Radiology

REVIEWS AND COMMENTARY • REVIEW

Functional MRI in Neuro-Oncology: State of the Art and Future Directions

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See also the review “Neuroimaging in Dementia: More than Typical Alzheimer Disease” by Haller et al in this issue.

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Since its discovery in the early 1990s, functional MRI (fMRI) has been used to study human brain function. One well-established application of fMRI in the clinical setting is the neurosurgical planning of patients with brain tumors near eloquent cortical areas. Clinical fMRI aims to preoperatively identify eloquent cortices that serve essential functions in daily life, such as hand movement and language. The primary goal of neurosurgery is to maximize tumor resection while sparing eloquent cortices adjacent to the tumor. When a lesion presents in the vicinity of an eloquent cortex, surgeons may use fMRI to plan their best surgical approach by determining the proximity of the lesion to regions of activation, providing guidance for awake brain surgery and intraoperative brain mapping. The acquisition of fMRI requires patient preparation prior to imaging, determination of functional paradigms, monitoring of patient performance, and both processing and analysis of images. Interpretation of fMRI maps requires a strong understanding of functional neuroanatomy and familiarity with the technical limitations frequently present in brain tumor imaging, including neurovascular uncoupling, patient compliance, and data analysis. This review discusses clinical fMRI in neuro-oncology, relevant ongoing research topics, and prospective future developments in this exciting discipline.

Supplemental material is available for this article.

At present, the main clinical application of functional MRI (fMRI) is in preoperative planning for patients with brain tumors (1–3). Eloquent areas in the brain represent the essential areas for carrying out neurologic functions (4) and include the language, motor, and sensory cortices (4). The goal of brain tumor surgery is twofold. The first is to maximize tumor resection, improving survival and decreasing symptoms. The second is to preserve adjacent eloquent areas, minimizing postsurgical deficits (5). The most widely used method for preoperative evaluation of language and motor functions is task-based fMRI, which relies on specific functional tasks to localize brain function and guide surgical resection (6). The inclusion of fMRI in neuro-oncologic preoperative planning has clear and established clinical benefits. Luna et al (7) recently demonstrated the reduction of pooled adverse event rates (from 21% to 11%) in patients who underwent fMRI as part of their preoperative planning.

The essential roles of preoperative fMRI are as follows: *(a)* planning the surgical approach for resection; *(b)* defining the relationship of brain lesions to eloquent areas; *(c)* assessing the need for intraoperative cortical stimulation and cortical mapping; *(d)* determining language dominance; *(e)* identifying crucial anatomic landmarks, such as the precentral (motor) gyrus; and *(f)* providing information to discuss with the patient before surgery.

The study of brain function is an evolving discipline that both presents new challenges for the clinical radiologist and provides a powerful new instrument to address crucial issues of neuro-oncology, as well as the broader field of cognitive neuroscience. Standard clinical fMRI requires preparation of the patient, proper equipment for delivery of functional paradigms, task performance monitoring, and postprocessing of the fMRI data (Fig 1). Radiologic interpretation of fMRI maps necessitates a strong understanding of functional neuroanatomy and familiarity with the interactions of various anatomic areas, as well as knowledge of the ways in which these interactions may change among disease states.

This review describes state-of-the-art clinical fMRI in neuro-oncology, discusses relevant research topics, and explores potential future directions.

State-of-the-Art fMRI Preoperative Planning

Patient Assessment and Preparation

The first steps of an optimal fMRI protocol are obtaining a detailed medical history, reviewing the imaging, and performing a dedicated examination. For more details, see Appendix S1. Language and/or motor deficits suggest that the tumor involves the associated ipsilateral eloquent cortex.

Recommended fMRI Task Paradigms

Many fMRI studies in the literature are performed in motivated, healthy, and young volunteers. The neuro-oncologic setting is often more challenging because patients may be neurologically impaired, tired, forgetful, older, hearing-impaired, or do not speak the same language as the fMRI specialist.

Abbreviations

BOLD = blood oxygen level dependent, fMRI = functional MRI, rsfMRI = resting-state fMRI

CME

Summary

Preoperative functional MRI (fMRI) improves surgical outcomes in patients with brain tumors; this review describes state-of-the-art clinical fMRI in neuro-oncology, relevant research topics, and future directions.

Essentials

- Preoperative functional MRI (fMRI) in patients with brain tumors has developed into a robust technique that improves surgical outcomes, and the demonstrated clinical benefit of fMRI in the preoperative setting necessitates the continued implementation of fMRI techniques.
- The oncologic setting differs markedly from investigations conducted in healthy volunteers due to the special attention required for fMRI performance in patients with neurologic or neurosurgical disorders.
- Optimization of clinical fMRI requires patient preparation and monitoring and adjustment of functional paradigms to account for difficulties that patients with brain tumors may have complying with paradigms; and interpretation of fMRI requires an understanding of functional neuroanatomy and familiarity with the technical challenges of fMRI, including neurovascular uncoupling.
- Brain tumors can compromise the language network by focally invading dominant eloquent areas and promoting reorganization of cortical function (neuroplasticity), which can be recognized through neuroimaging.
- Future directions in fMRI of brain tumors include overcoming the neurovascular uncoupling problem, application of artificial intelligence to fMRI, and better understanding the network nature of language function and how this network changes in response to the growth of brain tumors.

Generally accepted clinical fMRI paradigms are reported in the consensus paper from The American Society of Functional Neuroradiology. In addition, the following are suggestions for the optimization of paradigm selection.

Motor paradigms.—Motor tasks should be selected based on a patient's clinical condition and lesion location. Furthermore, it may be helpful to perform motor paradigms in patients with pertinent deficits, even if the lesion does not directly affect the motor cortex. Motor task paradigms should be tailored to the location of the lesion in the motor homunculus. For example, lesions adjacent to the midline should be assessed with leg and foot movement tasks; lesions closer to the reverse omega portion of the central sulcus should include finger tapping; and inferior lesions near the inferolateral aspect of the precentral gyrus should include face and tongue movement (Fig 2). For more details, See Appendix S1 and Figure S1.

Language paradigms.—Neurosurgeons generally want to know two things when requesting fMRI for language; these include *(a)* language lateralization (ipsilateral or contralateral to the tumor) and *(b)* localization of eloquent cortices near the lesion to be resected. Classically, the main productive speech area in the frontal lobe is known as Broca area and is located within the inferior frontal gyrus. Damage to this area can cause Broca (or expressive) aphasia. Intraoperative cortical stimulation in this area during an awake craniotomy should produce speech arrest. Frontal lesions necessitate productive speech paradigms like "phonemic fluency," in which patients silently generate words that begin with a given letter. Another productive paradigm that has achieved good concordance with intraoperative mapping is verb generation, whereby patients generate action words in reply to presented nouns (6,8). The main receptive speech area, known as Wernicke area, is in the posterior superior temporal gyrus. A lesion near this area is evaluated with receptive tasks that assess the ability to perform word finding. Generally, verbal fluency tasks requiring both language expression (primarily) and language comprehension (secondarily) routinely give rise to activation in Broca and Wernicke areas of the dominant hemisphere, in the presupplementary motor area (or the language supplementary motor area), fusiform gyrus, dorsolateral prefrontal cortex, and premotor cortex (Figs 3, 4) (9). Evaluation of auditory function can be performed through passive listening tasks, which activate the primary auditory cortex located in the Heschl gyrus (Fig 5). For language paradigms to stimulate Broca and Wernicke areas, a task block consisting of 20-second stimulation is generally recommended to achieve robust activation.

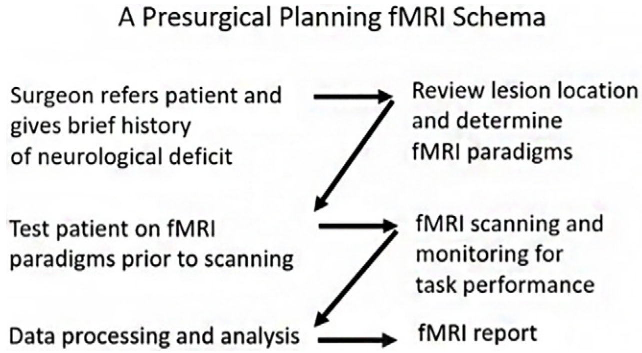

Figure 1: Diagram shows the typical workflow for clinical functional MRI (fMRI).

Particular attention should be paid to patients who are bilingual speakers (10). For more details, see Appendix S1.

Interpretation of language maps.—In routine clinical practice, visual inspection of the activation maps generated by two or three language tasks is commonly performed for determination of language dominance. Therefore, the interpretation of language maps is based on consistent activation across different language paradigms. Hemispheric dominance can also be quantified by calculating a language laterality index (11).

Intraoperative cortical stimulation can be performed to map different functions in the brain. Motor functions are usually evaluated during general anesthesia by stimulating the motor cortex and recording peripheral motor-evoked responses (12). Conversely, intraoperative language mapping with cortical stimulation is a complex procedure wherein the patient is not intubated but instead awoken from anesthesia following craniotomy and exposure of the brain. The neurosurgeon then proceeds to stimulate the brain while the patient performs language tasks. The language areas are localized to where cortical stimulation elicits speech arrest.

Preoperative fMRI can be combined with intraoperative cortical stimulation to optimize patient care. In certain cases where

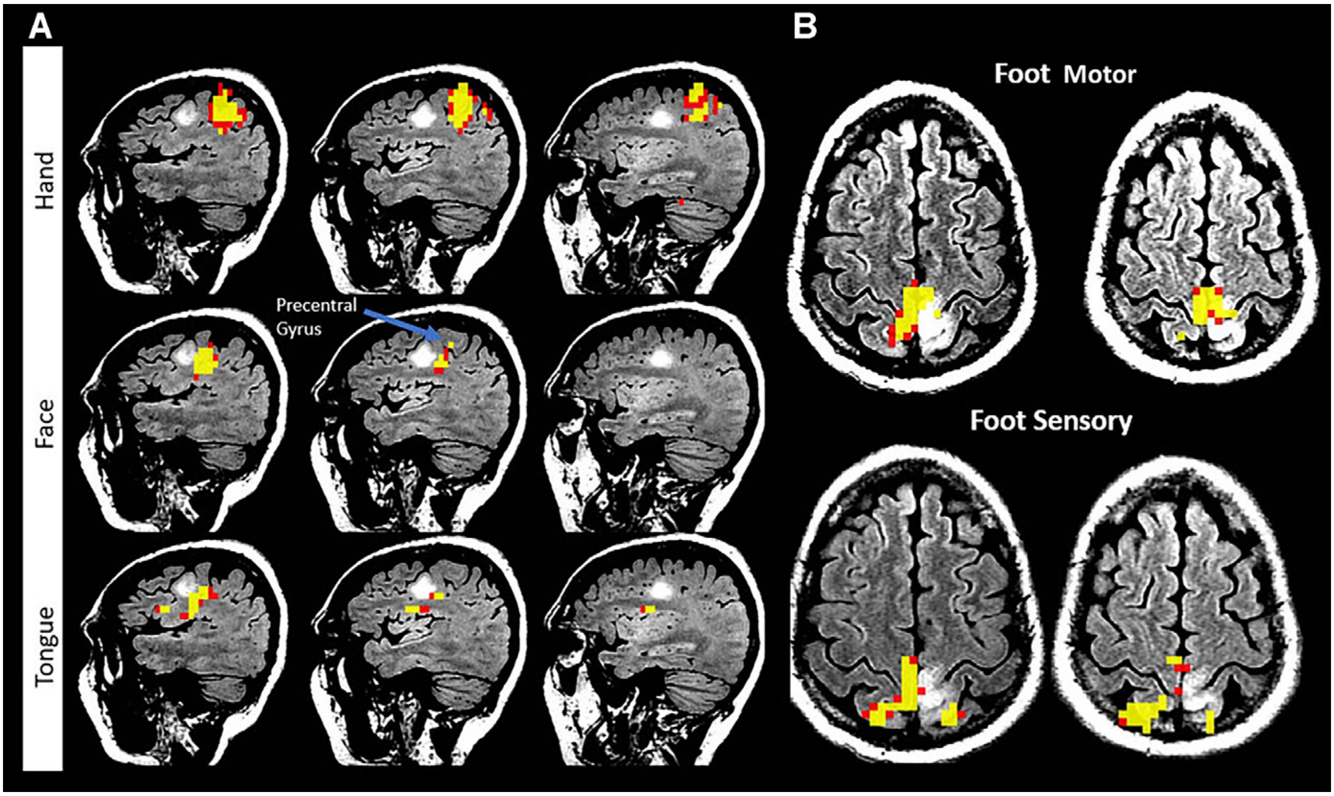

Figure 2: **(A)** Functional activation maps (uncorrected $P < .001$) obtained during hand, face, and tongue tasks overlaid on sagittal fluid-attenuated inversion-recovery MRI scans in a 39-year-old female patient with low-grade glioma in the deep anterior precentral gyrus show the functional activity (correlation $r > 0.6$, uncorrected $P < .001$) of hand, face, and tongue presented along the precentral gyrus (example facial activity, arrow). **(B)** Functional activation maps (uncorrected $P < .001$) obtained during foot motor and sensory tasks overlaid on axial fluid-attenuated inversion-recovery MRI scans in a 32-year-old male patient with low-grade glioma in the medial-most aspect of the left precentral (motor) and postcentral (sensory) gyri show the location of the foot motor and sensory homunculi, respectively. Foot motor and sensory activity is presented in the medial portion of the precentral and postcentral gyri, respectively (correlation $r > 0.6$, uncorrected $P < .001$). The colors indicate the level of statistical significance in terms of the correlation coefficient (corresponding to $0.6 \leq \text{red} \leq 0.75 < \text{yellow}$).

fMRI shows unequivocal language lateralization to the hemisphere contralateral to the lesion, intraoperative cortical stimulation can be avoided. In most cases, fMRI can serve to guide intraoperative cortical stimulation, thereby decreasing the time under anesthesia and the quantity of current delivered to the brain.

Pediatric population.—Specific challenges are present in pediatric clinical fMRI. Pediatric patients may have difficulty remaining still inside the scanner and tend to have a shorter attention span, thus functional examinations would need frequent interaction to encourage them to participate in the functional tasks. For the most part, the same functional paradigms can be used for adult and pediatric patients in the preoperative planning of brain tumors (Fig 6) (13,14). For more details, see Appendix S1.

Instruction and Practice in fMRI Administration

It is highly recommended that the fMRI specialist who will deliver the paradigms meets the patient before the imaging examination and ensures that the patient can follow instructions for the functional tasks that will be performed during the procedure. The inability of a patient to perform required paradigms should lead to tailoring of the paradigms to fit the patient's abilities. For example, if the patient is unable to perform hand or foot tasks due to clinical deficits, a sensory task like squeezing the patient's hand or foot may be substituted. This maneuver will identify the foot sensory area from which the foot motor area location can be implied. If the motor function of one extremity is relatively weaker than the other, the unilateral task paradigm, in addition to the bilateral task, can maximize the activity on the affected side.

For language fMRI, the Boston Naming Test can be used to evaluate the naming of objects (15). If the patient has language deficits, the application of multiple different or simplified language paradigms should improve brain activation. Head motion, which is a critical factor affecting fMRI quality, should be prevented by administering proper instructions before imaging. Paradoxically, anxious patients often complete the fMRI examination more readily than routine MRI examinations, possibly due to constant interaction with the fMRI specialist during paradigm delivery.

Acquisition and Monitoring Task Performance

Several options for paradigm delivery systems exist. A sophisticated setup of noise-canceling headphones and goggles may be used. However, limited space between the patient's head and the coil occasionally makes it more convenient to use a mirror attached to the coil, which reflects a projection screen. Headphones or in-room speakers can deliver task paradigms aurally to patients with poor eyesight. Whichever system is used, it is essential that the patient can see or hear the instructions.

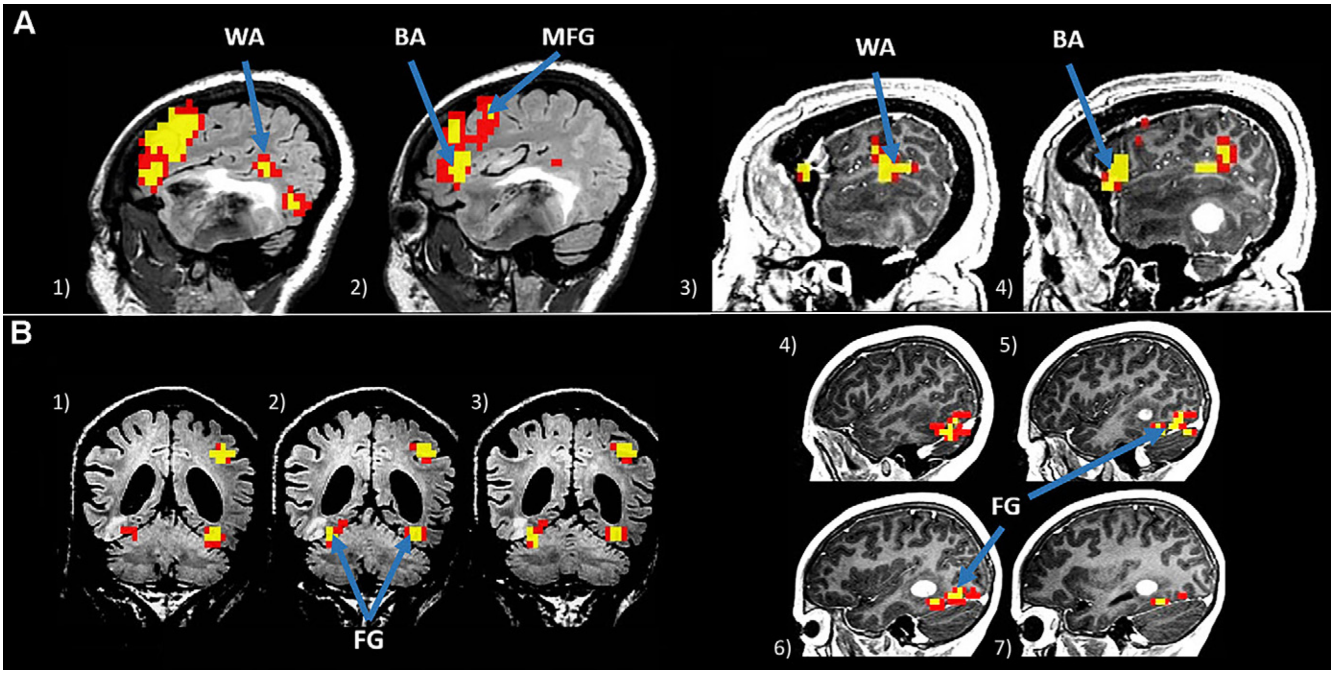

Figure 3: (A) Functional MRI (fMRI) scans in a 34-year-old female patient with isocitrate dehydrogenase–mutant anaplastic astrocytoma in the inferior aspect of Heschl gyrus (primary auditory cortex), abutting but not invading Wernicke area. Images 1 and 2 show phonemic fluency (letter) language task mapping overlaid on sagittal fluid-attenuated inversion-recovery images. Primary language areas can be identified, including Wernicke area (WA, arrow in 1) and Broca area (BA, arrow in 2). Activation of the middle frontal gyrus (MFG, arrow) can also be seen in image 2. Images 3 and 4 show the same phonemic fluency (letter) language task activation overlaid on sagittal three-dimensional T1-weighted postcontrast images, which display the enhancing portion of the lesion. **(B)** fMRI scans in a 14-year-old female patient with low-grade glioma in the inferior medial temporal lobe, inferior to Wernicke area and involving the fusiform gyrus (FG, arrows). Images 1–3 show face recognition task mapping overlaid on coronal fluid-attenuated inversion-recovery images, and images 4–7 show the same task activation overlaid on sagittal postcontrast three-dimensional T1-weighted images. The colors indicate the level of statistical significance in terms of the correlation coefficient (corresponding to 0.6 ≤ red ≤ 0.75 < yellow).

Recently, fMRI acquisition using two-dimensional multiband echo-planar imaging sequences has been proposed. These sequences rely on multiband radiofrequency excitation to simultaneously excite and acquire multiple sections and have shown promising applications in clinical practice (16–18). These sequences greatly improve temporal resolution without sacrificing spatial resolution. The use of multiband echo-planar imaging in fMRI to improve spatial and temporal resolution will be advantageous in the clinical setting.

Monitoring patient performance of the required paradigm during scanning is crucial. The operator should be able to see the patient's hand or foot movement from the control room or hear the patient's responses for overt (spoken aloud) language tasks. For more details, see Appendix S1.

Processing and Generating Maps

After fMRI data acquisition, image processing is performed to both maximize the signal associated with the task and minimize background noise. For more details on this topic, see Appendix S1.

The most widely used method for statistical analysis of fMRI data is a general linear model. This approach is widely used to generate clinical fMRI mapping and is implemented in most commercial software. The correlation coefficient is an important measure of the goodness of fit of a general linear model. The chosen model can be fit to the data using regression analysis. However, because this method is applied repeatedly to thousands of voxels in the brain, it must be adjusted for multiple comparisons using family-wise error correction. The most common method to overcome the issue combines the traditional *P* value threshold with a required minimum number of contiguous voxels, called the "cluster size threshold" (19). Several methods to derive cluster sizes, including Monte Carlo procedures or Gaussian random field theory, have been used to produce maps with an acceptable cluster size threshold (20).

Additionally, different individuals exhibit different vascular reactivities. For example, in children, the vascular reactivity (and consequently the blood oxygen level–dependent [BOLD] signal) is greater than in adults. The statistical analysis of task-based fMRI depends on finding a balance between type I and II errors. In presurgical clinical fMRI, multiple comparisons must be applied on a voxel-to-voxel basis. Nevertheless, setting a false discovery rate of 0.05 for each voxel of the brain may lead to false elimination of most of the correct activation (*P* value must be < .05 per 100 000 voxels considering the example of a brain with 100 000 voxels). Many studies have tried to overcome this problem (21,22). Details on considerations when finding a balanced threshold for type I and type II error rates are outlined in Appendix S1. An optimal threshold that allows for consistent localization of activation in the eloquent cortical areas adjacent to the lesion, while noise-related false-positive discoveries are minimized, should be chosen (Fig 7).

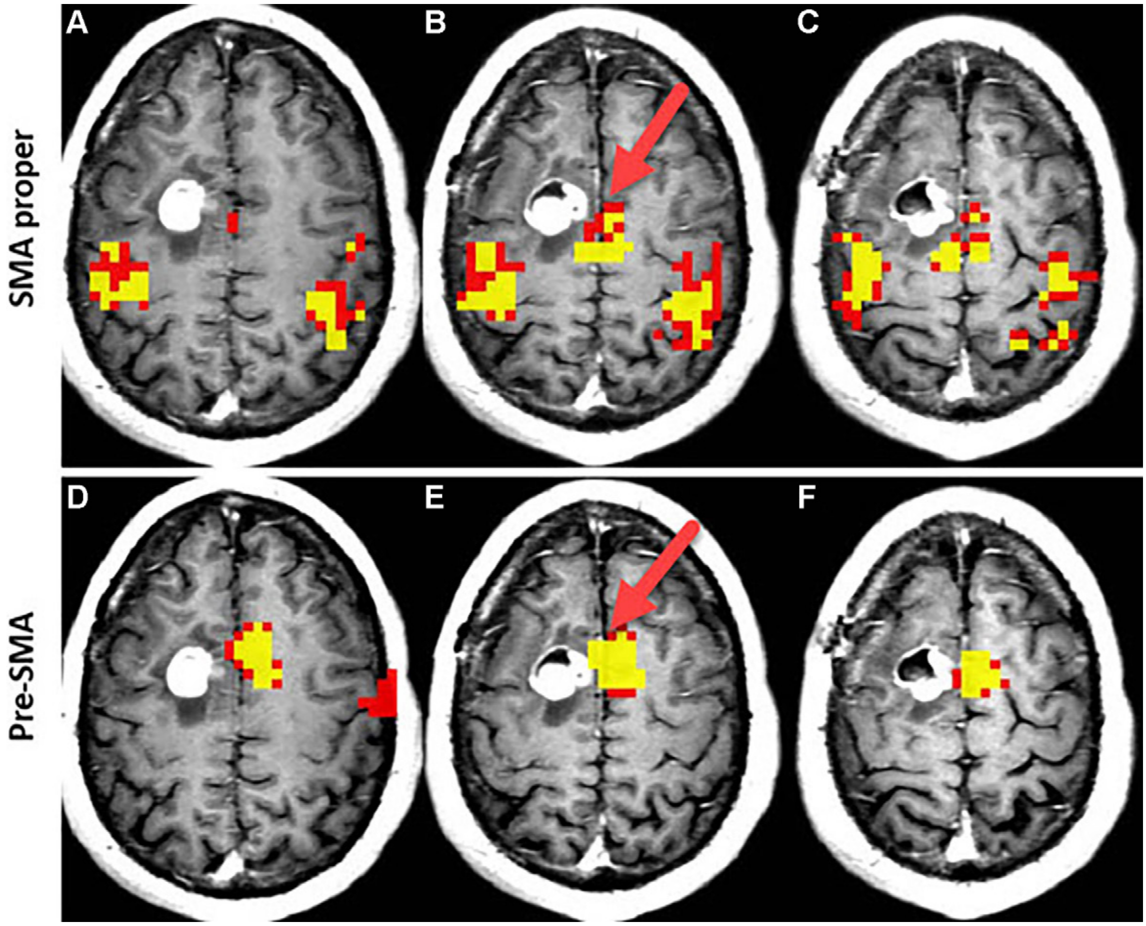

Figure 4: Functional localization (correlation $r > 0.6$, uncorrected $P < .001$) mapping of supplementary motor area (SMA) in a 41-year-old male patient with isocitrate dehydrogenase–mutant low-grade astrocytoma. **(A–F)** Axial three-dimensional T1-weighted postcontrast functional MRI scans show an enhancing tumor along the margins of the surgical cavity in the superior frontal gyrus. Typically, activity of the supplementary motor area proper can be localized during hand finger-tapping motor tasks (arrow in **B**), while activity of the presupplementary motor area, which is located anteriorly to the supplementary motor area proper, can be localized during phonemic fluency (letter) language tasks (arrow in **E**). The colors indicate the level of statistical significance in terms of the correlation coefficient (corresponding to $0.6 \le$ red $\le 0.75 <$ yellow).

Interpretation of the fMRI Map

Specific considerations are needed to correctly interpret fMRI results. Understanding the limitations of the technique is crucial for the correct interpretation of results. Studies comparing the accuracy of fMRI and electrocorticography in localizing eloquent cortices can help to set the expectation for fMRI findings and guide clinical decision-making. Babajani-Feremi et al (23) reported considerable concordance between electrocorticography, fMRI, and transcranial magnetic stimulation language mapping in patients with epilepsy. The main shortcomings of preoperative fMRI in neuro-oncology arise from various artifact sources and physiologic processes. For example, susceptibility artifacts often affect fMRI results in patients who have undergone prior neurosurgery (Fig 8). Prior hemorrhage or surgery, including titanium plates or staples, may lead to signal dropout or disturbance (24). False-negative results related to susceptibility artifacts can be readily recognized by viewing the source images. Another pitfall affecting fMRI interpretation is the venous effect. Magnetic susceptibility artifacts can be accentuated in draining veins due to high deoxyhemoglobin content, especially at higher field strengths, with the consequence of generating BOLD signal changes that can distort activation regions. This may result in false-positive activations by large cortical veins (25). The presence of developmental venous anomalies can also bias the interpretation of fMRI maps because they can resemble BOLD activations (26).

Furthermore, tumor neovasculature and its effects on BOLD response can negatively impact fMRI data. Active areas typically demonstrate an increase in fMRI signal due to overshoot of the diamagnetic oxyhemoglobin caused by increased blood flow, as compared with the paramagnetic deoxyhemoglobin caused by increased oxygen consumption. Tumor neovasculature (especially of malignant tumors) has impaired response to neuronal activity, which leads to decoupling of cerebral blood flow and the rate of oxygen consumption by the brain (27,28). This is known as neurovascular uncoupling and results in a decreased response of the vasculature to the paradigms being performed by the patient, leading to a muted BOLD fMRI signal (28). This phenomenon may produce pseudodominance or pseudo-reorganization due to decreased BOLD signal in the tumoral or peritumoral region (1,3,29–33). In neurovascular

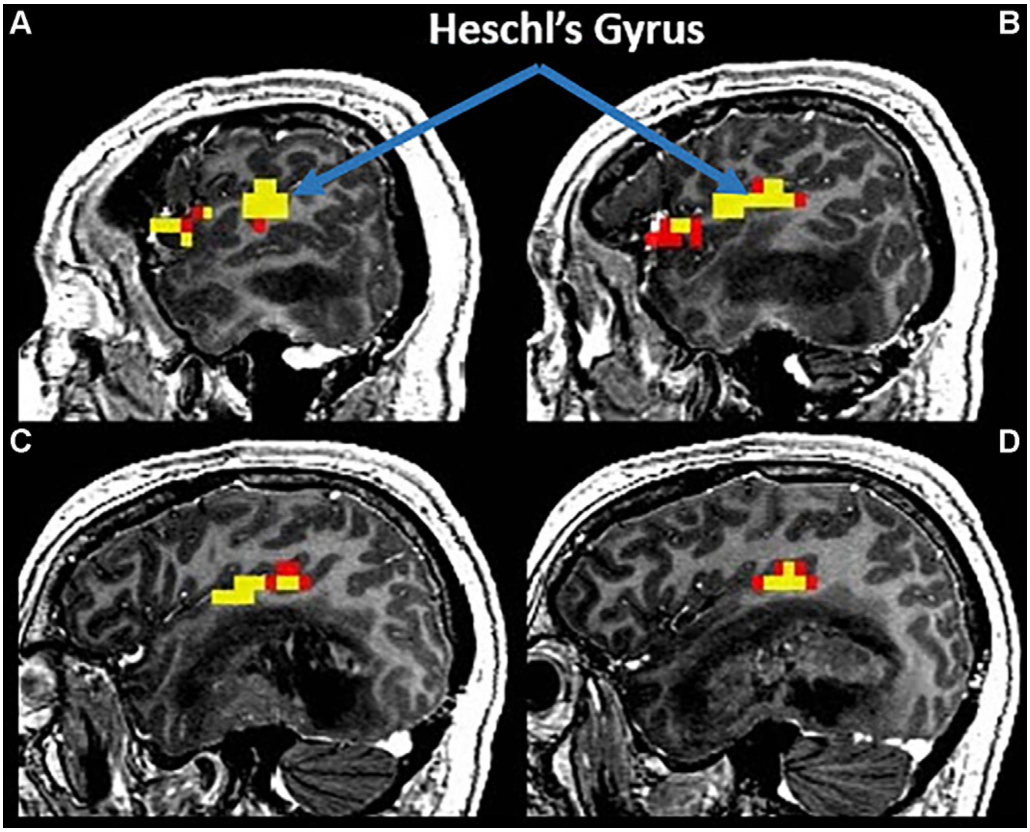

Figure 5: **(A–D)** Functional activation maps overlaid on sagittal three-dimensional T1-weighted postcontrast MRI scans in a 29-year-old male patient with isocitrate dehydrogenase–mutant nonenhancing anaplastic astrocytoma in the superior temporal gyrus show auditory functional activity in the Heschl gyrus in the posterior portion of the superior temporal gyrus (arrows in **A** and **B**). The activity was mapped during music listening (correlation $r > 0.6$, uncorrected $P < .001$). The colors indicate the level of statistical significance in terms of the correlation coefficient (corresponding to $0.6 \leq$ red $\leq 0.75 <$ yellow).

uncoupling, patients with left hemispheric tumors may appear to be right-dominant due to a false-negative result on fMRI scans in the region surrounding the tumor. Accurate laterality calculation may be challenging in these cases, calling for a multidisciplinary assessment of language dominance, including the patient's clinical performance, whole-brain fMRI evaluation, and intraoperative cortical stimulation (1,3). Fraga de Abreu et al (34) analyzed the effect of different types of tumors on BOLD signal in the primary motor cortex, concluding that glioblastoma multiforme displayed the strongest effect. Hart et al (35) demonstrated that functional changes surrounding high-grade tumor gradually decrease moving away from the mass and eventually normalize in distant areas. Low-grade gliomas also show limited amounts of neurovascular uncoupling (28). Neurovascular uncoupling represents one of the main limitations of clinical fMRI in the preoperative planning of brain tumors. A decrease of BOLD signal near a mass may prevent the accurate localization of functional activations (1,28). Also, decreased functional activation from neurovascular uncoupling may limit the capability of fMRI to predict clinical deficits (36). Thus, demonstration of neurovascular uncoupling is important for confirmation of false-negative results in the vicinity of brain tumors. Breath holding or breathing carbon dioxide are the main tests employed to quantify cerebrovascular reactivity and to localize neurovascular uncoupling. The presence of neurovascular uncoupling identified by these methods correlates to fMRI false-negative findings near tumors (37). Breath-holding tasks can be performed for quality control purposes as part of standard fMRI presurgical mapping protocols. This entails alternating breath-hold periods with normal self-paced respiration in a standard block paradigm design (6). The evaluation of BOLD signal during hypercapnia compared with normocapnia provides an estimate of cerebrovascular reactivity, which can be used to improve the interpretation of false-negative results at fMRI (37,38).

The potential to overcome the limitation of neurovascular uncoupling and obtain a clinically meaningful BOLD signal from the tumor surroundings is an important avenue for future research. Voss et al (39) demonstrated that neurovascular uncoupling may be partially overcome by incorporating an observed vaso-task dependency (ie, statistical dependency between local vasoreactivity using breath holding and task BOLD response) in the BOLD signal analysis, with improved accuracy in localization of eloquent cortices near brain tumors. Agarwal et al (40) investigated the role of resting-state BOLD amplitude of low-frequency fluctuations to enhance motor task activation in tumor-induced neurovascular uncoupling, with promising results.

Cerebrovascular disease exerts important effects on BOLD signal and should be considered when interpreting fMRI

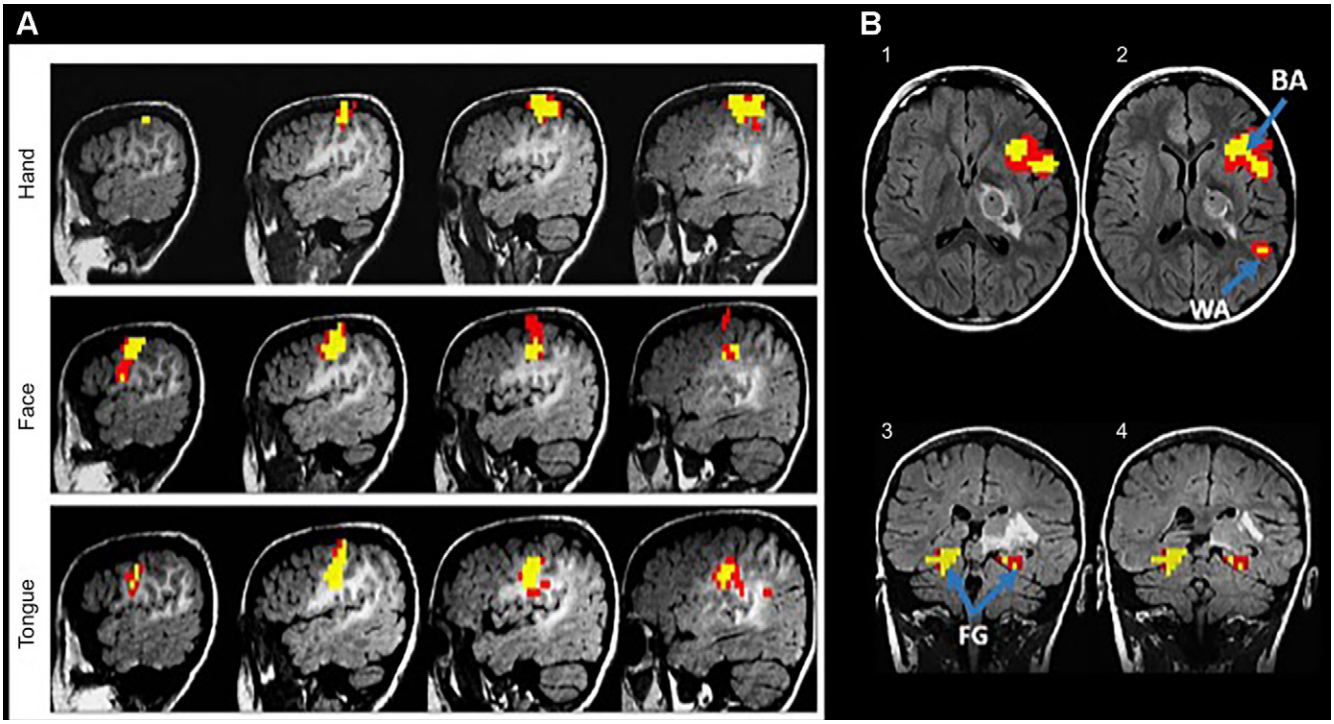

Figure 6: **(A)** Functional activation maps overlaid on sagittal fluid-attenuated inversion-recovery MRI scans in a 14-year-old female patient with low-grade glioma in the left supramarginal gyrus, who performed motor paradigms (hand, face, and tongue separately), show robust activations in the precentral gyrus. **(B)** Functional MRI scans in a 9-year-old male patient with pilocytic astrocytoma in the left basal ganglia who performed language tasks to localize primary language areas. Top: Axial fluid-attenuated inversion-recovery images show Broca area (BA, arrow in 2) and Wernicke area (WA, arrow in 2) during a phonemic fluency (letter) task. Bottom: Coronal fluid-attenuated inversion-recovery images show activation from a face recognition task to localize fusiform gyrus (FG, arrows in 3) in the inferior temporal gyrus. The colors indicate the level of statistical significance in terms of the correlation coefficient (corresponding to 0.6 ≤ red ≤ 0.75 < yellow).

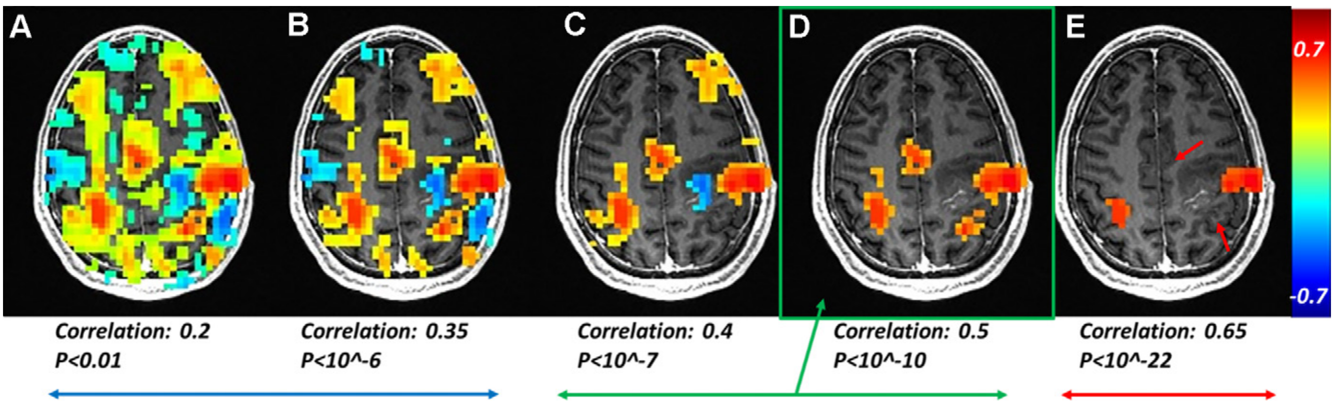

Figure 7: **(A–E)** Functional activation maps overlaid on axial postcontrast T1-weighted MRI scans show the effects of thresholding on the bilateral finger-tapping correlation map in a 42-year-old male patient with left parietal glioblastoma, right hand weakness, and focal motor seizure. Setting the threshold to lower correlation values (<0.35) increases the false-positive (type I) error rate **(A, B)**, while setting the threshold to correlation values greater than 0.65 and very low *P* values can create false-negative (type II) errors **(E)**. As a result, the functional connectivity of supplementary motor area and right motor and sensory areas is lost (arrows in **E**). In contrast, a correlation of 0.5 can correctly localize all expected eloquent regions, including bilateral hand motor and sensory area, as well as supplementary motor area **(D)**. The color scale indicates the level of statistical significance in terms of the correlation coefficient, ranging from −0.7 (blue, negative correlations) to 0.7 (red, positive correlations).

maps. Because the detection of brain activity on fMRI scans relies on the blood oxygenation level, hypoperfusion may limit the ability to explore brain functions in cerebrovascular disorders (41). In chronic ischemia, hypoperfused vascular territories have diminished cerebrovascular reserve, resulting in a ceiling effect that hinders the additional blood flow increase responsible for the BOLD signal, or at least decreases its dynamic range of response (41,42). Carotid artery stenosis is associated with decreased cerebrovascular reactivity, which is at least partially reversible after endarterectomy (43). As a consequence, patients with cerebrovascular disease may have decreased BOLD response in the vascular territories of stenotic vessels (42).

Finally, the interpretation of fMRI in the clinical setting also requires a careful evaluation of frequently consumed substances that may affect the BOLD signal, including alcohol and caffeine.

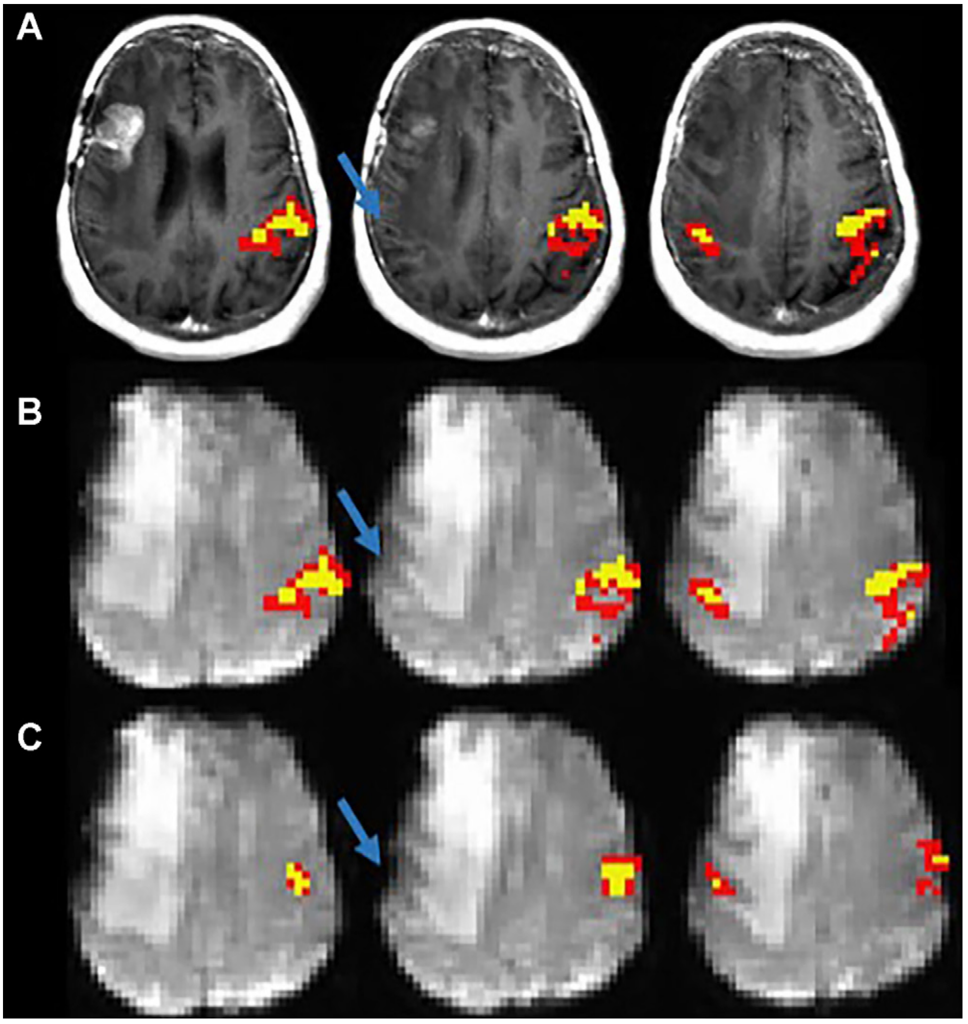

Figure 8: Example case with a susceptibility artifact induced by prior surgery in a 64-year-old male patient with glioblastoma and right frontal craniotomy. **(A)** Axial postcontrast T1-weighted functional MRI scans show the signal drop artifact (arrow) is not clearly visible. **(B)** Hand finger-tapping and **(C)** face movement task activation maps visualized on T2* MRI scans show the signal drop artifact is relatively weak or has no activation present in the corresponding region (arrows in **B** and **C**). The colors indicate the level of statistical significance in terms of the correlation coefficient (corresponding to $0.6 \le \text{red} \le 0.75 < \text{yellow}$).

Ethanol decreases BOLD signal by promoting vasodilation (44). Conversely, caffeine increases BOLD response by reducing baseline signal and promoting vasoconstriction, with a consequent increase in cerebral blood velocity (45).

Current Procedural Terminology Codes and Relative Value Units

The clinical utility of fMRI has led to the approval of current procedural terminology (CPT) codes specifically designed for fMRI (70554, 70555, and 96020). These codes generate generous relative value units of 2.11 for CPT code 70554 and 5.87 for codes 70555 and 96020, which can all be billed together.

Research Topics

Language Plasticity

More healthy individuals who are right-handed display left hemispheric dominance for language (91%–96%) compared with individuals who are ambidextrous or left-handed (73%–75%) (46,47). However, brain tumors can compromise the language network by focally invading dominant eloquent areas. To overcome impairment, the brain may recruit new areas to take over (or attempt to take over) the compromised function, a phenomenon known as language plasticity or reorganization. This process may occur within the peritumoral tissue (intrahemispheric reorganization) or across the hemispheres (interhemispheric reorganization) (48,49). Left hemispheric gliomas can affect the functional connectivity of surrounding language areas, defined as the temporal coincidence of spatially distant neurophysiologic events measured by fMRI activation (50), with long-distance effects on the contralateral hemisphere (51). Recruitment of right-sided language area homologs can be secondary to tumor invasion of the left hemisphere (52–55). While low-grade gliomas represent the classic model of tumor-induced brain plasticity due to their slow pace of growth (49), high-grade gliomas may also lead to reorganization (48,56). Debate remains despite several reports supporting the idea of improved clinical performance in patients who experience

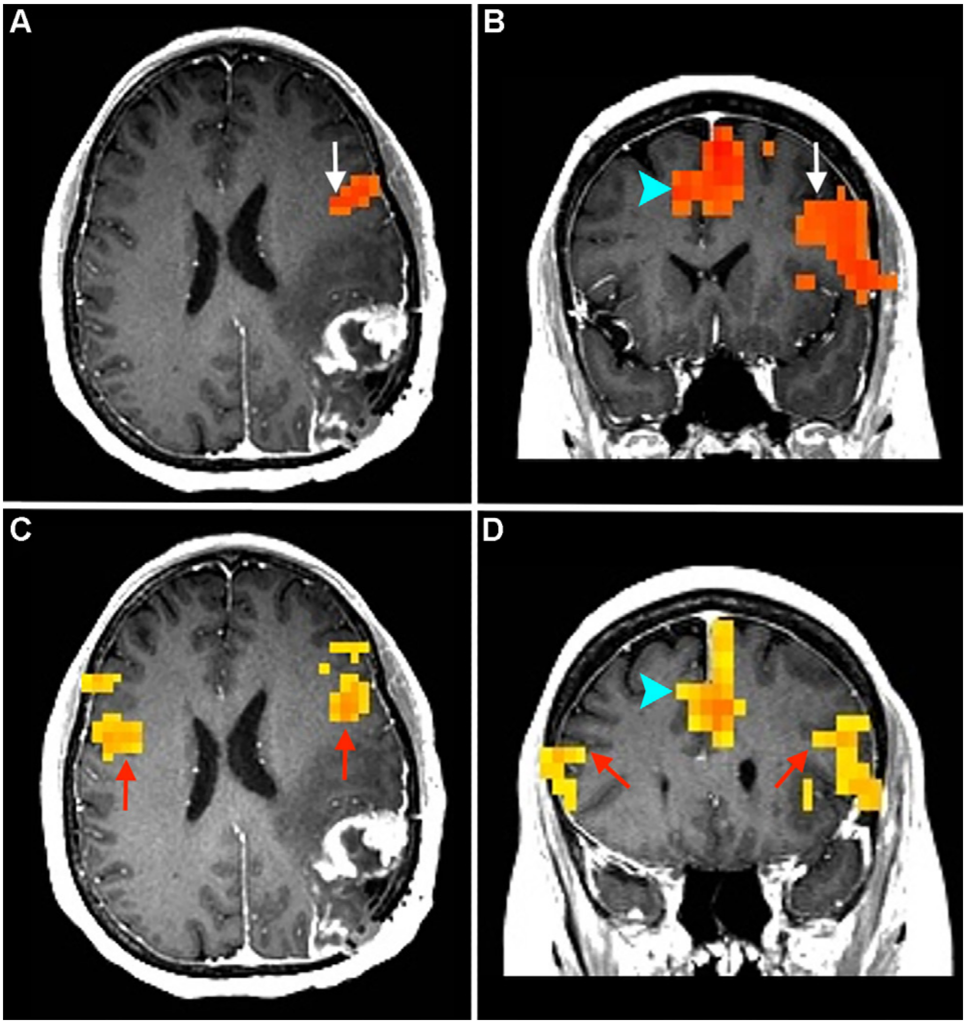

Figure 9: **(A, B)** Task-based functional MRI (fMRI) scans obtained during phonemic fluency language task activation and **(C, D)** resting-state fMRI scans overlaid on contrast-enhanced axial **(A, C)** and coronal **(B, D)** T1-weighted images in a 57-year-old female patient with recurrent postcentral glioblastoma show a left parietal high-grade glioma. Task-based fMRI scans show left activation of Broca area (arrow in **A** and **B**). Resting-state fMRI confirms the location of Broca area on the left; however, bilateral activation (arrows in **C** and **D**) is seen due to the presence of Broca area homolog. The activation of presupplementary motor area (arrowhead in **B** and **D**) is fairly similar in both techniques. Activation maps have been obtained with a correlation threshold of $r > 0.5$. The colors indicate the level of statistical significance in terms of the correlation coefficient (corresponding to 0.6 ≤ red ≤ 0.75 < yellow).

reorganization (57,58). Clinical fMRI interpretation must consider functional reorganization during the preoperative planning of brain tumor resection. In awake mapping for language, the concordance of fMRI showing right dominance on the fMRI scan but lack of speech arrest during intraoperative cortical stimulation of the left-sided tumor confirms the presence of atypical dominance. This finding may support more aggressive resection or a multistep surgical approach (59). Furthermore, fMRI can play an important role in monitoring plasticity changes (60). Longer-term studies are needed to monitor plasticity changes over time, especially for low-grade gliomas.

Resting-State fMRI

Resting-state fMRI (rsfMRI) assesses functional connectivity by measuring BOLD correlation without an imposed task (61) and works on the principle that different parts of the brain that form a network (eg, motor, language, or default mode network) demonstrate synchronous BOLD fluctuations at rest (62). Hence, a network can be identified by interrogating a focus in the brain known to be part of a network and searching for other foci whose BOLD fluctuations correlate with the initial focus (seed-to-voxel analysis). For example, interrogating a voxel in the left precentral gyrus will yield the motor system, including the bilateral motor homunculi and the supplementary motor areas. Alternatively, a network can be identified by independent component analysis. This technique can temporally and spatially disintegrate BOLD signal patterns and detect resting-state networks. Graph methods can also be employed to recognize a network, which is depicted as a collection of nodes linked by edges (63).

While task-based fMRI requires that a patient perform specific tasks for functional localization and is mainly used for the depiction of language and motor functions, rsfMRI has the

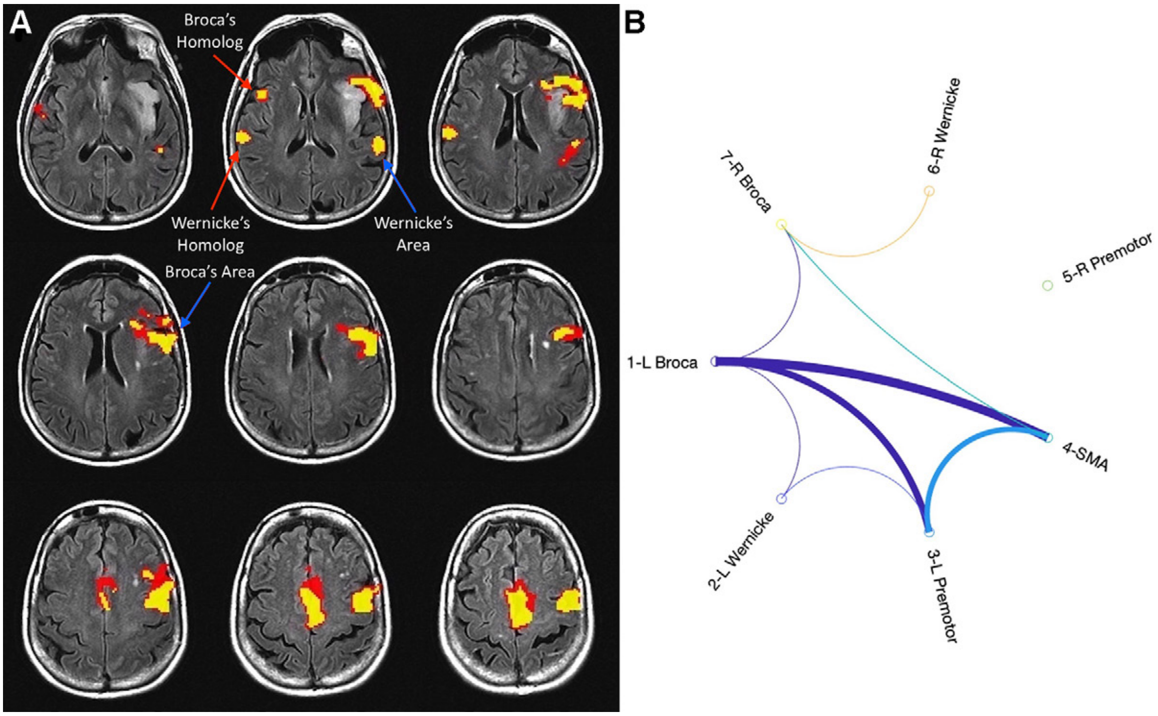

Figure 10: **(A)** Functional activation maps obtained during a phonemic fluency language task (threshold of *r* > 0.5) overlaid on axial fluid-attenuated inversion-recovery MRI scans in a 53-year-old male patient with left insular low-grade glioma show left-sided Broca and Wernicke area activation (blue arrows). Although the patient was strongly right-handed, right-sided homologs of Broca and Wernicke areas are noted (red arrows). The colors indicate the level of statistical significance in terms of the correlation coefficient (corresponding to 0.6 ≤ red ≤ 0.75 < yellow). **(B)** Graph theory–based diagram shows more clearly the relationship between active brain areas by revealing their mutual connectivity. With this approach, left language areas are represented as more strongly connected than right-sided ones, as depicted by thicker links.

advantage of being task-independent (64). The use of resting-state acquisitions in preoperative planning represents a potential alternative to conventional techniques for patients unable to cooperate with task-based paradigms, including young children, patients requiring sedation, and patients with paresis or aphasia (65,66). Park et al (67) reported higher specificity for rsfMRI compared with task-based fMRI in identifying Wernicke and Broca areas. Also, their study reported higher activation of nonlanguage areas in task-based fMRI compared with rsfMRI, including general networks related to attention and executive functions related to language tasks (67). These results may support the idea that rsfMRI is comparable to task-based fMRI for presurgical language mapping of brain tumors. However, despite some clear advantages of rsfMRI, its use in functional preoperative planning remains limited due to the lack of easily available software and the lack of U.S. Federal Drug Administration approval. Other disadvantages include suboptimal depiction of both language dominance and lateralization of eloquent areas (68). Homotopic connectivity remains a typical characteristic of the resting state (Fig 9) (62).

These limitations cause debate around the use of rsfMRI as a substitute for task-based fMRI in preoperative planning. Successful results for the presurgical application of rsfMRI have been reported for somatic motor functions in select populations, such as pediatric patients (69). The possibility of combining resting-state and task-based techniques at the analysis stage opens new research opportunities (70).

Network Theory, Brain Connectivity, and Functional Fingerprints

Historically, the brain has been described as a mosaic of multiple areas, each related to a specific function. This concept is known as localizationism (71). However, modern neuroscience suggests that the brain is actually organized as the sum of multiple networks (72) and that cognitive processes arise from the dynamic interaction of network components (73). Evidence to support this theory is provided by intraoperative stimulation and neuroimaging studies, especially those that focus on the language system (73). The historical model of language function, localizing speech comprehension in the superior temporal gyrus (Wernicke area) and speech production in the inferior frontal gyrus (Broca area), has changed over time (74). Duffau (75), among others, demonstrated that surgical resection of brain tumors that invade eloquent brain areas is feasible with limited postsurgical deficits. The original location of Broca area has been reviewed and extended to include a penumbra of brain tissue surrounding the inferior frontal gyrus, leading to negative speech responses during intraoperative cortical stimulation (76).

Presurgical fMRI using postprocessing techniques and computational models supports the network theory (77,78). Connectivity analyses, especially those relying on graph theory, can provide additional information concerning the relationship between eloquent cortices (Fig 10). Specific graph theoretical measures can characterize the effect on brain networks of tumors with different grades and locations (79). Graph theory can also highlight core components of a network by testing its stability through the progressive removal of connections (80). This technique has shown that the presupplementary motor area, premotor cortex, and Broca area are parts of a frontal core of the human language network (81) tightly connected to the Wernicke area, which appears consistent in healthy individuals regardless of their spoken language (10). In the future, these techniques may be used to aid in the identification of fundamental network components (core) and demonstrate clinical implications for the neurosurgeon who wants to achieve maximal resection while sparing crucial eloquent areas (81–83). Furthermore, connectivity analyses promise to improve our understanding of individual differences in brain organization, which will in turn promote personalized clinical decision-making. Individual connectivity profiles are both robust and reliable, allowing for the identification of functional "fingerprints" that can be accurately attributed to single individuals belonging to a large group (84). In the near future, functional fingerprinting may impact clinical practice, allowing us to evaluate the normal variability of network organization in healthy individuals, explore clinical drivers of reorganization, and identify pathologic changes at the single-patient level (85).

Artificial Intelligence and fMRI

Recently, the field of artificial intelligence (AI) in radiology has experienced exponential growth (86). Many AI applications have been proposed in neuro-oncology (87,88). The functional preoperative planning of brain tumors can benefit from these techniques at multiple levels. Niu et al (89) assessed the predictive performance of machine learning (neural network model) for presurgical mapping of hand motor areas based on rsfMRI data. An algorithm trained on healthy individuals was applied to predict hand motor activation in patients with brain tumors. The activation maps obtained from the AI model outperformed the conventional independent component analysis and generalized linear modeling approaches (89). AI has also been used to estimate language dominance based on task-based fMRI data (90,91). Additionally, the analysis of connectivity profiles with machine learning algorithms has been used to predict survival and clinical deficits. Yuan et al (92) used machine learning to predict the aphasia outcome of individual patients based on rsfMRI. Other authors have demonstrated that connectomic features can capture tumor-induced network alterations associated with prognosis to make predictive models of survival through AI, and with greater than 86% accuracy (93). AI algorithms may also offer a solution to one of the main problems plaguing rsfMRI and connectivity analyses, which is the complexity of analyzing and interpreting the results to identify meaningful patterns (94). Hacker et al (95) reliably computed resting-state network topography in single participants through supervised machine learning. Future applications of AI techniques will include the classification of connectivity data to answer specific questions in clinical practice (94). At the current stage, the translation of AI systems into the health care field remains limited by the logistical difficulties of AI algorithm implementation (96), the need for large amounts of data and external validation to ensure the generalizability of results (97), and sociocultural and ethical issues concerning the black box approach of certain AI techniques and the broader concept of automation (98).

Future Directions

For neuroradiology, one of the next challenges is to locate the common ground between clinical practice and modern neuroscience by incorporating the analysis of cognition into the evaluation of brain disorders. In this scenario, fMRI plays a pivotal role in connecting the clinical and academic worlds, as similar acquisition and data processing techniques are used in both experimental designs and patient care. For example, rsfMRI can highlight multiple networks related to mindfulness and various cognitive processing (62). The application of connectivity analyses, including graph theory, to fMRI data can provide complex information about the interplay between different networks (10,81). Another intriguing application of fMRI in neuro-oncology is more accurate resection planning via graph theory techniques to characterize eloquent cortices surrounding tumors (80–82). Finally, other potential applications for fMRI in neuro-oncology include the evaluation of patients' cognitive states in relation to postsurgical recovery and rehabilitation (99), the assessment of cognitive side effects of systemic treatments (100,101), and the detection of neuroplasticity (48). Looking forward, it may be that "routine" brain MRI examinations a decade from now will include fMRI and connectivity maps.

Conclusion

Presurgical functional MRI (fMRI) is a topic of significant interest and importance in the field of neuroimaging. Although studying its advantages in a formal and rigorous manner poses several challenges, primarily related to the randomization of patients, fMRI has proved to be a versatile and widely implemented technique that has delivered impressive results in the preoperative setting of brain tumors. In the field of neuro-oncology, the demonstrated clinical benefit of fMRI necessitates the continued implementation of this technique in both academic and private practices. Maximizing fMRI accessibility will improve patient care. With this goal in mind, neuroradiology can lead scientific development and spearhead mutually beneficial interactions between academia and industry. These interactions are necessary for the building of robust and clinically usable models that visualize, analyze, and interpret the impressive amount of data that fMRI generates and that connectivity analyses can further extract.

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