# Role of Functional Magnetic Resonance Imaging in the Presurgical Mapping of Brain Tumors

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**KEYWORDS**

• Brain mapping • Functional MR imaging • Task fMR imaging • Resting state fMR imaging • Presurgical mapping

**KEY POINTS**

- Functional neuroimaging has been shown to be a valuable tool in preoperative mapping of brain functions in patients with tumors and provides reliable in vivo assessment of the eloquent cortex to minimize the risk of postsurgical morbidity.
- Task-based functional magnetic resonance (tb-fMR) imaging is the most commonly used method for noninvasive assessment of eloquent cortex and can reliably display cortical activity, including sensorimotor, language, and visual functions.
- Emerging evidence suggests that resting state functional MR imaging is a promising tool in addition to tb-fMR imaging in clinical settings, and it has the potential to become the noninvasive standard tool for surgical planning and a biomarker of prognosis in patients with brain tumor.
- Although functional MR imaging is a powerful tool that can significantly influence the planning for brain tumor surgery, there are some limitations to this technique that should be addressed in order to optimally perform and interpret the results in clinical practice.

## INTRODUCTION

When approached with the task of brain tumor resection, finding a balance between maximizing resection and minimizing injury to eloquent brain parenchyma is paramount. Technological advances have enabled the functional mapping of regions of the brain, which can be used for many clinical applications and investigative opportunities. Specifically, the advent of blood oxygenation level–dependent (BOLD) functional magnetic resonance (fMR) imaging has allowed researchers and clinicians to measure physiologic fluctuations in brain oxygenation related to neuronal activity with good spatial resolution. When coupled with intraoperative awake functional mapping, an avoidance of unanticipated resection-related deficits can substantially reduce the risk of morbidity of neurosurgical procedures.[1] This article highlights the benefits that task-based fMR (tb-fMR) imaging has provided to surgical therapeutic practice.

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## BACKGROUND OF FUNCTIONAL MAGNETIC RESONANCE IMAGING (BLOOD OXYGENATION LEVEL–DEPENDENT SIGNAL, FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY DESIGN)

fMR imaging is typically performed using the BOLD contrast technique, described by Ogawa and colleagues[2] in 1990. Deoxygenated hemoglobin, being paramagnetic, results in increased local susceptibility changes. In contrast, oxygenated hemoglobin is diamagnetic. Gradient echo techniques sensitive to these susceptibility changes can be used to determine relative oxyhemoglobin versus deoxyhemoglobin concentrations in blood. The variation of BOLD signal changes as a function of time in response to neural activity is called the hemodynamic response function.[3] The principle of neurovascular coupling states that, for a given set of neurons that are active, there are changes in local field potential that induce regional neurovascular changes, which result in an overall influx of local oxygenated blood, thus increasing relative signal on BOLD magnetic resonance (MR) imaging. Therefore, during acquisition of BOLD MR imaging, a patient that is actively engaging in a particular task shows increased relative signal in brain areas subserving the task.

Using this principle, investigators designed specific functional tasks presented at regular or random intervals to study patients under alternating blocks of exposure or under the condition of sporadic measured events. Simple task-based experimental design allows the control of behavior in a manner that may be easily reproduced and from which clinicians can assign cortical functional regions. Through task structure previously measured in healthy persons, the same experimental design can be applied to patients that may have a lesion in the region responsible for a particular task.

## FUNCTIONAL MAGNETIC RESONANCE IMAGING: CURRENT CLINICAL APPLICATIONS

Clinical use of fMR imaging is a recent phenomenon with about 20 years of collective experience. The main clinical application is in the presurgical evaluation and mapping of patients with structural lesions such as brain tumors, and in patients with epilepsy.[4] Preoperative fMR imaging studies have been shown to be helpful to surgeons for mapping of eloquent cortex and proximity to the target lesion, allowing informed decisions to be made regarding potential risks or safety of surgical resection and the surgical trajectory, and may influence the need for intraoperative cortical mapping.[5] When fMR imaging is used for presurgical planning, the choice of task paradigms to be used depends mainly on the location of the lesion.[6] For example, if the tumor is located in the posterior frontal lobe, motor paradigms can be used to map the motor strip.

Presurgical mapping has also been extensively used in patients with epilepsy, primarily for hemispheric language lateralization. In patients with epilepsy, a higher percentage of patients show atypical language lateralization than in normal individuals. Sometimes there is discordance between expressive and receptive language lateralization. It has also been used for motor and visual cortical mapping in cases where malformations of cortical development or other resectable epileptogenic lesions are thought to be in close spatial proximity to such eloquent cortical regions.[7]

This evolution of fMR imaging in clinical practice has been facilitated by the development of a CPT (Current Procedural Terminology) code for this technique by the American Society of Functional Neuroradiology (ASFNR) as well as several other studies on this topic. Notwithstanding, it is not the scope of this article to discuss the clinical applications of presurgical fMR imaging mapping in patients with epilepsy, cortical developmental lesions, as well as cortical plasticity in patients with vascular malformations (such as arteriovenous malformations and cavernomas), which are amply reviewed by the authors and others elsewhere.[8–10]

## FUNCTIONAL MAGNETIC RESONANCE IMAGING APPLICATIONS IN BRAIN TUMOR SURGERY

The clinical application of fMR imaging has been well established in preoperative brain tumor surgery planning and it is currently part of routine preoperative work-up in patients with brain tumors that are close to areas of presumed selected eloquent brain function.[5,11] In this context, it is essential to maximize the lesion resection while preserving the adjacent eloquent cortex to minimize the postoperative neurologic and functional deficits.[12,13] Beyond significant anatomic variations of the individual human brains, lesions may result in mass effect, with anatomic distortion limiting assessment of normal anatomic landmarks; furthermore, slow-growing lesions may result in brain plasticity and recruitment of brain regions that are not typically associated with a specific task or function. As a result, the eloquent cortex areas adjacent to the tumor may not be localized accurately merely by structural brain imaging.[14–16] Clinical fMR imaging can identify the critical brain regions that are associated with patients' daily functions, such as motor, language, and visual functions. Preoperative identification of eloquent cortices could help neurosurgeons to select the best surgical approach, to plan the extent of the resection, and to optimize intraoperative direct cortical stimulation (DCS).[17–19] Notably, an important question for surgeons is to determine whether the lesion is ipsilateral or contralateral to the dominant language areas. Intraoperative DCS remains the gold standard in localizing the dominant language areas; however, this procedure is time consuming and has considerable procedural challenges and limitations. Taking these into consideration, using preoperative fMR imaging to determine the lesion and language laterality is a useful noninvasive alternative tool that is complementary to intraoperative DCS.[17–19]

Preoperative fMR imaging has several other advantages in addition to determining language laterality. The anatomic relationship of the lesion to adjacent eloquent areas can be examined using fMR imaging; the data can be processed to optimize visualization of essential cortical structures, including three-dimensional displays to guide resection; and fMR imaging maps can be incorporated into the neurosurgical navigation systems to guide the operation.[20]

## THE GENERAL WORKFLOW FOR CLINICAL FUNCTIONAL MAGNETIC RESONANCE IMAGING

To obtain fMR imaging brain maps effectively, several key measures should be considered in the process.[21] The selection of the fMR imaging paradigms to be used is largely determined by the location of the lesion or intended surgical target, and the relevant local brain function at risk.[22] Assessment of any existing neurologic deficits may inform the possibility of infiltrative neoplasm causing functional deficits that may not be recoverable. Alternatively, intact neurologic function could aid in cautious interpretation of signal voids in peritumoral regions that may be affected by neurovascular uncoupling (NVU), whereby underlying neuronal activity remains intact but the vascular response is attenuated or absent. This topic is discussed later in this article.

### *Prescan Interview and Training*

Reviewing recent and prior imaging studies is crucial for accurate lesion location and spread assessment, planning of the fMR imaging study, and selection of paradigms tailored to the individual patient. Patients' cooperation and performance are essential to achieve an optimal fMR imaging dataset.[23] Therefore, preprocedure patient training involves necessary steps, including interviewing and assessing the clinical status of the patient, giving detailed instructions, and modifying the paradigm practice to fit the patient's abilities and limitations, before the scan. MR imaging–compatible corrective glasses may be considered at this time if it is evident that the patient has a refractive error. A detailed explanation of the fMR imaging task commensurate with patient understanding is beneficial, serving to alleviate patient anxiety and increase patient compliance for the study. The incorporation of patient instruction before the fMR imaging scan has been shown to increase the reliability of the data.[24]

### *Data Acquisition*

Because current fMR imaging techniques are limited in spatial resolution, a high-resolution anatomic scan, typically T1 weighted, is necessary to subsequently map the functional activations to structural images.[25] The inclusion of white matter imaging, most commonly diffusion tensor imaging, can be complementary to BOLD fMR imaging.

The stimulus paradigm is typically administered visually by displaying text or instructions via projector-mirror system or via specialized goggles, or by using specialized headphones for tasks with auditory presentation. During fMR imaging studies, patients may be monitored using a video camera to determine compliance for movement tasks, specifically the various motor tasks. Performance on selected language tasks may also be determined by using response systems such as button boxes.[23,26] However, the performance of covert language tasks cannot be monitored directly and should be assumed based on the patient performance during the prescan training.[27] Real-time activation maps can be used for a general quality control check (**Fig. 1**); motion or other artifacts can be readily discerned on real-time maps, and any suboptimal task paradigms may be repeated at this time.

Clinical fMR imaging uses a block design, whereby a specific task is performed for a sustained period of time (routinely 20–30 seconds), called the active period (or task phase), followed by the same period of rest (control phase), where the subject is instructed to stay still (as in a motor task) or performed a control task; the active and rest blocks are then repeated for a specified number of times to generate ample signal. Block designs are generally easier to perform, more efficient, and produce more statistically robust results compared with event-related designs.[28]

Because BOLD fMR imaging is inherently noisy and the signal changes caused by activation are

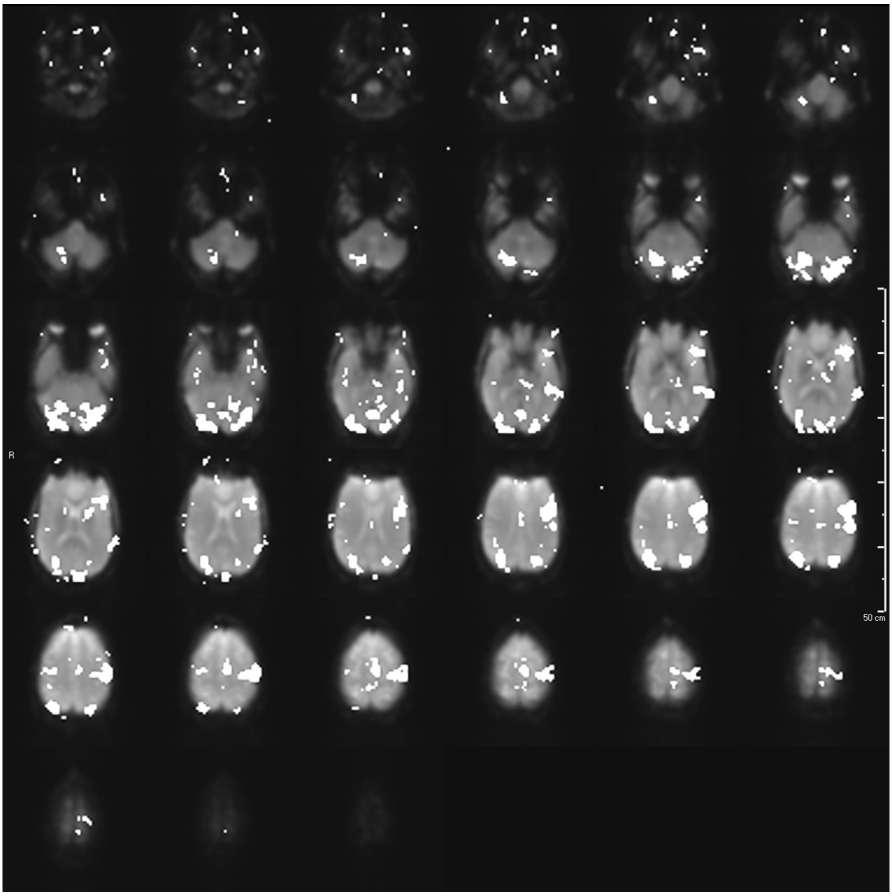


**Fig. 1.** Real-time BOLD fMR imaging maps obtained during scanning can alert the supervising radiologist if motion or other artifact necessitates repeating the study. However, the real-time maps only show absolute signal change over a certain threshold; therefore, both positive and negative signal changes would be highlighted. To determine positive changes, calculated t scores immediately following the task may be used. Images showing areas of positive signal change correlated with the task, t>4 in this case (images showing the combined signal changes and negative signal changes t<4 are not displayed).

on the order of 3% to 5% from baseline, the repetition of the tasks is necessary to ensure adequate signal to noise.[6,21,22,29] The use of a high field strength is essential; although a 1.5-T MR system is acceptable, the current standard is the use of a 3-T MR imaging scanner. Most functional MR imaging performed clinically uses acquisition of ultrafast images; for example, single shot T2* gradient recalled echo echo-planar technique, with a temporal resolution of approximately 2000 milliseconds and spatial resolution of 3 to 5 mm. A typical fMR imaging study paradigm generally acquires between 90 and 120 whole brain volumes in 3 to 4 minutes.

## Postprocessing and Quality Control

After data acquisition, several preprocessing steps are needed before the statistical analysis and creation of activation maps. Quality control (QC) analysis is also an essential step, which includes assessment of patient head motion, functional-anatomic alignment, susceptibility artifacts, and data outlier volumes.[30,31]

The minimum processing steps for fMR imaging analysis are motion correction and spatial smoothing. Motion correction is performed on each fMR imaging volume, with the first acquired volume typically as the target. Spatial smoothing is performed using a spatial gaussian filter, typically of the order of 1.5 to 3 times full width at half maximum the native voxel size. fMR imaging data are often detrended to account for linear drifts during scanning. If field maps are obtained, they can be used to correct for susceptibility-related distortion. As an alternative to gradient echo–based imaging, spin echo methods can also be used to minimize these susceptibility artifacts; however, they provide lower BOLD effect and lower contrast and have not been widely used.[26] Slice timing correction can be useful to correct for temporal shifts of image acquisition within a repetition time; however, in clinical practice with block paradigm design, this is not necessary.[32–34]

### *Functional Magnetic Resonance Imaging Data Analysis*

A regression analysis using a general linear model (GLM) is most commonly used for fMR imaging analysis. From the fMR imaging data, a signal intensity curve is generated over time for each voxel within the brain.[35] As noted, any area of the brain that is active during the task period results in slightly increased BOLD signal because of relative increase in oxyhemoglobin compared with deoxyhemoglobin. An idealized hemodynamic response curve is convolved with the task design to generate a task-specific reference waveform across the acquisition period. Simply put, any voxel that shows similar modulation of signal with the reference curve is determined to be correlated with the task. For each voxel, this reference curve is fitted and those voxels exceeding a preset statistical threshold are considered active. During this regression analysis, additional regressors may be added as confounds. In clinical practice, motion confounds are often not included, because motion time courses may be highly correlated with a task. A design matrix is then constructed that designates beta coefficients of the variables of interest, followed by calculation of contrasts, or weighted combinations of the beta coefficients, to determine the signal of interest.[6,21,22] For example, in a typical motor task, the contrast of interest is the time period during which the patient moved a specific part of the body. If 2 different active states are present in the task (for example, a widely used 3-phase hand motor task paradigm described later in this article), the contrast may specify activation during movement of 1 of the hands, or activation during movement of either hand.

A typical fMR imaging study comprises approximately 100,000 voxels. A separate GLM analysis is performed for each voxel, which is also referred to as a massive univariate analysis. Given the large number of calculations performed, various methods are used to minimize the activation errors because the surgical resection of areas labeled as no activation may result in significant morbidity. These methods include (but are not limited to) multiple correction methods, such as family-wise error, Bonferroni correction, and false discovery rate, or cluster-based thresholding methods.[36]

Following statistical analysis, activation maps can then be created, and the fMR imaging data coregistered to the patient's high-resolution anatomic images for localization. At this point, the final activation maps are thresholded, to strike a balance between sensitivity of localization and specificity. No single method of thresholding is widely used, and typically the activation maps are thresholded in a qualitative fashion, to visualize robust activation in an area of interest while minimizing depiction of noisy spurious foci. There have been methods to attempt to standardize the thresholding of activation maps, such as using a percentage of the maximum activation in a region.[37]

### *Role of Streamlined Postprocessing Tools*

Research-level BOLD fMR imaging postprocessing software is very accurate but requires significant experience in image processing as well as computer programming for generation of custom-made scripts for postprocessing; the main disadvantage of using this software is the lack of built in functions to export postprocessed images to PACS (Picture Archiving and Communication System) servers and neuronavigation systems efficiently. There are several commercial US Food and Drug Administration–approved software packages available that are more user friendly, allow better image overlays on high-resolution anatomic images, and are compatible with both PACS servers and neuronavigation software. The coregistered images can be downloaded to the neurosurgical computer. The neurosurgeon can then visualize three-dimensional reconstructions that define the relationship between the lesion and the eloquent cortices to guide the brain tumor resection. Many of these packages, being built on top of research software engines, also provide multiple options for customization such as statistical thresholding, image registration, as well as for QC analysis. At the same time, research software allows for additional processing in situations where the processing with the commercially available packages is inadequate.[30,31]

## COMMONLY USED TASKS

### *Motor Tasks*

tb-fMR imaging for motor function is frequently used to identify the primary motor cortex, by localizing the 3 main motor areas: foot, hand or fingers, and face/tongue. These areas are arranged in the precentral gyrus medially to laterally following the motor homunculus. Because the hand motor tasks are relatively easy to perform and show robust activation of the motor cortex, these tasks should be performed if the primary motor cortex is to be localized. There are also secondary motor areas that may be important for preoperative planning (ie, the supplementary motor area [SMA] along the medial surface of the frontal lobe) that are also shown on these motor tasks.[38]

Most of the motor tasks that we use at our institution have a block design paradigm with 30 seconds of rest alternating with 30 seconds of activity within each cycle, with visual instructions to stop or go. For foot motor activation, we instruct patients to continuously and gently plantar flex and dorsiflex the foot at the ankle bilaterally during the task period. Occasionally, this causes motion transfer to the head. As an alternative, patients may be instructed to curl their toes (or perform flexion and extension of the toes bilaterally) to minimize bulk body motion. Orofacial tasks can also be challenging because of induction of head motion during the task. We usually perform a vertical tongue movement task where the patient is asked to perform continuous gentle up and down movement of the tongue (alternately touching the roof and floor of the mouth with the tongue), taking care not to move the jaw. If the patient has difficulty with this task, lip puckering may be used as an alternative for eliciting activation in the lower face sensorimotor cortex. For hand sensorimotor activation, a finger movement task including bilateral simultaneous sequential finger tapping is performed with a similar block design, eliciting activation of the somatosensory cortex. The movement tasks often show good activation of the supplemental motor areas in addition to the primary motor cortex in the precentral gyrus. We often use a more complex 3-phase hand-grasp task as an alternative or complementary task for hand motor activation while minimizing sensory activation. In this task, we use a dynamic visual display and the patient is instructed to gently open and close each hand sequentially corresponding with the block length (typically 20 seconds), with an identical rest period following these, repeated multiple times. **Fig. 2** shows activation in the primary hand motor area and SMA in addition to the premotor SMA (language).

## *Language Tasks*

fMR imaging has been shown to be reliable for the prediction of hemispheric language dominance.[39–41] Numerous paradigms are typically used to elicit the activation in the eloquent cortex related to language function. Certain paradigms have been specially designed to elicit activation primarily in the speech production areas (expressive paradigms), and in the receptive language regions (receptive paradigms), whereas others may activate both regions. Language activation paradigms may be further divided into semantic, phonological, or verbal fluency paradigms.

Data published on language presurgical fMR imaging studies are varied because of the complexity of language function and different paradigms applied for this purpose in different institutions. Recent studies emphasize the need to evaluate all components of linguistic functions in preoperative mapping, because language evaluations do not account for particular aspects of grammar, even if patients may have postoperative language deficits. Therefore, it is necessary to identify a specific battery of linguistic tests to characterize cortical language representation at the individual level.[42,43] It may be necessary to perform additional tasks in multilingual patients.

Based on recent clinical experience using lexical semantic tasks, at least 6 core clinically relevant language areas can be identified using fMR imaging: (1) the Broca's area, in the posterior third of the inferior frontal gyrus; (2) the Exner's area, in the posterior middle frontal gyrus; (3) Supplementary speech area (pre-SMA); (4) angular gyrus; (5) the Wernicke's area, inferior (mid to anterior superior temporal gyrus [STG]) and superior (posterior STG and supramarginal gyrus) components; and (6) basal temporal language area.

In 2017, Benjamin and colleagues[44] studied 22 patients with epilepsy and tumor who underwent Wada test and fMR imaging to determine a clinician-driven individualized thresholding, to reliably identify these 6 language regions. Their results suggest that experienced clinicians can form conjunctions from 2 sets of 3 language tasks to generate equivalent maps by individualized thresholding which these maps differ from and are rated as of better quality than those generated with a fixed threshold. They concluded that a fixed threshold, without expert clinician input, may lead to inaccurate mapping in presurgical planning for language localization.[44]

Language tasks may differ in their sensitivity and specificity, which is another important factor to consider during paradigm selection. Some studies suggest that the use of expressive language paradigms could be associated with greater specificity than receptive and semantic tasks based on this study.[45]

Choice of task paradigm may need to be adjusted for patients with neurologic deficits such as speaking and reading difficulties. Specifically, in patients with reading or visual difficulties,

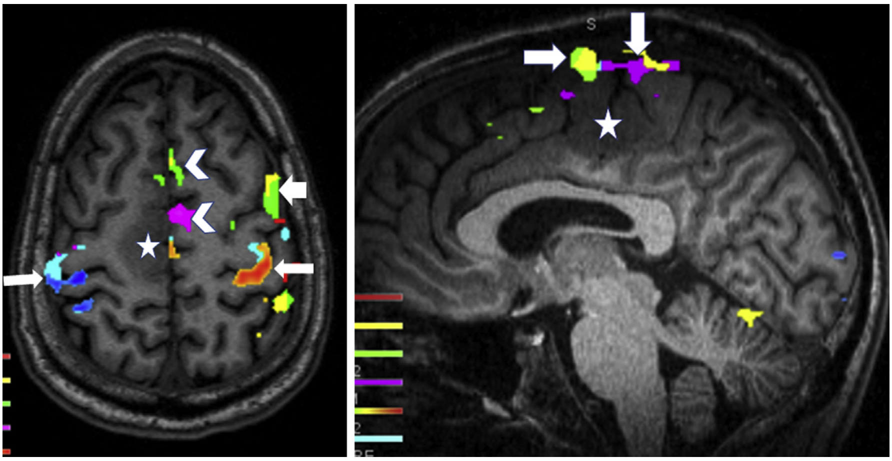

Fig. 2. Patient with tumor centered (*star*) in the posterior aspect of the right superior frontal gyrus. Primary functional area of concern is supplemental motor area and pre-supplemetary motor area. An area of activation is seen in the posterior aspect of the left superior frontal gyrus contralateral to the lesion, representing SMA activation (shown by chevrons on axial and arrows on sagittal images) during hand motor (*orange and blue*), finger motor (*light blue*), and foot motor (*pink*) tasks. Anterior to this, an area of convergent activation is seen with sentence completion (*yellow*) and silent word generation (*green*) tasks. The primary hand motor cortex (*arrows*) and dorsolateral prefrontal cortex (*short arrow*) are seen.

a language task paradigm could be tested via auditory input rather than visual, still activating language, visual, and auditory pathways. Although language dominance is usually left sided, many variations may occur. Surgery involving the mesial temporal lobe ipsilateral to the side of language dominance can result in postoperative memory-related word-finding difficulty, highlighting the value of preoperative fMR imaging assessment.[46]

The ASFNR recommended task algorithms with the aim of balancing varying levels of sensitivity and specificity as well as strengths in lateralization and localization and balancing paradigms that primarily activate frontal/expressive regions (silent word generation [SWG], antonym generation, object naming) and those that primarily activate temporal/receptive areas (sentence completion [SC], passive story listening).[47] In a study using the ASFNR paradigm, SC and SWG tasks were used for language localization and hemispheric lateralization to identify the primary language cortex. The standardized language tasks used were shown to have a high level of intrasubject intrascan repeatability for language mapping in a large cohort of patients undergoing presurgical fMR imaging across several years using both threshold-dependent and threshold-independent approaches. On the ASFNR Web site, parameters for language tasks paradigms are listed, as well as direct download of relevant task PowerPoint files for ASFNR members that can be directly incorporated into the stimulus presentation software.

As per the ASFNR recommendations, the most robust task for language activation is the sentence completion task, which shows good expressive and receptive language activation. The SWG task is a good choice for productive language activation as well as for language lateralization. Additional tasks include the rhyming task, noun-verb association task for productive language activation, and several tasks that preferentially activate receptive areas such as the reading comprehension, listening comprehension, or the passive story listening tasks. The object naming task is also an expressive task that can be used to elicit activation in visual recognition areas centered in the fusiform gyrus; however, this activation can be inconsistent.

There have been recent review articles discussing the current standards of presurgical language mapping using task-based fMR imaging in greater detail.[48] Figs. 3 and 4 show convergent activation on these maps performed with a battery of expressive (productive) and receptive tasks in patients with inferior frontal gyrus (see Fig. 3) and STG (see Fig. 4) lesions.

## *Visual Paradigms*

The primary visual cortex is organized to regionally correspond with the receptor field of the retina. As such, the visual cortex can be mapped through systematic visual stimulation. Typically, this is done via a visual stimulus that produces a spreading wave of activity such as an expanding

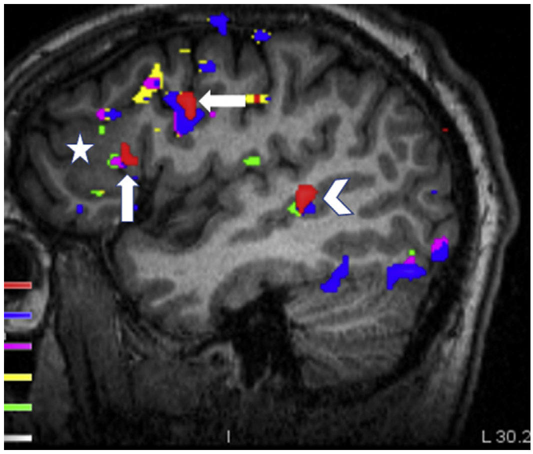


**Fig. 3.** Patient with infiltrative tumor in the left inferior frontal gyrus pars triangularis and orbitalis (*star*). Primary area of concern is primary productive language. An area of convergent productive language activation (*up arrow*) is seen in the pars triangularis related to the rhyming task (*red*), verb-noun association task (*pink*), and SWG task (*green*). Receptive language activation is also seen as a convergent area of activation along the posterior aspect of the superior temporal sulcus (*chevron*) related to the rhyming task, the SWG task, and the reading comprehension task (*blue*). Additional secondary language-related activation noted in the middle frontal gyrus and prefrontal cortex (*left arrow*).

ring or rotating wedge pattern, elucidating primary visual cortices and distinguishing between areas involved in central or peripheral vision. Often, visual fMR imaging is used to delineate eloquent visual cortex from the planned margin of surgical resection, and preoperative maps correspond well with intraoperative cortical stimulation.[49]

In addition, essential to vision are the networks that facilitate synchronized eye movements, image comprehension, and the understanding of spatial relationships. Areas involved in these networks include the frontal eye fields (precentral sulcus), supplementary eye fields (medial frontal cortex), visuospatial attention region (intraparietal sulcus), visuospatial processing region (temporoparietal junction), visual motion detection (middle temporal cortex/V5), visual cortex (occipital lobes: V1 to V4), and executive working memory (dorsolateral

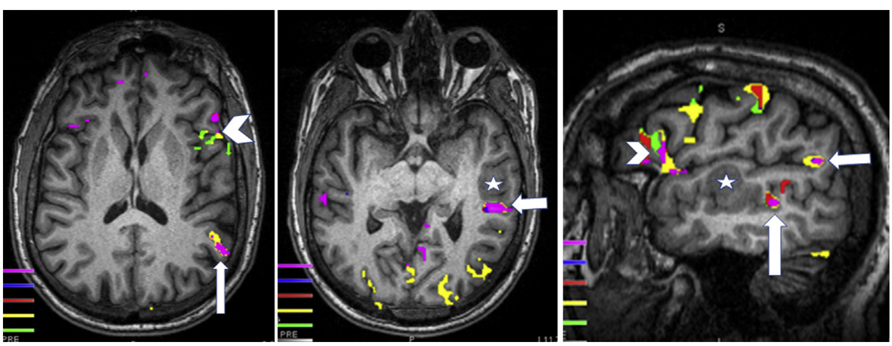

**Fig. 4.** Patient with mass lesion (*star*) in the left superior temporal gyrus, with primary area of concern being the primary receptive language areas. Axial image on left shows left lateralized productive language areas in the inferior frontal gyrus (*chevron*). The sentence completion task (*yellow*) shows activation in the left inferior frontal gyrus, as well as in the left supramarginal gyrus (*up arrow*) consisting of receptive language region often referred to as the Geschwind region, in this case also lateralized to the left. SWG (*green*) shows productive language activation, whereas listening comprehension (*pink*) shows primarily receptive activation. The axial image on the right shows additional convergent receptive language activation in the left temporal lobe (*block arrow*) immediately posterior to the lesion. The sagittal image shows the relationship of the lesion to the left posterior temporal receptive language activation (*up arrow*), as well as convergent inferior frontal gyrus productive language activation (*chevron*), and finally convergent receptive language activation in the left supramarginal gyrus (*left arrow*).

prefrontal cortex). Although clinical task fMR imaging has not attempted to routinely characterize these regions, the advent of resting state fMR imaging described later in this article has allowed delineation of these regions for potential operative planning.

Visual pathways are so clearly shown by fMR imaging that they can even be evaluated in patients under light sedation, as has been done during presurgical planning in young or uncooperative children to minimize risk of vision loss during resection. In 1 case series, preoperative fMR imaging data were synchronized with frameless stereotactic guidance to determine visual structure–sparing approaches in 6 children who ultimately underwent surgery. No cases of unexpected visual field deficits resulting from false-negative visual cortex delineation occurred.[50]

### Memory Paradigm

Memory paradigms have not gained general acceptance for clinical fMR imaging, although much work has been performed at a research level using such paradigms.[7,39] These paradigms can be difficult to perform and interpret, and susceptibility artifacts near the skull base can be a major limitation.

### Breath-Hold Cerebrovascular Reactivity Mapping

A major limitation of blood oxygen level fMR imaging in the clinical setting is NVU. As described earlier, BOLD fMR imaging is an indirect measure of neuronal activity based on related hemodynamic changes.[7] This measure requires the presence of a physiologic vascular response to performance of a task.

Hypercapnic challenges have been used to effectively evaluate brain cerebrovascular reactivity with exogenous carbon dioxide gas administration during MR imaging. However breath-hold tasks have been proved equivalent in evaluating the hemodynamic reserve capacity with BOLD fMR imaging.[51]

At our institution, we routinely perform a breath-hold task with all fMR imaging studies for mapping cerebrovascular reactivity. This breath-hold technique includes short-duration breath holds with a longer duration of normal relaxed breathing (16 seconds of a breath hold following inspiration alternating with a 40-second block of normal breathing), repeated multiple times. Monitoring of this task performance is performed by the use of a standard respiratory belt. Postprocessing is performed with specific modeling to account for the differing durations of the task and the control blocks.[23] The derived information is used to validate the ability of a perfusion bed to respond to the physiologic stimulus and reliability of the fMR imaging mapping.[23] This task is another important quality metric that is used in clinical fMR imaging.

### Limitations of Task-Base Functional Magnetic Resonance Imaging

Foremost among limitations of task fMR imaging for network localization and lateralization is the need to use tasks appropriate to the relevant anatomic structures of concern. Language and memory networks in particular are complex, involving multiple discrete sites and the connections between them, necessitating the use of multiple tasks in presurgical fMR imaging protocols to increase the sensitivity of fMR imaging language mapping.[52] Tasks used in their localization must have sufficient discriminating power, and the potential for the introduction of bias or artifact must be recognized. Many potential causes of task paradigm failure exist. For example, a large cohort study of patients with tumor and epilepsy with more than 2300 attempted paradigms found that failures were mostly related to problems in patient compliance, or tumor-induced neurologic disorder, especially from deficits affecting speech paradigms (likely caused by longer examination times, and increased cooperation, cognitive demand, and patience required from the patient). Other failures resulted from technical issues such as motion or foreign body artifacts, or scanner problems (system crash, head-coil defect). Physiologic limitations in BOLD imaging occur in the diagnostic power of the BOLD signal, which largely depends on changes of hemoglobin oxygenation state.[53] Intratumoral hemorrhage, tumor mass effect, hyperperfusion, steal phenomena, or drug effects may modify local hemodynamics and thereby produce failures and false-negative results.[45,54]

Another problem associated with fMR imaging in the clinical setting is NVU. As mentioned earlier, BOLD fMR imaging is an indirect measure of neuronal activity based on the related hemodynamic changes. The absence of activation on BOLD fMR imaging does not always imply the lack of neuronal activity. There are conditions under which the BOLD response may be disturbed, such as with large vascular malformations; brain tumors with associated neovascularity, including some low-grade tumors; and in situations with severe proximal arterial stenosis or strokes. This NVU may give rise to false-negative activation.[23,28,55] NVU can result in underrepresentation or nondetection of eloquent cortex (**Fig. 5**). In such settings, the detection of NVU may necessitate the use of complementary electrophysiologic intraoperative mapping.[23]

In contrast, false-positive results on fMR imaging mapping depict an incorrectly large area compared with actual eloquent structures established via direct electrical stimulation testing. Use

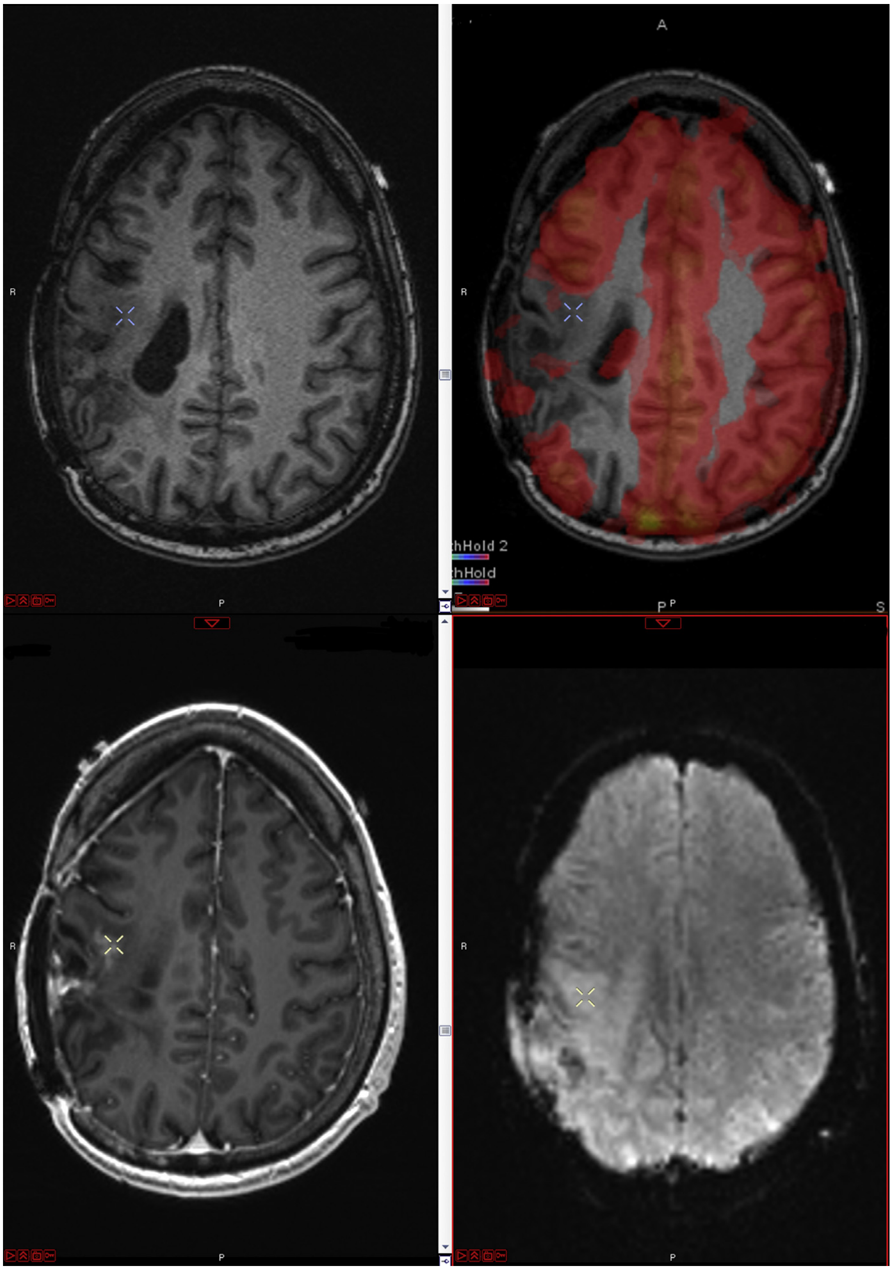


**Fig. 5.** Demonstration of NVU in a patient with a right parietal lesion, previously resected, with recurrent enhancement and consideration of reresection. The crosshairs localize to the enhancing lesion of interest. The bottom right raw echo-planar images show no significant susceptibility in this region, despite overlying craniotomy. The top right breath-hold cerebrovascular reactivity maps overlaid onto T1-weighted images show absence of cerebrovascular reactivity in the location of the lesion and posterior to it. (*Top left*) Precontrast T1; (*bottom left*) postcontrast T1.

of such an fMR imaging map could lead to a lesser extent of resection, reducing the benefits of cytoreduction.[53]

## RESTING STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING

In recent years, resting-state fMR (rs-fMR) imaging has emerged as a powerful adjunct tool to tb-fMR imaging in neuroscience research.[56–58] Significant progress has also been made in attempting to use rs-fMR imaging as a clinical tool.[59–61] The greatest potential of rs-fMR imaging in clinical practice is in presurgical mapping. There are several advantages of rs-fMR imaging compared with tb-fMR imaging in this setting, because there is no need to perform a specific task. This technique is most helpful in situations where patients cannot fully comply with performing the tb-fMR imaging because of cognitive deficits, language barriers, and/or physical disability.[29,62,63]

rs-fMR imaging assesses low-frequency fluctuations (0.1–0.01 Hz) in the BOLD signal while the patient is at rest. Functionally connected regions of the brain show synchronous spontaneous neural activity even if they are anatomically distant.[64] rs-fMR imaging analysis methods can be categorized as model-dependent and model-free methods. Seed-based correlation analysis is a model-dependent method that examines correlations between the time series of a predefined region of interest (ROI), called seed region, and its relationship to other brain regions. Model-free or data-driven computational methods include independent component analysis (ICA). ICA decomposes rs-fMR imaging data into a sum of independent components, each component corresponding with a spatial representation and a time course, without the need of an a priori ROI.[65,66]

## APPLICATION OF RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING IN PRESURGICAL MAPPING

An initial experimental study by Zhang and colleagues[57] assessed the use of rs-fMR imaging in presurgical planning of 4 patients with tumors located near motor and somatosensory cortices. Their result showed spatial reliability and specificity of the rs-fMR imaging technique for mapping the sensorimotor cortex. To date, several rs-fMR imaging studies have investigated the feasibility of this technique for preoperative mapping in the clinical setting, as well comparing rs-fMR imaging with tb-fMR imaging or intraoperative DCS.[53] Overall, rs-fMR imaging has shown comparable results with other techniques in the assessment of functional connectivity (FC), and several studies showed the efficacy of rs-fMR imaging in mapping the motor, sensorimotor, and language network, using both seed-based analysis and ICA. However, some investigators focused their interest on the evaluation of FC changes in motor networks during the postoperative period, as well as the FC alterations in default mode network and its relationship with the intellectual decline in patients with glioma.[67–69]

A study by Ding and colleagues[70] used an improved component automatic identification method to localize the common resting state networks (RSNs) in patients with brain metastases. They showed that ICA can effectively and reliably identify RSNs from rs-fMR imaging data in both individual patients and controls. In addition, the RSNs in the patients showed a distinct spatial shift compared with those in the control group, and the spatial shift of specific brain regions was correlated to the tumor location, suggesting functional disruptions and reorganizations caused by the lesions. Furthermore, higher cognitive networks, including default mode, executive control, dorsal attention, and language networks, showed significantly larger spatial shifts than perceptual networks (somatomotor, auditory, and visual networks), supporting a functional dichotomy between the 2 networks even in abnormal alterations associated with the lesions. Overall, their findings suggested that ICA is a promising method for presurgical localization of multiple RSNs from rs-fMR imaging data in patients.

A study by Tie and colleagues[71] in healthy individuals showed that language networks obtained from rs-fMR imaging showed significant similarities with language networks obtained from tb-fMR imaging, especially in the left frontal and temporal/parietal regions. These results were also reproduced in patients with brain tumors and epilepsy.[72] Rosazza and colleagues[73] reported a similar significant correlation of the results of ROI rs-fMR imaging and ICA in 40 healthy individuals. Kumar and colleagues[74] retrospectively reviewed a cohort of patients with brain tumor who underwent preoperative fMR imaging language mapping. Their results showed that rs-fMR imaging can be a valuable tool for clinical preoperative language mapping when a patient cannot perform tasks or if the tb-fMR imaging results are inadequate for accurate brain mapping.

Although rs-fMR imaging has shown potential to localize primary motor and sensory regions equally to tb-fMR imaging in patients with brain tumors,[63,75–77] the data-driven resting-derived sensorimotor networks typically cannot specify and differentiate functional subregions along the central sulcus. Recent developments in accelerated image acquisition techniques may improve the specificity of clinical rs-fMR imaging scans. In healthy volunteers scanned for the Human Connectome Project, high-temporal-resolution rs-fMR imaging has provided separation between the hand, foot, and mouth motor regions; however, the extent to which these advantages might support presurgical planning is yet to be determined.[76,78] In a study by Voets and colleagues,[76] presurgical localization of the primary sensorimotor cortex using fMR imaging was assessed in patients with gliomas. Sensorimotor network was successfully identified in 60.9% of rs-fMR imaging and in 97.9% of patients when using accelerated rs-fMR imaging. The investigators concluded that rs-fMR imaging offers benefits when tb-fMR imaging is not feasible but the data require rapid (or prohibitively long) sampling to attain similar statistical sensitivity.

A recent study by Leuthardt and colleagues[79] using a supervised machine learning approach for rs-fMR imaging reported a significantly higher failure rate of tb-fMR imaging compared with rs-fMR imaging. Studies in patients with neurologic diseases reported high consistency between rs-fMR imaging and tb-fMR imaging in identification of the motor network.[57,80,81] Similarly, high concordance of cortical stimulation mapping, and reproducibility of rs-fMR imaging–derived motor maps comparable with that of tb-fMR imaging in healthy subjects, have been reported in some studies.[57,75,80,82] However, rs-fMR imaging results in language mapping have been variable among studies on this topic. An investigation by Sair and colleagues[83] in patients with brain tumors showed moderate group-level consistency in rs-fMR imaging versus tb-fMR imaging language network identification, and a significant subject-level variability. Also, several studies have reported infiltration and abnormal NVU, which are associated with higher tumor grade but also can be present in the low-grade gliomas, and can alter the BOLD contrast and FC both in rs-fMR imaging and tb-fMR imaging.[84–88] A recent study by Lemée and colleagues compared the preoperative language mapping using rs-fMR and tb-fMR imaging for cortical mapping during awake craniotomies. They suggested that rs-fMR imaging is an easy technique to implement, allowing the identification of functional brain language areas with a greater sensitivity than the tb-fMR imaging, although it might have lower specificity.[89] Furthermore, Park and colleagues[90] conducted a study to compare a supervised classifier-based analysis of rs-fMR imaging data with the tb-fMR imaging in presurgical language mapping. Their results showed that presurgical language mapping with rs-fMR imaging is comparable with, and to some extent superior to, tb-fMR imaging. They reported that language tb-fMR imaging also activated the task-general brain networks (ie, not language specific) in addition to the Broca and Wernicke areas, whereas classifier-based analysis of rs-fMR imaging generated maps confined to language-specific brain regions.[90]

A recent study by Vakamudi and colleagues[81] has shown the feasibility of the real-time rs-fMR imaging of the sensorimotor and language networks in patients with brain tumors. The investigators suggested that this novel approach not only allows real-time monitoring of data quality but also has the potential for real-time presurgical mapping of eloquent cortex in patients with brain tumors with high concordance relative to task activation and DCS localization, within the constraints of impaired neurovascular coupling and/or cortical reorganization.

A major limitation of rs-fMR imaging in clinical practice has been the lack of standardization among studies. Despite advances, there is a lack of standardization of physiologic parameters, pharmacologic interventions, and characterization of disease-related vascular changes, with limited existing data on how these changes might affect the BOLD signal.[91] There are also some limitations within analysis methods. Seed-based analysis is based on predetermined ROIs, which can be arbitrary or driven by tb-fMR imaging.[92] Given that some patients have brain-distorting lesions, the collective database of ROIs may not be useable.[20] Although task versus rs-fMR imaging techniques differ in terms of reliability in functional mapping, certain approaches show similar reliability with respect to mapping the sensorimotor network, and rs-fMR imaging has shown promising results as a noninvasive diagnostic and prognostic tool. However, it is important to address other drawbacks of this technique, such as NVU and artifact susceptibility, to provide the most accurate functional assessment in clinical practice.[91,93]

Overall, rs-fMR imaging has shown concordant results with other techniques such as tb-fMR imaging or DCS in brain network identification.[59,61,94–96] Current evidence shows great promise for the future application of rs-fMR imaging in presurgical planning. rs-fMR imaging may also represent an opportunity for preoperative planning in pediatric patients.[53] So far, only a limited number of studies have been conducted in pediatric populations using passive motor, language, and visual stimuli in candidates for tumor or epilepsy surgery. Other areas of future rs-fMR imaging in patients with brain tumors may also include postsurgery longitudinal follow-up,[97,98] as well as the relationship between presurgery and postsurgery rs-fMR imaging data and patients' neuropsychological battery for evaluation of brain plasticity.[53,99,100]

## SUMMARY

Significant advances have been made in the assessment of brain FC since the discovery of synchronous BOLD signals. Functional neuroimaging has been shown to be a valuable tool in preoperative mapping of the eloquent cortex in neurosurgical patients, minimizing the risk of postsurgical morbidity. tb-fMR imaging is the most commonly used method for noninvasive assessment of brain function in clinical settings and can reliably show cortical activity, including sensorimotor, language, and visual functions. rs-fMR imaging has also shown great promise in preoperative brain mapping, as well as postoperative neuroplasticity and functional recovery. Nonetheless, it is important to be aware of the limitations of these techniques, such as patient compliance, artifact susceptibility, and NVU, in order to provide the most accurate functional assessment of the brain.

## CLINICS CARE POINTS

- Functional MR (fMR) Imaging is an integral part of presurgical planning in patients with brain tumors and it provides reliable in vivo assessment of the eloquent cortex to help minimize the risk of postsurgical morbidity.
- Task-based fMRI (tb-fMRI) is the most commonly used technique for noninvasive assessment of eloquent cortex and can reliably demonstrate brain regions involved in sensorimotor, language, and visual functions.
- Resting state fMRI (rs-fMRI) is increasingly being used in addition to tb-fMRI and has the potential to become the noninvasive standard tool for surgical planning in patients with brain tumor.
- Although fMRI has been shown to be a reliable tool, there are some limitations to this technique, such as neurovascular uncoupling and susceptibility artifact, that should be addressed in order to provide the most accurate functional assessment in clinical practice.

## DISCLOSURE

The authors have no disclosures.

## REFERENCES


1. Saito T, Muragaki Y, Maruyama T, et al. Intraoperative functional mapping and monitoring during glioma surgery. Neurol Med Chir (Tokyo) 2015;55(1):1–13.
2. Ogawa S, Lee TM, Kay AR, et al. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 1990;87(24):9868–72.
3. Heeger DJ, Ress D. What does fMRI tell us about neuronal activity? Nat Rev Neurosci 2002;3(2): 142–51.
4. Pillai JJ. The evolution of clinical functional imaging during the past 2 decades and its current impact on neurosurgical planning. AJNR Am J Neuroradiol 2010;31(2):219–25.
5. Petrella JR, Shah LM, Harris KM, et al. Preoperative functional MR imaging localization of language and motor areas: effect on therapeutic decision making in patients with potentially resectable brain tumors. Radiology 2006;240(3):793–802.
6. Bogomolny DL, Petrovich NM, Hou BL, et al. Functional MRI in the brain tumor patient. Top Magn Reson Imaging 2004;15(5):325–35.
7. Gujar SK, Sair HI, Pillai JJ. Functional magnetic resonance imaging. CT and MRI of the whole body. 6th edition. Elsevier; 2017. p. 489–98. Chapter 16.
8. Chaudhary UJ, Duncan JS. Applications of blood-oxygen-level-dependent functional magnetic resonance imaging and diffusion tensor imaging in epilepsy. Neuroimaging Clin N Am 2014;24(4):671–94.
9. Pillai JJ, Williams HT, Faro S. Functional imaging in temporal lobe epilepsy. Semin Ultrasound CT MR 2007;28(6):437–50.
10. Soldozy S, Akyeampong DK, Barquin DL, et al. Systematic review of functional mapping and cortical reorganization in the setting of arteriovenous malformations, redefining anatomical eloquence. Front Surg 2020;7:514247.
11. Gabriel M, Brennan NP, Peck KK, et al. Blood oxygen level dependent functional magnetic resonance imaging for presurgical planning. Neuroimaging Clin N Am 2014;24(4):557–71.
12. Gupta A, Shah A, Young RJ, et al. Imaging of brain tumors: functional magnetic resonance imaging and diffusion tensor imaging. Neuroimaging Clin N Am 2010;20(3):379–400.
13. Brennan NP, Peck KK, Holodny A. Language mapping using fMRI and direct cortical stimulation for brain tumor surgery: the good, the bad, and the questionable. Top Magn Reson Imaging 2016; 25(1):1–10.

14. Fisicaro RA, Jost E, Shaw K, et al. Cortical plasticity in the setting of brain tumors. Top Magn Reson Imaging 2016;25(1):25–30.
15. Holodny AI, Schulder M, Ybasco A, et al. Translocation of Broca's area to the contralateral hemisphere as the result of the growth of a left inferior frontal glioma. J Comput Assist Tomogr 2002; 26(6):941–3.
16. Li Q, Dong JW, Del Ferraro G, et al. Functional translocation of broca's area in a low-grade left frontal glioma: graph theory reveals the novel, adaptive network connectivity. Front Neurol 2019; 10:702.
17. Ille S, Sollmann N, Hauck T, et al. Combined noninvasive language mapping by navigated transcranial magnetic stimulation and functional MRI and its comparison with direct cortical stimulation. J Neurosurg 2015;123(1):212–25.
18. 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(5):808–19.
19. Babajani-Feremi A, Narayana S, Rezaie R, et al. Language mapping using high gamma electrocorticography, fMRI, and TMS versus electrocortical stimulation. Clin Neurophysiol 2016;127(3):1822–36.
20. Lang S, Duncan N, Northoff G. Resting-state functional magnetic resonance imaging: review of neurosurgical applications. Neurosurgery 2014; 74(5):453–64 [discussion 464–5].
21. Belyaev AS, Peck KK, Brennan NM, et al. Clinical applications of functional MR imaging. Magn Reson Imaging Clin N Am 2013;21(2):269–78.
22. Brennan NP. Preparing the patient for the fMRI study and optimization of paradigm selection and delivery. Informa Healthcare Inc; 2008. p. 13–22.
23. Pillai JJ, Mikulis DJ. Cerebrovascular reactivity mapping: an evolving standard for clinical functional imaging. AJNR Am J Neuroradiol 2015; 36(1):7–13.
24. Silva MA, See AP, Essayed WI, et al. Challenges and techniques for presurgical brain mapping with functional MRI. Neuroimage Clin 2018;17: 794–803.
25. Zacá D, Pillai JJ. BOLD fMRI for presurgical planning: Part I. In: Pillai JJ, editor. Functional brain tumor imaging. New York (N Y): Springer; 2014. p. 59–78.
26. Jones RA, Brooks JA, Moonen CTW. Ultra-fast fMRI. Functional MRI: An introduction to methods. 2001. p. 93.
27. Peck KK, Cho NS, Holodny AI. Methods of analysis: functional MRI for presurgical planning. Neuroimaging Clin N Am 2021;31(1):23–32.
28. Zaca D, Pillai JJ. BOLD fMRI for presurgical planning: part 1. Functional Brain Tumor Imaging. 2014. p. 59–78.
29. Fox MD, Snyder AZ, Vincent JL, et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005;102(27):9673–8.
30. González-Ortiz S, Oleaga L, Pujol T, et al. Simple fMRI postprocessing suffices for normal clinical practice. AJNR Am J Neuroradiol 2013;34(6): 1188–93.
31. Pillai JJ. The significance of streamlined postprocessing approaches for clinical FMRI. AJNR Am J Neuroradiol 2013;34(6):1194–6.
32. Friston KJ, Ashburner J, Frith CD, et al. Spatial registration and normalization of images. Hum Brain Mapp 1995;3(3):165–89.
33. Murphy K, Birn RM, Bandettini PA. Resting-state fMRI confounds and cleanup. Neuroimage 2013; 80:349–59.
34. Muschelli J, Nebel MB, Caffo BS, et al. Reduction of motion-related artifacts in resting state fMRI using aCompCor. Neuroimage 2014;96:22–35.
35. Friston KJ, Holmes AP, Worsley KJ, et al. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1994;2(4): 189–210.
36. Loring DW, Meador KJ, Allison JD, et al. Now you see it, now you don't: statistical and methodological considerations in fMRI. Epilepsy Behav 2002; 3(6):539–47.
37. Voyvodic JT. Reproducibility of single-subject fMRI language mapping with AMPLE normalization. J Magn Reson Imaging 2012;36(3):569–80.
38. Boecker H, Kleinschmidt A, Requardt M, et al. Functional cooperativity of human cortical motor areas during self-paced simple finger movements. A high-resolution MRI study. Brain 1994;117(Pt 6): 1231–9.
39. Gaillard WD. Functional MR imaging of language, memory, and sensorimotor cortex. Neuroimaging Clin N Am 2004;14(3):471–85.
40. Rutten GJ, Ramsey NF, van Rijen PC, et al. FMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. Neuroimage 2002; 17(1):447–60.
41. Sabbah P, Chassoux F, Leveque C, et al. Functional MR imaging in assessment of language dominance in epileptic patients. Neuroimage 2003;18(2):460–7.
42. Połczyńska MM, Japardi K, Bookheimer SY. Lateralizing language function with pre-operative functional magnetic resonance imaging in early proficient bilingual patients. Brain Lang 2017;170: 1–11.

43. Rofes A, Miceli G. Language mapping with verbs and sentences in awake surgery: a review. Neuropsychol Rev 2014;24(2):185–99.
44. Benjamin CF, Walshaw PD, Hale K, et al. Presurgical language fMRI: mapping of six critical regions. Hum Brain Mapp 2017;38(8):4239–55.
45. Weng HH, Noll KR, Johnson JM, et al. Accuracy of presurgical functional MR imaging for language mapping of brain tumors: a systematic review and meta-analysis. Radiology 2018;286(2):512–23.
46. van Heerden J, Desmond PM, Phal PM. Functional MRI in clinical practice: a pictorial essay. J Med Imaging Radiat Oncol 2014;58(3):320–6.
47. Black DF, Vachha B, Mian A, et al. American society of functional neuroradiology-recommended fMRI Paradigm Algorithms for presurgical language assessment. AJNR Am J Neuroradiol 2017;38(10):E65–73.
48. Agarwal S, Sair HI, Gujar S, et al. Language mapping with fMRI: current standards and reproducibility. Top Magn Reson Imaging 2019;28(4): 225–33.
49. Black DF, Little JT, Johnson DR. Neuroanatomical considerations in preoperative functional brain mapping. Top Magn Reson Imaging 2019;28(4): 213–24.
50. Li W, Wait SD, Ogg RJ, et al. Functional magnetic resonance imaging of the visual cortex performed in children under sedation to assist in presurgical planning. J Neurosurg Pediatr 2013;11(5):543–6.
51. Kastrup A, Krüger G, Neumann-Haefelin T, et al. Assessment of cerebrovascular reactivity with functional magnetic resonance imaging: comparison of CO(2) and breath holding. Magn Reson Imaging 2001;19(1):13–20.
52. Unadkat P, Fumagalli L, Rigolo L, et al. Functional MRI task comparison for language mapping in neurosurgical patients. J Neuroimaging 2019; 29(3):348–56.
53. Castellano A, Cirillo S, Bello L, et al. Functional MRI for surgery of gliomas. Curr Treat Options Neurol 2017;19(10):34.
54. Tyndall AJ, Reinhardt J, Tronnier V, et al. Presurgical motor, somatosensory and language fMRI: technical feasibility and limitations in 491 patients over 13 years. Eur Radiol 2017;27(1):267–78.
55. Zaca D, Hua J, Pillai JJ. Cerebrovascular reactivity mapping for brain tumor presurgical planning. World J Clin Oncol 2011;2(7):289–98.
56. Stufflebeam SM, Liu H, Sepulcre J, et al. Localization of focal epileptic discharges using functional connectivity magnetic resonance imaging. J Neurosurg 2011;114(6):1693–7.
57. 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(6 Suppl):226–36.
58. Mitchell TJ, Hacker CD, Breshears JD, et al. A novel data-driven approach to preoperative mapping of functional cortex using resting-state functional magnetic resonance imaging. Neurosurgery 2013;73(6):969–82 [discussion 982–3].
59. Tanaka N, Stufflebeam SM. Presurgical mapping of the language network using resting-state functional connectivity. Top Magn Reson Imaging 2016;25(1): 19–24.
60. Kokkonen SM, Nikkinen J, Remes J, et al. Preoperative localization of the sensorimotor area using independent component analysis of resting-state fMRI. Magn Reson Imaging 2009;27(6):733–40.
61. Lee MH, Miller-Thomas MM, Benzinger TL, et al. Clinical resting-state fMRI in the preoperative setting: are we ready for prime time? Top Magn Reson Imaging 2016;25(1):11–8.
62. Gusnard DA, Raichle ME, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2001;2(10): 685–94.
63. Liu H, Buckner RL, Talukdar T, et al. Task-free presurgical mapping using functional magnetic resonance imaging intrinsic activity. J Neurosurg 2009;111(4):746–54.
64. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010;20(8):519–34.
65. Yeh CJ, Tseng YS, Lin YR, et al. Resting-state functional magnetic resonance imaging: the impact of regression analysis. J Neuroimaging 2015;25(1): 117–23.
66. Wu L, Caprihan A, Bustillo J, et al. An approach to directly link ICA and seed-based functional connectivity: application to schizophrenia. Neuroimage 2018;179:448–70.
67. Esposito R, Mattei PA, Briganti C, et al. Modifications of default-mode network connectivity in patients with cerebral glioma. PLoS One 2012;7(7): e40231.
68. Zhang H, Shi Y, Yao C, et al. Alteration of the intra- and cross- hemisphere posterior default mode network in frontal lobe glioma patients. Sci Rep 2016;6:26972.
69. Xu H, Ding S, Hu X, et al. Reduced efficiency of functional brain network underlying intellectual decline in patients with low-grade glioma. Neurosci Lett 2013;543:27–31.
70. Ding JR, Zhu F, Hua B, et al. Presurgical localization and spatial shift of resting state networks in patients with brain metastases. Brain Imaging Behav 2019;13(2):408–20.
71. Tie Y, Rigolo L, Norton IH, et al. Defining language networks from resting-state fMRI for surgical

planning–a feasibility study. Hum Brain Mapp 2014;35(3):1018–30.
72. Branco P, Seixas D, Deprez S, et al. Resting-state functional magnetic resonance imaging for language preoperative planning. Front Hum Neurosci 2016;10:11.
73. Rosazza C, Minati L, Ghielmetti F, et al. Functional connectivity during resting-state functional MR imaging: study of the correspondence between independent component analysis and region-of-interest-based methods. AJNR Am J Neuroradiol 2012;33(1):180–7.
74. Kumar VA, Heiba IM, Prabhu SS, et al. The role of resting-state functional MRI for clinical preoperative language mapping. Cancer Imaging 2020;20(1):47.
75. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 2009; 106(31):13040–5.
76. Voets NL, Plaha P, Parker Jones O, et al. Presurgical localization of the primary sensorimotor cortex in gliomas. Clin Neuroradiol 2021;31:245–56. https://doi.org/10.1007/s00062-020-00879-1.
77. Rosazza C, Aquino D, D'Incerti L, et al. Preoperative mapping of the sensorimotor cortex: comparative assessment of task-based and resting-state FMRI. PLoS One 2014;9(6):e98860.
78. Smith SM, Beckmann CF, Andersson J, et al. Resting-state fMRI in the human connectome project. Neuroimage 2013;80:144–68.
79. Leuthardt EC, Guzman G, Bandt SK, et al. Integration of resting state functional MRI into clinical practice - a large single institution experience. PLoS One 2018;13(6):e0198349.
80. Shimony JS, Zhang D, Johnston JM, et al. Resting-state spontaneous fluctuations in brain activity: a new paradigm for presurgical planning using fMRI. Acad Radiol 2009;16(5):578–83.
81. Vakamudi K, Posse S, Jung R, et al. Real-time presurgical resting-state fMRI in patients with brain tumors: Quality control and comparison with task-fMRI and intraoperative mapping. Hum Brain Mapp 2020;41(3):797–814.
82. Mannfolk P, Nilsson M, Hansson H, et al. Can resting-state functional MRI serve as a complement to task-based mapping of sensorimotor function? A test-retest reliability study in healthy volunteers. J Magn Reson Imaging 2011;34(3):511–7.
83. Sair HI, Yahyavi-Firouz-Abadi N, Calhoun VD, et al. Presurgical brain mapping of the language network in patients with brain tumors using resting-state fMRI: Comparison with task fMRI. Hum Brain Mapp 2016;37(3):913–23.
84. 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(2):489–97.
85. Jiang Z, Krainik A, David O, et al. Impaired fMRI activation in patients with primary brain tumors. Neuroimage 2010;52(2):538–48.
86. 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 Am J Neuroradiol 2000;21(8):1415–22.
87. Agarwal S, Sair HI, Airan R, et al. Demonstration of brain tumor-induced neurovascular uncoupling in resting-state fMRI at ultrahigh field. Brain Connect 2016;6(4):267–72.
88. Pak RW, Hadjiabadi DH, Senarathna J, et al. Implications of neurovascular uncoupling in functional magnetic resonance imaging (fMRI) of brain tumors. J Cereb Blood Flow Metab 2017;37(11): 3475–87.
89. Lemée JM, Berro DH, Bernard F, et al. Resting-state functional magnetic resonance imaging versus task-based activity for language mapping and correlation with perioperative cortical mapping. Brain Behav 2019;9(10):e01362.
90. Park KY, Lee JJ, Dierker D, et al. Mapping language function with task-based vs. resting-state functional MRI. PLoS One 2020;15(7):e0236423.
91. Chen JE, Glover GH. Functional magnetic resonance imaging methods. Neuropsychol Rev 2015; 25(3):289–313.
92. Caballero-Gaudes C, Reynolds RC. Methods for cleaning the BOLD fMRI signal. Neuroimage 2017;154:128–49.
93. Agarwal S, Lu H, Pillai JJ. Value of frequency domain resting-state functional magnetic resonance imaging metrics amplitude of low-frequency fluctuation and fractional amplitude of low-frequency fluctuation in the assessment of brain tumor-induced neurovascular uncoupling. Brain Connect 2017;7(6):382–9.
94. Hou BL, Bhatia S, Carpenter JS. Quantitative comparisons on hand motor functional areas determined by resting state and task BOLD fMRI and anatomical MRI for pre-surgical planning of patients with brain tumors. Neuroimage Clin 2016; 11:378–87.
95. Cochereau J, Deverdun J, Herbet G, et al. Comparison between resting state fMRI networks and responsive cortical stimulations in glioma patients. Hum Brain Mapp 2016;37(11):3721–32.
96. Qiu TM, Yan CG, Tang WJ, et al. Localizing hand motor area using resting-state fMRI: validated with direct cortical stimulation. Acta Neurochir (Wien) 2014;156(12):2295–302.
97. Boyer A, Deverdun J, Duffau H, et al. Longitudinal changes in cerebellar and thalamic spontaneous neuronal activity after wide-awake surgery of brain tumors: a resting-state fMRI study. Cerebellum 2016;15(4):451–65.

98. Ives-Deliperi VL, Butler JT. Functional mapping in pediatric epilepsy surgical candidates: functional magnetic resonance imaging under sedation with chloral hydrate. Pediatr Neurol 2015;53(6): 478–84.
99. Vassal M, Charroud C, Deverdun J, et al. Recovery of functional connectivity of the sensorimotor network after surgery for diffuse low-grade gliomas involving the supplementary motor area. J Neurosurg 2017;126(4):1181–90.
100. Kristo G, Raemaekers M, Rutten GJ, et al. Inter-hemispheric language functional reorganization in low-grade glioma patients after tumour surgery. Cortex 2015;64:235–48.