more robust and reliable than the presurgical alternatives.

The transformation into an advanced functional mapping device with very close links to imaging is inherently linked to the recent combination of magnetic stimulation with precise neuronavigation based on structural MRI data, defining the technique as nTMS (▶ **Fig. 5**) [12, 106]. Systems with the highest accuracy to identify and spatially enclose functional brain tissue use electric-field-based neuronavigation, which can be achieved through individual modelling that takes into account parameters such as skull thickness, affecting the coil-cortex distance, and coil tilting [12, 106]. Importantly, a simple method to guide magnetic stimulation (e. g., using standard coil location with respect to external landmarks of the skull) would not be acceptable for preoperative mapping in neurooncology as there is a high risk of imprecision [12, 106]. The starting point for mapping by nTMS is given by co-registration of the respective structural MRI (i. e., high-resolution 3D contrast-enhanced T1-weighted sequences) to the actual head of the patient. Once registration is completed, the stimulation coil can be freely navigated during mapping and tracked on the MRI-based head model within the nTMS system, thus allowing stimulation across hemispheres to pinpoint sites responsible for brain functions such as active movement or speech and language [11, 12].

The primary use case for nTMS in neuro-oncology is the mapping of motor function to identify the motor hotspot and boundaries of the primary motor cortex (▶ **Fig. 5**). Using electromyography (EMG) of upper and lower extremity muscles during cortical stimulation by the coil, motor-evoked potentials (MEPs) can be elicited and related to a specific site of stimulation. When such MEPs reach a certain amplitude threshold and fall within a muscle-characteristic latency, motor-positive points are defined that are considered



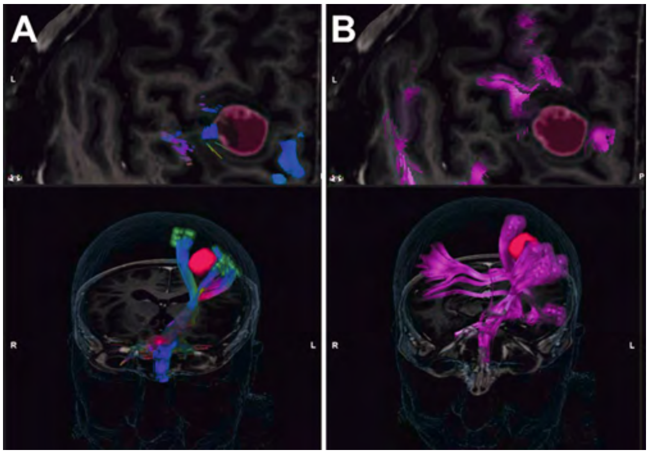
▶ **Fig. 5** Navigated transcranial magnetic stimulation (nTMS). Neuronavigational view with a three-dimensional (3D) head model based on a contrast-enhanced T1-weighted sequence for motor mapping **A** and language mapping **B** by nTMS in a patient with a left-hemispheric contrast-enhancing tumor affecting the ventral precentral and opercular region of the inferior frontal gyrus. The white spots indicate motor-positive stimulation points **A** or language-positive stimulation points **B**, i. e. points that are considered part of the cortical primary motor or language representation. Judgement is based on motor-evoked potentials (MEPs) for nTMS motor mapping, which are derived from continuously recorded electromyography (EMG) of upper and lower extremity muscles contralateral to the tumor-affected hemisphere during stimulation **C**. Regarding language mapping, transient impairments during performance of a task such as object naming can be elicited by nTMS, which can be used to judge on the spatial location and characteristics of language-positive stimulation points (e. g., typically speech arrests due to targeted stimulation of the Broca's area or semantic paraphasia occurs due to stimulation of parietal or posterior temporal cortex). The use of precise neuronavigation qualifies nTMS as a preoperative tool to map cortical function, which is established through infrared tracking of the coil during stimulation and registration of the patient's head to the respective image data **D**. The stimulating coil can then be tracked during pulse application in relation to individual brain anatomy **D**.

essential for primary motor function [108, 109]. Compared to DES, presurgical nTMS has repeatedly demonstrated high accuracy [110, 111]. Notably, significantly better agreement between nTMS and DES has been achieved for determining the primary motor cortex when compared to fMRI against DES [110, 111]. Furthermore, motor mapping by nTMS may make it possible to reveal plastic reallocation of the motor cortex related to tumor growth, demonstrating location changes of the primary motor area by repeated mapping over time [112, 113]. Regarding clinical outcome, use of preoperative nTMS motor mapping could improve the extent of tumor resection and survival [114]. Yet, data from randomized controlled trials are currently lacking to confirm positive impact on the clinical course besides the distinct value of the technique for tumor resection planning and intraoperative guidance.

Furthermore, language mapping by nTMS is increasingly used in patients with language-eloquent brain tumors (▶ **Fig. 5**). The principle is that stimulation by nTMS can cause several instances of transient impairment (e. g., during performance of an object-naming task), which can be recorded and spatially correlated to the site of stimulation [109, 115, 116]. Correlations of results from nTMS language mapping to DES are not as satisfactory as for motor mapping, which currently suggests primary application for so-called "negative mapping" (i. e., a language-negative stimulation spot of nTMS is almost always also negative during DES) [117, 118]. Thus, several methodological studies have been performed to increase the specificity of nTMS language mapping, testing a variety of stimulation protocol optimizations (e. g., coil orientation or frequency of stimulation) [119–121].

Function-based tractography

Fiber tractography may become most powerful when combined with functional data. Activation maps derived from fMRI-based motor or language assessment or derived from nTMS mapping can be used for ROI seeding, with the aim of establishing tractography based on individual functional data [12, 13]. In this context, previous studies have proposed that fMRI-guided fiber track-

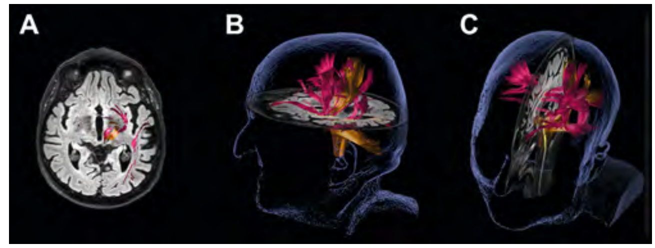


▶ **Fig. 6** Fiber tractography based on functional mapping. Fiber tracking using motor maps **A** and language maps **B** derived from navigated transcranial magnetic stimulation (nTMS) allows delineation of subcortical white matter (WM) pathways. Using the nTMS-derived motor map (motor-positive nTMS points, green) as the region of interest (ROI) for tractography allows for delineation of the corticospinal tract (CST) in somatotopic organization (separate parts for upper and lower extremity muscle representations, separated by the tumor volume in red; **A**). Similarly, using the nTMS-derived language map (language-positive nTMS points, purple) as the ROI enables tracking of language-related WM pathways within the brain purely based on functional data **B**.

ing enables reconstruction of relevant WM bundles belonging to a specific functional system, and that the evaluation of the lesion-to-activation distance (i. e., distance measurement between the tumor and a specific WM bundle as derived from fiber tractography) may be relevant to assess postoperative functional outcome [122–124]. Specifically, it has been proposed that the risk of postoperative functional decline is considerably lower in patients in whom the lesion-to-activation distance was at least 10 mm [123, 124]. Similar to the approach using fMRI-derived activation maps as functional seeding data, motor- or language-positive points derived from nTMS can also be used to generate ROIs for tractography of the CST or language-related subcortical pathways such as the AF (▶ **Fig. 6**) [125–128]. Furthermore, nTMS-based tractography may enable preoperative risk stratification for surgery-related motor or language impairment, making it possible to define a cutoff value of a minimum tract-to-tumor distance to avoid perioperative functional decline [129–132]. In essence, the combination of multi-sequence MRI with functional data from fMRI or nTMS and derived tractography represents a seamless multi-modal approach that combines structural and functional information for imaging in neuro-oncological patients (▶ **Fig. 7**).

Conclusion

Advanced imaging and mapping during the preoperative workup of neuro-oncological patients enables the noninvasive assessment of a multitude of characteristics relevant to tumor grading and prediction. With advancements in scanner technology including parallel imaging for the acceleration of acquisitions, a multi-sequence protocol including imaging for diffusion, perfusion,



▶ **Fig. 7** Multi-modal fiber tractography. Fiber tracts belonging to the corticospinal tract (CST, orange) and the language network (pink) as derived from tractography using cortical maps of navigated transcranial magnetic stimulation (nTMS) for generation of regions of interest (ROIs). Motor and language mapping, nTMS-based tractography, and magnetic resonance imaging (MRI) can be effectively combined within a multi-modal approach to outline individual structural and functional anatomy. Fibers are fused with a fluid-attenuated inversion recovery (FLAIR) sequence in axial view **A** and displayed within a three-dimensional (3D) head model in sagittal view **B** and parasagittal view **C**.

metabolism, and function in addition to conventional structural sequences becomes feasible in most patients within a reasonable scan time. The use of preoperatively acquired MRI data in combination with nTMS mapping harbors great potential for comprehensive multi-modal approaches that integrate structural with functional data.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Ostrom QT, Cioffi G, Gittleman H et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. Neuro-oncology 2019; 21: v1–v100. doi:10.1093/neuonc/noz150

[2] Ostrom QT, Gittleman H, Xu J et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. Neuro-oncology 2016; 18: v1–v75. doi:10.1093/neuonc/now207

[3] Louis DN, Perry A, Wesseling P et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-oncology 2021. doi:10.1093/neuonc/noab106

[4] Sanai N, Berger MS. Surgical oncology for gliomas: the state of the art. Nat Rev Clin Oncol 2018; 15: 112–125. doi:10.1038/nrclinonc.2017.171

[5] Martinez-Garcia M, Alvarez-Linera J, Carrato C et al. SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017). Clinical & translational oncology: official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 2018; 20: 22–28. doi:10.1007/s12094-017-1763-6

[6] Weller M, van den Bent M, Hopkins K et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol 2014; 15: e395–e403. doi:10.1016/S1470-2045(14)70011-7

[7] Smits M. MRI biomarkers in neuro-oncology. Nature reviews Neurology 2021. doi:10.1038/s41582-021-00510-y

[8] Smits M, van den Bent MJ. Imaging Correlates of Adult Glioma Genotypes. Radiology 2017; 284: 316–331. doi:10.1148/radiol.2017151930

[9] Verburg N, de Witt Hamer PC. State-of-the-art imaging for glioma surgery. Neurosurgical review 2021; 44: 1331–1343. doi:10.1007/s10143-020-01337-9

[10] Henderson F, Abdullah KG, Verma R et al. Tractography and the connectome in neurosurgical treatment of gliomas: the premise, the progress, and the potential. Neurosurgical focus 2020; 48: E6. doi:10.3171/2019.11.FOCUS19785

[11] Haddad AF, Young JS, Berger MS et al. Preoperative Applications of Navigated Transcranial Magnetic Stimulation. Front Neurol 2020; 11: 628903. doi:10.3389/fneur.2020.628903

[12] Sollmann N, Krieg SM, Saisanen L et al. Mapping of Motor Function with Neuronavigated Transcranial Magnetic Stimulation: A Review on Clinical Application in Brain Tumors and Methods for Ensuring Feasible Accuracy. Brain Sci 2021; 11. doi:10.3390/brainsci11070897

[13] Jarret J, Bore A, Bedetti C et al. A methodological scoping review of the integration of fMRI to guide dMRI tractography. What has been done and what can be improved: A 20-year perspective. Journal of neuroscience methods 2021; 367: 109435. doi:10.1016/j.jneumeth.2021.109435

[14] Villanueva-Meyer JE, Mabray MC, Cha S. Current Clinical Brain Tumor Imaging. Neurosurgery 2017; 81: 397–415. doi:10.1093/neuros/nyx103

[15] Ellingson BM, Bendszus M, Boxerman J et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro-oncology 2015; 17: 1188–1198. doi:10.1093/neuonc/nov095

[16] Zhang B, MacFadden D, Damyanovich AZ et al. Development of a geometrically accurate imaging protocol at 3 Tesla MRI for stereotactic radiosurgery treatment planning. Phys Med Biol 2010; 55: 6601–6615. doi:10.1088/0031-9155/55/22/002

[17] Willems PW, van der Sprenkel JW, Tulleken CA et al. Neuronavigation and surgery of intracerebral tumours. Journal of neurology 2006; 253: 1123–1136. doi:10.1007/s00415-006-0158-3

[18] Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis – a technical review. NMR in biomedicine 2002; 15: 456–467. doi:10.1002/nbm.783

[19] Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci 2008; 34: 51–61. doi:10.1007/s12031-007-0029-0

[20] Jolapara M, Patro SN, Kesavadas C et al. Can diffusion tensor metrics help in preoperative grading of diffusely infiltrating astrocytomas? A retrospective study of 36 cases. Neuroradiology 2011; 53: 63–68. doi:10.1007/s00234-010-0761-y

[21] Liu X, Tian W, Kolar B et al. MR diffusion tensor and perfusion-weighted imaging in preoperative grading of supratentorial nonenhancing gliomas. Neuro-oncology 2011; 13: 447–455. doi:10.1093/neuonc/noq197

[22] White ML, Zhang Y, Yu F et al. Diffusion tensor MR imaging of cerebral gliomas: evaluating fractional anisotropy characteristics. AJNR American journal of neuroradiology 2011; 32: 374–381. doi:10.3174/ajnr.A2267

[23] Houillier C, Wang X, Kaloshi G et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology 2010; 75: 1560–1566. doi:10.1212/WNL.0b013e3181f96282

[24] Xiong J, Tan W, Wen J et al. Combination of diffusion tensor imaging and conventional MRI correlates with isocitrate dehydrogenase 1/2 mutations but not 1p/19q genotyping in oligodendroglial tumours. European radiology 2016; 26: 1705–1715. doi:10.1007/s00330-015-4025-4

[25] Xiong J, Tan WL, Pan JW et al. Detecting isocitrate dehydrogenase gene mutations in oligodendroglial tumors using diffusion tensor imaging metrics and their correlations with proliferation and microvascular density. Journal of magnetic resonance imaging: JMRI 2016; 43: 45–54. doi:10.1002/jmri.24958

[26] Eidel O, Neumann JO, Burth S et al. Automatic Analysis of Cellularity in Glioblastoma and Correlation with ADC Using Trajectory Analysis and Automatic Nuclei Counting. PLoS One 2016; 11: e0160250. doi:10.1371/journal.pone.0160250

[27] Bette S, Huber T, Gempt J et al. Local Fractional Anisotropy Is Reduced in Areas with Tumor Recurrence in Glioblastoma. Radiology 2017; 283: 499–507. doi:10.1148/radiol.2016152832

[28] Pasternak O, Sochen N, Gur Y et al. Free water elimination and mapping from diffusion MRI. Magn Reson Med 2009; 62: 717–730. doi:10.1002/mrm.22055

[29] Metz MC, Molina-Romero M, Lipkova J et al. Predicting Glioblastoma Recurrence from Preoperative MR Scans Using Fractional-Anisotropy Maps with Free-Water Suppression. Cancers (Basel) 2020; 12. doi:10.3390/cancers12030728

[30] Henderson F Jr, Parker D, Vijayakumari AA et al. Enhanced Fiber Tractography Using Edema Correction: Application and Evaluation in High-Grade Gliomas. Neurosurgery 2021; 89: 246–256. doi:10.1093/neuros/nyab129

[31] Jellison BJ, Field AS, Medow J et al. Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. AJNR American journal of neuroradiology 2004; 25: 356–369

[32] Farquharson S, Tournier JD, Calamante F et al. White matter fiber tractography: why we need to move beyond DTI. Journal of neurosurgery 2013; 118: 1367–1377. doi:10.3171/2013.2.JNS121294

[33] Duffau H. Diffusion tensor imaging is a research and educational tool, but not yet a clinical tool. World neurosurgery 2014; 82: e43–e45. doi:10.1016/j.wneu.2013.08.054

[34] Jeurissen B, Leemans A, Tournier JD et al. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. Human brain mapping 2013; 34: 2747–2766. doi:10.1002/hbm.22099

[35] Wu EX, Cheung MM. MR diffusion kurtosis imaging for neural tissue characterization. NMR in biomedicine 2010; 23: 836–848. doi:10.1002/nbm.1506

[36] Van Cauter S, Veraart J, Sijbers J et al. Gliomas: diffusion kurtosis MR imaging in grading. Radiology 2012; 263: 492–501. doi:10.1148/radiol.12110927

[37] Zhang H, Schneider T, Wheeler-Kingshott CA et al. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage 2012; 61: 1000–1016. doi:10.1016/j.neuroimage.2012.03.072

[38] Masjoodi S, Hashemi H, Oghabian MA et al. Differentiation of Edematous, Tumoral and Normal Areas of Brain Using Diffusion Tensor and Neurite Orientation Dispersion and Density Imaging. J Biomed Phys Eng 2018; 8: 251–260

[39] Kadota Y, Hirai T, Azuma M et al. Differentiation between glioblastoma and solitary brain metastasis using neurite orientation dispersion and density imaging. J Neuroradiol 2020; 47: 197–202. doi:10.1016/j.neurad.2018.10.005

[40] Tuch DS. Q-ball imaging. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine 2004; 52: 1358–1372. doi:10.1002/mrm.20279

[41] Alexander DC. Multiple-fiber reconstruction algorithms for diffusion MRI. Annals of the New York Academy of Sciences 2005; 1064: 113–133. doi:10.1196/annals.1340.018

[42] Kuhnt D, Bauer MH, Egger J et al. Fiber tractography based on diffusion tensor imaging compared with high-angular-resolution diffusion imaging with compressed sensing: initial experience. Neurosurgery 2013; 72 (Suppl. 1): 165–175. doi:10.1227/NEU.0b013e318270d9fb

[43] Caverzasi E, Hervey-Jumper SL, Jordan KM et al. Identifying preoperative language tracts and predicting postoperative functional recovery using HARDI q-ball fiber tractography in patients with gliomas. Journal of neurosurgery 2016; 125: 33–45. doi:10.3171/2015.6.JNS142203

[44] Zhylka A, Sollmann N, Kofler F et al. Tracking the Corticospinal Tract in Patients With High-Grade Glioma: Clinical Evaluation of Multi-Level Fiber Tracking and Comparison to Conventional Deterministic Approaches. Frontiers in Oncology 2021; 11. doi:10.3389/fonc.2021.761169

[45] Oz G, Alger JR, Barker PB et al. Clinical proton MR spectroscopy in central nervous system disorders. Radiology 2014; 270: 658–679. doi:10.1148/radiol.13130531

[46] Wilson M, Andronesi O, Barker PB et al. Methodological consensus on clinical proton MRS of the brain: Review and recommendations. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine 2019; 82: 527–550. doi:10.1002/mrm.27742

[47] Al-Okaili RN, Krejza J, Woo JH et al. Intraaxial brain masses: MR imaging-based diagnostic strategy–initial experience. Radiology 2007; 243: 539–550. doi:10.1148/radiol.2432060493

[48] Julia-Sape M, Coronel I, Majos C et al. Prospective diagnostic performance evaluation of single-voxel 1H MRS for typing and grading of brain tumours. NMR in biomedicine 2012; 25: 661–673. doi:10.1002/nbm.1782

[49] Howe FA, Barton SJ, Cudlip SA et al. Metabolic profiles of human brain tumors using quantitative in vivo 1H magnetic resonance spectroscopy. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine 2003; 49: 223–232. doi:10.1002/mrm.10367

[50] Choi C, Ganji SK, DeBerardinis RJ et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 2012; 18: 624–629. doi:10.1038/nm.2682

[51] Crawford FW, Khayal IS, McGue C et al. Relationship of pre-surgery metabolic and physiological MR imaging parameters to survival for patients with untreated GBM. Journal of neuro-oncology 2009; 91: 337–351. doi:10.1007/s11060-008-9719-x

[52] Suh CH, Kim HS, Jung SC et al. Perfusion MRI as a diagnostic biomarker for differentiating glioma from brain metastasis: a systematic review and meta-analysis. European radiology 2018; 28: 3819–3831. doi:10.1007/s00330-018-5335-0

[53] Abrigo JM, Fountain DM, Provenzale JM et al. Magnetic resonance perfusion for differentiating low-grade from high-grade gliomas at first presentation. The Cochrane database of systematic reviews 2018; 1: CD011551. doi:10.1002/14651858.CD011551.pub2

[54] Alsop DC, Detre JA, Golay X et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine 2015; 73: 102–116. doi:10.1002/mrm.25197

[55] Essig M, Shiroishi MS, Nguyen TB et al. Perfusion MRI: the five most frequently asked technical questions. Am J Roentgenol American journal of roentgenology 2013; 200: 24–34. doi:10.2214/Am J Roentgenol.12.9543

[56] Knopp EA, Cha S, Johnson G et al. Glial neoplasms: dynamic contrast-enhanced T2*-weighted MR imaging. Radiology 1999; 211: 791–798. doi:10.1148/radiology.211.3.r99jn46791

[57] Aronen HJ, Gazit IE, Louis DN et al. Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. Radiology 1994; 191: 41–51. doi:10.1148/radiology.191.1.8134596

[58] Shin JH, Lee HK, Kwun BD et al. Using relative cerebral blood flow and volume to evaluate the histopathologic grade of cerebral gliomas: preliminary results. Am J Roentgenol American journal of roentgenology 2002; 179: 783–789. doi:10.2214/ajr.179.3.1790783

[59] Sadeghi N, Salmon I, Decaestecker C et al. Stereotactic comparison among cerebral blood volume, methionine uptake, and histopathology in brain glioma. AJNR Am J Neuroradiol 2007; 28: 455–461

[60] Law M, Yang S, Babb JS et al. Comparison of cerebral blood volume and vascular permeability from dynamic susceptibility contrast-enhanced perfusion MR imaging with glioma grade. AJNR Am J Neuroradiol 2004; 25: 746–755

[61] Kremer S, Grand S, Remy C et al. Cerebral blood volume mapping by MR imaging in the initial evaluation of brain tumors. J Neuroradiol 2002; 29: 105–113

[62] Danchaivijitr N, Waldman AD, Tozer DJ et al. Low-grade gliomas: do changes in rCBV measurements at longitudinal perfusion-weighted MR imaging predict malignant transformation? Radiology 2008; 247: 170–178. doi:10.1148/radiol.2471062089

[63] Paulson ES, Schmainda KM. Comparison of dynamic susceptibility-weighted contrast-enhanced MR methods: recommendations for measuring relative cerebral blood volume in brain tumors. Radiology 2008; 249: 601–613. doi:10.1148/radiol.2492071659

[64] Schmainda KM, Prah MA, Rand SD et al. Multisite Concordance of DSC-MRI Analysis for Brain Tumors: Results of a National Cancer Institute Quantitative Imaging Network Collaborative Project. AJNR American journal of neuroradiology 2018; 39: 1008–1016. doi:10.3174/ajnr.A5675

[65] Zeng Q, Jiang B, Shi F et al. 3D Pseudocontinuous Arterial Spin-Labeling MR Imaging in the Preoperative Evaluation of Gliomas. AJNR American journal of neuroradiology 2017; 38: 1876–1883. doi:10.3174/ajnr.A5299

[66] Qiao XJ, Ellingson BM, Kim HJ et al. Arterial spin-labeling perfusion MRI stratifies progression-free survival and correlates with epidermal growth factor receptor status in glioblastoma. AJNR American journal of neuroradiology 2015; 36: 672–677. doi:10.3174/ajnr.A4196

[67] Liu T, Cheng G, Kang X et al. Noninvasively evaluating the grading and IDH1 mutation status of diffuse gliomas by three-dimensional pseudo-continuous arterial spin labeling and diffusion-weighted imaging. Neuroradiology 2018; 60: 693–702. doi:10.1007/s00234-018-2021-5

[68] Flies CM, Snijders TJ, Van Seeters T et al. Perfusion imaging with arterial spin labeling (ASL)-MRI predicts malignant progression in lowgrade (WHO grade II) gliomas. Neuroradiology 2021. doi:10.1007/s00234-021-02737-4

[69] Gulani V, Calamante F, Shellock FG et al. Gadolinium deposition in the brain: summary of evidence and recommendations. The Lancet Neurology 2017; 16: 564–570. doi:10.1016/S1474-4422(17)30158-8

[70] Neuwelt EA. Mechanisms of disease: the blood-brain barrier. Neurosurgery 2004; 54: 131–140. doi:10.1227/01.neu.0000097715.11966.8e

[71] Smirniotopoulos JG, Murphy FM, Rushing EJ et al. Patterns of contrast enhancement in the brain and meninges. Radiographics 2007; 27: 525–551. doi:10.1148/rg.272065155

[72] Kammer NN, Coppenrath E, Treitl KM et al. Comparison of contrast-enhanced modified T1-weighted 3D TSE black-blood and 3D MP-RAGE sequences for the detection of cerebral metastases and brain tumours. European radiology 2016; 26: 1818–1825. doi:10.1007/s00330-015-3975-x

[73] Finck T, Gempt J, Zimmer C et al. MR imaging by 3D T1-weighted black blood sequences may improve delineation of therapy-naive high-grade gliomas. European radiology 2021; 31: 2312–2320. doi:10.1007/s00330-020-07314-6

[74] Finck T, Gempt J, Krieg SM et al. Assessment of the Extent of Resection in Surgery of High-Grade Glioma-Evaluation of Black Blood Sequences for Intraoperative Magnetic Resonance Imaging at 3 Tesla. Cancers (Basel) 2020; 12. doi:10.3390/cancers12061580

[75] Monch S, Sollmann N, Hock A et al. Magnetic Resonance Imaging of the Brain Using Compressed Sensing – Quality Assessment in Daily Clinical Routine. Clin Neuroradiol 2020; 30: 279–286. doi:10.1007/s00062-019-00789-x

[76] Greve T, Sollmann N, Hock A et al. Highly accelerated time-of-flight magnetic resonance angiography using spiral imaging improves conspicuity of intracranial arterial branches while reducing scan time. Eur Radiol 2020; 30: 855–865. doi:10.1007/s00330-019-06442-y

[77] Sasi SD, Ramaniharan AK, Bhattacharjee R et al. Evaluating feasibility of high resolution T1-perfusion MRI with whole brain coverage using compressed SENSE: Application to glioma grading. Eur J Radiol 2020; 129: 109049. doi:10.1016/j.ejrad.2020.109049

[78] Duan Y, Zhang J, Zhuo Z et al. Accelerating Brain 3D T1-Weighted Turbo Field Echo MRI Using Compressed Sensing-Sensitivity Encoding (CS-SENSE). Eur J Radiol 2020; 131: 109255. doi:10.1016/j.ejrad.2020.109255

[79] Singh G, Manjila S, Sakla N et al. Radiomics and radiogenomics in gliomas: a contemporary update. Br J Cancer 2021; 125: 641–657. doi:10.1038/s41416-021-01387-w

[80] Sohn CK, Bisdas S. Diagnostic Accuracy of Machine Learning-Based Radiomics in Grading Gliomas: Systematic Review and Meta-Analysis. Contrast Media Mol Imaging 2020; 2020: 2127062. doi:10.1155/2020/2127062

[81] Abdel RazekAAK, Alksas A, Shehata M et al. Clinical applications of artificial intelligence and radiomics in neuro-oncology imaging. Insights Imaging 2021; 12: 152. doi:10.1186/s13244-021-01102-6

[82] Mueller WM, Yetkin FZ, Hammeke TA et al. Functional magnetic resonance imaging mapping of the motor cortex in patients with cerebral tumors. Neurosurgery 1996; 39: 515–520. doi:10.1097/00006123-199609000-00015

[83] Schulder M, Maldjian JA, Liu WC et al. Functional image-guided surgery of intracranial tumors located in or near the sensorimotor cortex. Journal of neurosurgery 1998; 89: 412–418. doi:10.3171/jns.1998.89.3.0412

[84] Ruff IM, Petrovich Brennan NM, Peck KK et al. Assessment of the language laterality index in patients with brain tumor using functional MR imaging: effects of thresholding, task selection, and prior surgery. AJNR American journal of neuroradiology 2008; 29: 528–535. doi:10.3174/ajnr.A0841

[85] Tyndall AJ, Reinhardt J, Tronnier V et al. Presurgical motor, somatosensory and language fMRI: Technical feasibility and limitations in 491 patients over 13 years. European radiology 2017; 27: 267–278. doi:10.1007/s00330-016-4369-4

[86] Zhang D, Johnston JM, Fox MD et al. Preoperative sensorimotor mapping in brain tumor patients using spontaneous fluctuations in neuronal activity imaged with functional magnetic resonance imaging: initial experience. Neurosurgery 2009; 65: 226–236. doi:10.1227/01.NEU.0000350868.95634.CA

[87] Cochereau J, Deverdun J, Herbet G et al. Comparison between resting state fMRI networks and responsive cortical stimulations in glioma patients. Human brain mapping 2016; 37: 3721–3732. doi:10.1002/hbm.23270

[88] Bizzi A, Blasi V, Falini A et al. Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. Radiology 2008; 248: 579–589. doi:10.1148/radiol.2482071214

[89] Bartos R, Jech R, Vymazal J et al. Validity of primary motor area localization with fMRI versus electric cortical stimulation: a comparative study. Acta neurochirurgica 2009; 151: 1071–1080. doi:10.1007/s00701-009-0368-4

[90] Meier MP, Ilmberger J, Fesl G et al. Validation of functional motor and language MRI with direct cortical stimulation. Acta neurochirurgica 2013; 155: 675–683. doi:10.1007/s00701-013-1624-1

[91] Giussani C, Roux FE, Ojemann J et al. 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: 113–120. doi:10.1227/01.NEU.0000360392.15450.C9

[92] Kuchcinski G, Mellerio C, Pallud J et al. Three-tesla functional MR language mapping: comparison with direct cortical stimulation in gliomas. Neurology 2015; 84: 560–568. doi:10.1212/WNL.0000000000001226

[93] Beisteiner R, Pernet C, Stippich C. Can We Standardize Clinical Functional Neuroimaging Procedures? Front Neurol 2018; 9: 1153. doi:10.3389/fneur.2018.01153

[94] Langs G, Sweet A, Lashkari D et al. Decoupling function and anatomy in atlases of functional connectivity patterns: language mapping in tumor patients. NeuroImage 2014; 103: 462–475. doi:10.1016/j.neuroimage.2014.08.029

[95] Archip N, Clatz O, Whalen S et al. Non-rigid alignment of pre-operative MRI, fMRI, and DT-MRI with intra-operative MRI for enhanced visualization and navigation in image-guided neurosurgery. NeuroImage 2007; 35: 609–624. doi:10.1016/j.neuroimage.2006.11.060

[96] Amoruso L, Geng S, Molinaro N et al. Oscillatory and structural signatures of language plasticity in brain tumor patients: A longitudinal study. Human brain mapping 2021; 42: 1777–1793. doi:10.1002/hbm.25328

[97] Deverdun J, van Dokkum LEH, Le Bars E et al. Language reorganization after resection of low-grade gliomas: an fMRI task based connectivity study. Brain imaging and behavior 2020; 14: 1779–1791. doi:10.1007/s11682-019-00114-7

[98] Bryszewski B, Tybor K, Ormezowska EA et al. Rearrangement of motor centers and its relationship to the neurological status of low-grade glioma examined on pre- and postoperative fMRI. Clinical neurology and neurosurgery 2013; 115: 2464–2470. doi:10.1016/j.clineuro.2013.09.034

[99] Holodny AI, Schulder M, Liu WC et al. Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: implications for image-guided neurosurgery. AJNR American journal of neuroradiology 1999; 20: 609–612

[100] Holodny AI, Schulder M, Liu WC et al. The effect of brain tumors on BOLD functional MR imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. AJNR American journal of neuroradiology 2000; 21: 1415–1422

[101] Hou BL, Bradbury M, Peck KK et al. Effect of brain tumor neovasculature defined by rCBV on BOLD fMRI activation volume in the primary motor cortex. NeuroImage 2006; 32: 489–497. doi:10.1016/j.neuroimage.2006.04.188

[102] Pillai JJ, Zaca D. Comparison of BOLD cerebrovascular reactivity mapping and DSC MR perfusion imaging for prediction of neurovascular uncoupling potential in brain tumors. Technology in cancer research & treatment 2012; 11: 361–374. doi:10.7785/tcrt.2012.500284

[103] Zaca D, Jovicich J, Nadar SR et al. Cerebrovascular reactivity mapping in patients with low grade gliomas undergoing presurgical sensorimotor mapping with BOLD fMRI. Journal of magnetic resonance imaging: JMRI 2014; 40: 383–390. doi:10.1002/jmri.24406

[104] Chang EF, Clark A, Smith JS et al. Functional mapping-guided resection of low-grade gliomas in eloquent areas of the brain: improvement of long-term survival. Clinical article. Journal of neurosurgery 2011; 114: 566–573. doi:10.3171/2010.6.JNS091246

[105] Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000; 406: 147–150. doi:10.1038/35018000

[106] Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. Neurophysiologie clinique = Clinical neurophysiology 2010; 40: 7–17. doi:10.1016/j.neucli.2010.01.006

[107] Ilmoniemi RJ, Ruohonen J, Karhu J. Transcranial magnetic stimulation – a new tool for functional imaging of the brain. Critical reviews in biomedical engineering 1999; 27: 241–284

[108] Saisanen L, Julkunen P, Niskanen E et al. Motor potentials evoked by navigated transcranial magnetic stimulation in healthy subjects. Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society 2008; 25: 367–372. doi:10.1097/WNP.0b013e31818e7944

[109] Krieg SM, Lioumis P, Makela JP et al. Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. Acta neurochirurgica 2017; 159: 1187–1195. doi:10.1007/s00701-017-3187-z

[110] Krieg SM, Shiban E, Buchmann N et al. Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. Journal of neurosurgery 2012; 116: 994–1001. doi:10.3171/2011.12.JNS111524

[111] Weiss Lucas C, Nettekoven C, Neuschmelting V et al. Invasive versus non-invasive mapping of the motor cortex. Human brain mapping 2020; 41: 3970–3983. doi:10.1002/hbm.25101

[112] Conway N, Wildschuetz N, Moser T et al. Cortical plasticity of motor-eloquent areas measured by navigated transcranial magnetic stimulation in patients with glioma. Journal of neurosurgery 2017: 1–11. doi:10.3171/2016.9.JNS161595

[113] Bulubas L, Sollmann N, Tanigawa N et al. Reorganization of Motor Representations in Patients with Brain Lesions: A Navigated Transcranial Magnetic Stimulation Study. Brain topography 2018; 31: 288–299. doi:10.1007/s10548-017-0589-4

[114] Krieg SM, Sollmann N, Obermueller T et al. Changing the clinical course of glioma patients by preoperative motor mapping with navigated transcranial magnetic brain stimulation. BMC cancer 2015; 15: 231. doi:10.1186/s12885-015-1258-1

[115] Sollmann N, Tanigawa N, Ringel F et al. Language and its right-hemispheric distribution in healthy brains: an investigation by repetitive transcranial magnetic stimulation. NeuroImage 2014; 102: 776–788. doi:10.1016/j.neuroimage.2014.09.002

[116] Krieg SM, Sollmann N, Tanigawa N et al. Cortical distribution of speech and language errors investigated by visual object naming and navigated transcranial magnetic stimulation. Brain structure & function 2016; 221: 2259–2286. doi:10.1007/s00429-015-1042-7

[117] Picht T, Krieg SM, Sollmann N et al. A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. Neurosurgery 2013; 72: 808–819. doi:10.1227/NEU.0b013e3182889e01

[118] Sollmann N, Kubitscheck A, Maurer S et al. Preoperative language mapping by repetitive navigated transcranial magnetic stimulation and diffusion tensor imaging fiber tracking and their comparison to intraoperative stimulation. Neuroradiology 2016; 58: 807–818. doi:10.1007/s00234-016-1685-y

[119] Sollmann N, Fuss-Ruppenthal S, Zimmer C et al. Investigating Stimulation Protocols for Language Mapping by Repetitive Navigated Transcranial Magnetic Stimulation. Front Behav Neurosci 2018; 12: 197. doi:10.3389/fnbeh.2018.00197

[120] Krieg SM, Tarapore PE, Picht T et al. Optimal timing of pulse onset for language mapping with navigated repetitive transcranial magnetic stimulation. NeuroImage 2014; 100: 219–236. doi:10.1016/j.neuroimage.2014.06.016

[121] Sollmann N, Ille S, Obermueller T et al. The impact of repetitive navigated transcranial magnetic stimulation coil positioning and stimulation parameters on human language function. European journal of medical research 2015; 20: 47. doi:10.1186/s40001-015-0138-0

[122] Kleiser R, Staempfli P, Valavanis A et al. Impact of fMRI-guided advanced DTI fiber tracking techniques on their clinical applications in patients with brain tumors. Neuroradiology 2010; 52: 37–46. doi:10.1007/s00234-009-0539-2

[123] Haberg A, Kvistad KA, Unsgard G et al. Preoperative blood oxygen level-dependent functional magnetic resonance imaging in patients with primary brain tumors: clinical application and outcome. Neurosurgery 2004; 54: 902–914

[124] Krishnan R, Raabe A, Hattingen E et al. Functional magnetic resonance imaging-integrated neuronavigation: correlation between lesion-to-motor cortex distance and outcome. Neurosurgery 2004; 55: 904–914

[125] Frey D, Strack V, Wiener E et al. A new approach for corticospinal tract reconstruction based on navigated transcranial stimulation and standardized fractional anisotropy values. NeuroImage 2012; 62: 1600–1609. doi:10.1016/j.neuroimage.2012.05.059

[126] Krieg SM, Buchmann NH, Gempt J et al. Diffusion tensor imaging fiber tracking using navigated brain stimulation–a feasibility study. Acta neurochirurgica 2012; 154: 555–563. doi:10.1007/s00701-011-1255-3

[127] Sollmann N, Negwer C, Ille S et al. Feasibility of nTMS-based DTI fiber tracking of language pathways in neurosurgical patients using a fractional anisotropy threshold. Journal of neuroscience methods 2016; 267: 45–54. doi:10.1016/j.jneumeth.2016.04.002

[128] Negwer C, Ille S, Hauck T et al. Visualization of subcortical language pathways by diffusion tensor imaging fiber tracking based on rTMS language mapping. Brain imaging and behavior 2017; 11: 899–914. doi:10.1007/s11682-016-9563-0

[129] Sollmann N, Wildschuetz N, Kelm A et al. Associations between clinical outcome and navigated transcranial magnetic stimulation characteristics in patients with motor-eloquent brain lesions: a combined navigated transcranial magnetic stimulation-diffusion tensor imaging fiber tracking approach. Journal of neurosurgery 2018; 128: 800–810. doi:10.3171/2016.11.JNS162322

[130] 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. doi:10.3390/cancers12051264

[131] Sollmann N, Fratini A, Zhang H et al. Associations between clinical outcome and tractography based on navigated transcranial magnetic stimulation in patients with language-eloquent brain lesions. Journal of neurosurgery 2019: 1–10. doi:10.3171/2018.12.JNS182988

[132] Rosenstock T, Grittner U, Acker G et al. Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation data. Journal of neurosurgery 2017; 126: 1227–1237. doi:10.3171/2016.4.JNS152896