Functional Magnetic Resonance Imaging

Description

Functional magnetic resonance imaging (fMRI) is a noninvasive method for the evaluation of eloquent brain areas. Images are collected while specific activities are performed in order to assist in the presurgical localization of critical cortical areas and evaluation of language lateralization. fMRI is also being investigated in combination with diffusion tensor imaging (DTI), which measures white matter tract organization, and electroencephalogram (fMRI-EEG) to identify seizure focus.

Background

Before neurologic surgery for seizure disorders or resection of brain tumors, localization of certain areas of the brain, such as speech centers, is important. For example, from 25% to 60% of patients who undergo left anterior temporal lobectomy develop dysnomia (language/naming difficulties). Most often these "eloquent" areas are assessed using the Wada test and direct electrical stimulation. Both of these tests are invasive and require involvement of various specialists. Direct intracortical electrical stimulation involves functional mapping of the exposed cortex with electrodes, which may elicit a motor or verbal response including arrest of speech, random answering, or perseveration to stimulation. The Wada test is an inactivating method that blocks the function of one hemisphere by injection of amobarbital into the carotid artery, allowing functional testing of the reserve capacity of the non-anesthetized hemisphere.

Functional MRI (fMRI) is an activation method that uses sequences based on T2-weighted blood oxygen level-dependent (BOLD) response. These studies are often done on MR scanners with field strengths of 1.5 Tesla or greater. The interhemispheric difference between activated volumes in the left and right hemispheric regions of interest is calculated as the laterality index (LI), which ranges from -1 to 1. A positive LI is considered left-dominant, while a negative LI is right-dominant. Functional MRI-determined laterality indices may be derived for several different functional areas (regions of interest) that include either Broca's area (language production) or Wernicke's area (language comprehension). Various thresholds (e.g., -0.1 to +0.1, or -0.5 to +0.5) have been proposed to differentiate laterality from bilaterality. Bilateral activation patterns can result from the detection of language-associated, but not language-essential cortex. Therefore, bilateral activation is not necessarily indicative of a bilateral distribution of language-essential cortex and may be task-dependent. In addition, sensitivity and specificity may change with the application of different statistical thresholds.
Functional magnetic resonance imaging (fMRI) may be considered medically necessary as a complementary test in the preoperative evaluation of patients with refractory epilepsy or brain tumors who are candidates for neurosurgery when the lesion is in close proximity to an eloquent area of the brain (e.g., controlling verbal or motor function) and testing is expected to have an important role in assessing the spatial relationship between the lesion and eloquent brain area.

Functional MRI is considered investigational for all other applications.

Rationale

Presurgical Mapping of Eloquent Cortex

Technical Performance

fMRI Protocols: Some research focuses on improving and establishing standardized protocols for pre-surgical evaluation of the eloquent cortex. For example, one report from 2007 described a routine preoperative functional magnetic resonance imaging (fMRI) protocol in 81 consecutive patients (70 with tumors on the left side and 11 with tumors on the right side and language deficits). (1) Patients were trained to recall simple sentences (picture cues) or to generate words in a category (word cues). Although 11 patients were not able to complete the more cognitively demanding word generation task, the combination of tasks allowed localization of both the Broca (language expressive) and Wernicke (language receptive) areas and determination of hemispheric language dominance in 79 (98%) patients. Based on the fMRI findings, surgical plans were modified in 9 (11%) patients (7 patients underwent radiation therapy instead of surgery, and 2 patients had partial resection of large malignant gliomas). Results of the surgeries were not described. The authors noted that, although functional MRI is capable of localizing the center of a functional area, resection borders cannot be reliably determined by this technique.

Laterality Index Thresholds: Ruff et al. assessed the language laterality index (LI) across different statistical thresholds in 13 patients with brain tumor and 7 controls; results were not compared with the Wada test. (2) In both groups, the language LI varied as a result of statistical thresholding, presence of tumor, prior surgery, and language task. Three patients demonstrated a shift in the LI between hemispheres as a function of statistical threshold. The study found no optimal threshold for reliably determining the LI. In another report, Wellmer et al. assessed whether currently recommended thresholds for the fMRI-lateralization index (LI) allowed identification of atypical dominant patients (i.e., not left-dominant) with sufficient safety for presurgical settings. (3) Of 65 patients who had presurgical workup for epilepsy surgery, 22 were identified as atypical dominant by the Wada test. Lateralization indices were calculated for 3 functionally determined regions of interest comprising Broca’s area, a
prefrontal area outside Broca’s, and temporoparietal cortex overlapping with the Wernicke area. In patients in whom the Wada test results were compatible with typical left dominance, the fMRI-LI ranged from 1 to -0.61. Among patients with atypical language dominance according to the Wada test, fMRI-LI of the frontal and temporoparietal regions of interest ranged from 1 to -1. Depending on the chosen LI threshold for unilateral language dominance, between 2 and 5 patients (9% and 23%, respectively) of this sample of atypical dominant patients would have been misclassified as typical dominant.

Clinical Validity

In 2011, Dym et al. reported a meta-analysis of fMRI-determined lateralization of language function compared to the Wada test. (4) Inclusion criteria were examination of the same patients with both fMRI and the Wada test; preoperative examination of at least 4 patients; and reporting of the concordance in individual patients. Twenty-three studies with a total of 442 patients were included in the meta-analysis. Language dominance for each patient was classified as typical (left hemispheric language dominance) or atypical (right hemispheric language dominance or bilateral language representation), with most studies using a lateralization index threshold of 0.2. Sensitivity was defined as the ability of functional MRI (fMRI) to depict atypical language representation, and specificity was the ability of fMRI to depict typical language representation. Most of the studies did not specify whether the evaluators were blinded to the results of the other test. With the Wada test as the reference standard, fMRI had a sensitivity of 83.5% and specificity of 88.1%. Specificity was significantly higher with use of a word generation task (95.6%) than with a semantic decision task (69.5%). This analysis may oversimplify the role of fMRI, which in addition to providing information on hemispheric dominance, provides information on the localization of language and motor areas in relation to the tumor or lesion. It is also unlikely that current fMRI protocols utilize a single task (e.g., word generation) to evaluate the eloquent cortex.

**Intracortical Mapping as the Reference Standard:** Bizzi et al. reported the sensitivity and specificity of fMRI for mapping language and motor functions using intraoperative intracortical mapping as the reference standard. (5) Thirty-four consecutive patients with a focal mass adjacent to eloquent cortex were included in the study. A site-by-site comparison between fMRI and intracortical mapping was performed with verb generation or finger tapping of the contralateral hand. A total of 251 sites were tested, 141 in patients evaluated with verb generation and 110 in patients evaluated with finger tapping. For hand motor function alone, sensitivity and specificity were 88% and 87%, respectively. For language, sensitivity and specificity were 80% and 78%, respectively. The fMRI for Broca’s area showed 100% sensitivity and 68% specificity, while the fMRI for Wernicke’s area showed 64% sensitivity and 85% specificity. Sensitivity of fMRI decreased from 93% for World Health Organization Grade II gliomas to 65% for grade IV gliomas. In another study, fMRI was concordant with direct electrical stimulation in 23 of 26 (88%) cases. (6)

**Wada Testing as the Reference Standard:** Szaflarski et al. compared presurgical mapping by fMRI with either verb generation or semantic decision/tone decision and the Wada test in 28 patients with epilepsy. (7) The study found moderate correlation between the two tasks (r: 0.495) and between the language tasks and the Wada test (r: 0.652 and r: 0.735). It was estimated that the language tasks explained approximately 58% of the variability of the Wada test with moderate convergent validity. With a LI threshold of ± 0.25, 8 of the 28 patients (29%) may have been misclassified based on fMRI alone. In another study, fMRI was concordant with the Wada test in 78 of 83 (94%) cases. (6)
Postoperative Language Changes as the Reference Standard: In 2003, Sabsevitz and colleagues reported on a series of 24 consecutive patients who underwent both fMRI and Wada testing before left anterior temporal lobectomy for seizure disorders. While both tests were predictive of language changes, in this study, fMRI had a sensitivity of 100% and specificity of 57%, while results for the Wada test were 100% and 43%, respectively. (8) In 2013, this group of investigators reported that 32 of 229 (14%) epilepsy patients showed discordance between fMRI and Wada testing and that discordance was highest when either of the tests indicated that language was bilateral. (9, 10) Ten of the 32 patients had discordant results, underwent left temporal lobe surgery, and had preoperative and 6-month postoperative language testing. Out of the 10 patients, fMRI was more accurate in predicting naming outcomes in 7 patients, the Wada test was more accurate in 2 patients, and the 2 tests were equally accurate in 1 patient. (10) Results from this small prospective study suggest that fMRI may be more accurate than the Wada test in predicting postsurgical language outcomes.

Clinical Outcomes

Use of preoperative fMRI in combination with intra-operative MRI (ioMRI) was reported in 2009 to allow more complete resection of tumors without affecting eloquent neurologic function. (11) In this case series of 29 patients, preoperative fMRI was performed to identify and coregister areas of brain activation for motor, speech, and short-term memory prior to brain tumor resection. Areas of brain activation that were identified preoperatively were superimposed on 1.5-T or 3-T scanners during the operative procedure, allowing the surgeon to avoid brain areas where damage would result in a postoperative neurologic deficit. Post-operative neurologic morbidity was reported to be low in the 27 patients in whom an fMRI-guided tumor resection was possible; 7 patients (26%) had transient neurologic impairments consisting of left hemiparesis, speech apraxia, motor apraxias, speech and motor apraxia, or temporary word-finding difficulty. No permanent neurologic impairment was observed in the 27 patients.

In a 2011 report, Wengenroth et al. compared localization of eloquent tumor-adjacent brain areas by fMRI versus structural MRI imaging in 77 consecutive patients with brain tumors of the central region. (12) During fMRI, the patients performed self-paced tongue up and down movements with closed lips, complex finger tapping with sequential finger-to-thumb opposition, as well as repetitive toe flexion-extension of the side contralateral to the respective lesion. The motor hand area was localized in 76/77 patients (99%) by fMRI and in 66/77 patients (86%) by structural MRI. Motor areas of the foot and tongue were investigated in 70 patients and could be identified by fMRI in 96% (tongue representation) and 97% (foot representation) of patients. Morphologic landmarks for the motor hand area were found to be reliable in the unaffected hemisphere (97% success rate) but not in the tumor-affected hemisphere (86% success rate). In 14% of patients, it was not possible to identify the motor hand area at all according to anatomic criteria. There are no reliable morphological landmarks for motor foot and tongue areas, and these representations could only be located by fMRI. After consideration of the clinical condition, tumor etiology, and fMRI results, the decision for neurosurgical operation was made in 52 patients (67.5%). In 16 patients, the decision against surgery was based mainly on fMRI results, which provided evidence that major neurologic impairments would be expected after surgery. fMRI-based risk assessment before surgery had a high correlation with the clinical outcome and corresponded in 46 of 52 operative patients (88%) who had only minimal deficits or functional improvement postoperatively.
Petrella and colleagues reported on the impact of fMRI preoperatively on 39 consecutive patients with brain tumors in 2006. (13) In 4 patients, additional tests, e.g., the Wada test, were not ordered because of the fMRI result. Treatment plans differed in 19 patients after fMRI, with a more aggressive approach recommended after imaging in 18 patients. However, the impact of the altered treatment plans on patient outcome was not assessed. The fMRI resulted in reduced surgical time for 22 patients; it also led to decisions to perform craniotomy in 13 patients in whom less invasive approaches had been initially planned.

Medina et al evaluated 60 consecutive patients prior to surgery in a 2005 report. (6) Language mapping was performed in 53 patients; motor mapping was done in 33, and visual mapping was conducted in 7. The fMRI study revealed change in anatomic location or lateralization of language-receptive (Wernicke) in 28% of patients and in language-expressive (Broca) in 21%. In 38 (63%) patients, fMRI helped to avoid further studies, including Wada test. In 31 (52%) and 25 (42%) of the patients, intraoperative mapping and surgical plans were altered because of fMRI results.

Other authors have reported that successful pre-operative fMRI decreased intracortical mapping time from about 50 minutes to 30 minutes and total operating time from an average 8.5 hours to about 7 hours. (14)

### Localization of Seizure Focus with EEG-fMRI

In a 2007 report, the preoperative localization of epileptic focus was assessed in 29 complex cases (unclear focus and/or multifocality) that had been rejected for epilepsy surgery. (15) Patients were included in the study if they had no contraindications for MRI, had more than 10 interictal discharges in 40 minutes of a previously recorded electroencephalogram (EEG), and if the reason for rejection was the inability to localize a single source with EEG. The results of the fMRI were considered robust if a consensus-defined interictal electrical discharge was associated with a significant positive blood oxygen level-dependent (BOLD) response. In 8 patients (28%), a robust fMRI response was considered to be topographically related to interictal electrical discharges. The EEG-fMRI findings improved localization in 4 of 6 unclear foci and advocated 1 of multiple foci in another patient; in 4 other patients, multiple foci were confirmed. As a result of the testing, 4 patients (14%) were considered to be surgical candidates, and one of the 4 had undergone surgery at the time of the publication. The authors of this European-based study describe this as the first report of the clinical use of EEG-fMRI.

Moeller et al. reported an EEG-fMRI study for the workup of 9 patients with refractory frontal lobe epilepsy who did not have a clear lesion or seizure focus. (16) A minimum of 10 interictal discharges in 60 minutes in previously recorded scalp EEGs was required to be in the study, and the number of interictal discharges recorded during the fMRI session ranged from 9 to 744. There was concordance between spike localization and positive BOLD response in 8 of the patients, and positron emission tomography (PET) and single-photon emission computed tomography (SPECT) results corresponded with BOLD signal changes in 6 of 7 studies. Surgery was subsequently performed on 2 patients, one of whom was seizure-free at the time of publication.

A 2011 multicenter study compared presurgical interictal discharge-related BOLD signal changes with intracranial EEG and postoperative outcome in 23 patients with refractory epilepsy. (17) The 23 patients were selected for analysis based on a diagnosis of focal cortical dysplasia from structural MRI.
or histology out of 65 patients who were undergoing presurgical evaluation for refractory focal epilepsy. The EEG-fMRI results were not used in the planning of intracranial EEG or surgical resections. Twelve of the 23 patients (52%) had interictal discharges during EEG-fMRI recording, and 11 of the 12 (92%) had significant interictal discharge-related hemodynamic changes. In the 11 patients with a BOLD response, fMRI results were concordant with the intracranial EEG-determined seizure onset zone in 5 patients (45%), and the majority (4 of the 5) had a 50% or greater reduction in seizure frequency following resective surgery. The other 6 of 11 patients had widespread or discordant regions of fMRI signal change, and the majority (n=5) had either a poor surgical outcome or a widespread seizure onset zone that precluded surgery. This study is described as the first prospective systematic evaluation of the potential role of EEG-fMRI in the presurgical evaluation of patients with focal cortical dysplasia. It should be considered exploratory. Another 2011 paper from many of the same investigators describes a recently developed method to evaluate EEG-fMRI results in the absence of visually identifiable interictal epileptiform spikes. (18)

Another potential use of EEG-fMRI is to facilitate the implantation strategy of invasive subdural electrodes. In a 2013 study, van Houdt et al. conducted a retrospective comparison of pre-surgical EEG-fMRI with invasive electrocorticographic data and surgical outcomes in 16 patients. (19) Patients were selected who had interictal epileptiform activity during fMRI acquisition, had acceptable quality of EEG and fMRI data, and were candidates for surgery. In each patient at least one of the EEG-fMRI areas was concordant with an interictally active electrocorticographic anatomical brain region. For areas that were covered with subdural grids, 76% of the BOLD regions were concordant with interictally active electrocorticographic electrodes. However due to limited spatial sampling, 51% of the active BOLD regions were not covered with electrodes. EEG-fMRI BOLD areas included the resected area in 93% of the cases.

Practice Guidelines and Position Statements

The American College of Radiology (ACR) and the American Society of Neuroradiology (ASNR) jointly published a 2012 guideline stating that fMRI using BOLD is a proven and useful tool for the evaluation of eloquent cortex in relation to a focal brain lesion, such as neoplasm or vascular malformation. (20) The guideline’s primary indications for fMRI include presurgical planning, surgical planning, and therapeutic follow-up for the assessment of intracranial tumoral disease and assessment of language functions for epilepsy surgery.

Summary

Overall, the literature indicates that functional magnetic resonance imaging (fMRI) is complementary to the Wada test and direct electrical stimulation in localizing certain eloquent functions. Evidence suggests that although bilateral activation patterns in fMRI cannot be conclusively interpreted, fMRI in patients who are to undergo neurosurgery for seizures or brain tumors may help to define eloquent areas, reduce surgical time, and alter treatment decisions. Therefore, fMRI may be considered medically necessary in the preoperative evaluation for patients being considered for neurosurgery, when the lesion is in close proximity to an eloquent area of the brain (e.g., controlling verbal or motor function) and testing is expected to have an important role in assessing the spatial relationship between the lesion and eloquent brain area.
The use of EEG-fMRI to identify seizure focus requires additional study and is considered investigational.

**Medicare National Coverage**

There is no national coverage decision specifically for functional MRI. The national coverage decision on magnetic resonance imaging (220.2) provides general guidelines or examples of what may be considered covered rather than as a restrictive list of specific covered indications. (21) Imaging of cortical bone and calcifications, and procedures involving spatial resolution of bone and calcifications, are the only indications specifically listed as not covered. All other uses of MRI for which CMS has not specifically indicated coverage or non-coverage are eligible for coverage through individual local contractor discretion.

**References**


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Signature on File
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