 Functional Magnetic Resonance Imaging of the Brain

**Description**

Functional magnetic resonance imaging (fMRI) is a noninvasive method for localizing areas of brain function and has been used for the presurgical evaluation of eloquent brain areas. Images are collected while specific activities are performed to assist in the localization of critical cortical areas and evaluation of language lateralization. Functional magnetic resonance imaging is also being investigated in combination with diffusion tensor imaging, which measures white matter tract organization, and electroencephalography (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 magnetic resonance imaging (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. fMRI-determined LIs 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 (eg, -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.
Simultaneous EEG-fMRI is being investigated for the localization of seizures. EEG-fMRI combines the temporal resolution of EEG and the spatial resolution of fMRI. Simultaneous EEG-fMRI may allow the detection of cerebral hemodynamic changes associated with seizures and interictal epileptiform discharges that are identified on scalp EEG. Another potential use of EEG-fMRI is to facilitate the implantation strategy of invasive subdural electrodes.

Regulatory Status
There are several fMRI hardware (eg, fMRI Hardware System; NordicNeuroLab AS) and fMRI software packages (eg, BrainAcquireRx™/BrainProcessRx™ Data Suite; Kyron Clinical Imaging) with 510(k) marketing clearance from the U.S. Food and Drug Administration for use in conjunction with a MRI scanner to perform fMRI. FDA Product Code: LNH

Related Policies
6.01.21 Magnetoencephalography/Magnetic Source Imaging

Policy
*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

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 (eg, 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
Functional magnetic resonance imaging (fMRI) might be thought of as a type of diagnostic test to determine the location of eloquent cortex or seizure focus. Assessment of a diagnostic technology typically focuses on 3 categories of evidence: technical performance, diagnostic accuracy, and impact on health outcomes

- Technical performance refers to how well the technology measures and records the parameter(s) that it is purported to evaluate. Evaluation of technical performance may include various measures of validity (eg, criterion validity, construct validity) and reliability (eg, test-retest reliability, agreement among multiple reviewers).
- Diagnostic accuracy is the ability of a test to accurately diagnose a clinical condition in relevant populations of patients compared to a reference standard. Measures of diagnostic accuracy include sensitivity, specificity, predictive values, likelihood ratios, and area under the curve analysis.
- Demonstration that the diagnostic information can be used to improve patient outcomes is essential to determining the utility of a diagnostic technology. In most cases, an indirect chain of evidence needs to be constructed to determine whether there is a tight linkage between the diagnostic technology and improvement in health outcomes.
For fMRI, comparators for language laterality may be the Wada test and intracortical mapping. Health outcomes can be directly assessed by the impact of the test on surgical outcomes.

Presurgical Mapping of Eloquent Cortex

Technical Performance

Some research has focused on establishing and improving standardized protocols and analysis for presurgical evaluation of the eloquent cortex. For example, Stippich et al has described a routine preoperative 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). 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 fMRI findings, surgical plans were modified in 9 (11%) patients. The authors noted that, although fMRI is capable of localizing the center of an area, resection borders cannot be reliably determined by this technique. Ruff et al (2008) found no optimal threshold for reliably determining the language laterality index (LI). (2) In addition to the statistical threshold, the language LI varied as a result of presence of tumor, prior surgery, and language task. In another report, Wellmer et al assessed whether currently recommended thresholds for the fMRI LI helped identify atypical dominant patients (ie, not left-dominant) with sufficient safety for presurgical settings. (3) Depending on the chosen LI threshold for unilateral language dominance, between 2 (9%) and 5 (23%) patients in this sample would have been misclassified as typical dominant.

Diagnostic Accuracy

Wada Testing as the Reference Standard

In 2011, Dym et al reported a meta-analysis of fMRI-determined lateralization of language function compared with the Wada test. (4) Twenty-three studies (total N=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 LI threshold of 0.2. Sensitivity was defined as the ability of fMRI to depict atypical language representation, and specificity was the ability of fMRI to depict typical language representation. Most studies did not specify whether evaluators were blinded to results of the other test. With the Wada test as the reference standard, fMRI had a sensitivity of 84% and specificity of 88%. Specificity was significantly higher with use of a word generation task (96%) than with a semantic decision task (70%). This analysis may have oversimplified 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 use a single task (eg, word generation) to evaluate the eloquent cortex.

Intracortical Mapping as the Reference Standard

Bizzi et al (2008) 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 the 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. Functional MRI for the Broca area showed 100% sensitivity and 68% specificity, while fMRI for the Wernicke 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 (88%) of 26 cases.

Postoperative Language Changes as the Reference Standard
In 2003, Sabsevitz et al 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.(7) In 2013, this group of investigators reported that 32 (14%) of 229 epilepsy patients showed discordance between fMRI and Wada testing, and that discordance was highest when either test indicated that language was bilateral.(8,9) For 10 patients who had discordant results, underwent left temporal lobe surgery, and had preoperative and 6-month postoperative language testing, 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.9 Results from this small prospective study suggested that fMRI may be more accurate than the Wada test in predicting postsurgical language outcomes.

Effect on Health Outcomes
Use of preoperative fMRI in combination with intraoperative MRI has been reported to allow more complete resection of tumors without affecting eloquent neurologic function.(10) 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 before brain tumor resection. Areas of brain activation that were identified preoperatively were superimposed on 1.5- or 3-Telsa scanners during the operative procedure, allowing the surgeon to avoid brain areas where damage would result in a postoperative neurologic deficit. Postoperative neurologic morbidity was reported to be low in the 27 patients in whom an fMRI-guided tumor resection was possible.

In a 2011 report, Wengenroth et al compared localization of eloquent tumor-adjacent brain areas by fMRI to structural MRI in 77 consecutive patients with brain tumors of the central region.(11) The motor hand area was localized in 76 (99%) of 77 patients by fMRI and in 66 (86%) of 77 patients 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). After consideration of the clinical condition, tumor etiology, and fMRI results, the decision for neurosurgery was made in 52 (68%) patients. 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. Functional MRI-based risk assessment before surgery had a high correlation with the clinical outcome and corresponded in 46 (88%) of 52 operative patients who had functional improvement or only minimal deficits postoperatively.
Petrella et al reported on the impact of fMRI preoperatively on 39 consecutive patients with brain tumors in 2006. (12) 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 outcomes 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 (2005) evaluated 60 consecutive patients preoperatively.6 Language mapping was performed in 53 patients, motor mapping was done in 33, and visual mapping was in 7. The fMRI study revealed change in anatomic location or lateralization of language reception (Wernicke) in 28% of patients and in language expression (Broca) in 21%. In 38 (63%) patients, fMRI helped to avoid further studies, including the Wada test. In 31 (52%) and 25 (42%) of the patients, intraoperative mapping and surgical plans, respectively, were altered because of fMRI results. Others have reported that successful preoperative 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. (13)

Section Summary: Presurgical Mapping of the Eloquent Cortex
The diagnostic accuracy of fMRI has been compared to the Wada test and to intracortical mapping to evaluate postoperative language changes. Sensitivity and specificity depend on the specific task, but have been shown to be predictive of hemispheric dominance in a substantial percentage of patients. In a study that used postoperative language changes as the reference standard, both fMRI and the Wada test had high sensitivity and moderate specificity. When results were discordant between tests, fMRI was slightly more accurate. Evidence on health outcomes 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.

Localization of Seizure Focus With Simultaneous Electroencephalography and fMRI

Some small studies have evaluated surgical outcomes following use of simultaneous electroencephalography (EEG) and fMRI to identify seizure focus.

In a 2007 report, the preoperative localization of epileptic focus was assessed in 29 complex patients (unclear focus and/or multifocality) who had been rejected for epilepsy surgery. (14) Patients were selected if they had no contraindications for MRI, had more than 10 interictal discharges in 40 minutes of a previously recorded EEG, and if the reason for denial of surgery 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 fMRI response. In 8 (28%) patients, a robust fMRI response was considered to be topographically related to interictal electrical discharges. As a result of the testing, 4 (14%) patients were considered to be surgical candidates, and 1 of the 4 had undergone surgery at the time of publication. Moeller et al (2009) 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. (15) The number of interictal discharges recorded during the fMRI session ranged from 9 to 744. There was concordance between spike localization and positive fMRI response in 8 patients. Surgery was subsequently performed on 2 patients, 1 of whom was seizure-free at the time of publication.
A 2011 multicenter study compared presurgical ictal discharge-related blood oxygen level dependent (BOLD) signal changes with intracranial EEG and postoperative outcomes in 23 patients with refractory epilepsy. The 23 patients were selected based on a diagnosis of focal cortical dysplasia from structural MRI or histology. The EEG-fMRI results were not used in the planning of intracranial EEG or surgical resections. In the 11 patients with a BOLD response, fMRI results were concordant with the intracranial EEG-determined seizure onset zone in 5 (45%) patients. The other 6 of 11 patients had widespread or discordant regions of fMRI signal change, and 5 had either a poor surgical outcome or a widespread seizure onset zone that precluded surgery. It should be considered exploratory. Another 2011 study from many of the same investigators described a newer method to evaluate simultaneous EEG-fMRI results in the absence of visually identifiable interictal epileptiform spikes.

In a 2013 study, van Houdt et al conducted a retrospective comparison of presurgical EEG-fMRI with invasive electrocorticographic data and surgical outcomes in 16 patients. 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 1 of the simultaneous EEG-fMRI areas was concordant with an interictally active electrocorticographic anatomic brain region. For areas 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. Simultaneous EEG-fMRI BOLD areas included the resected area in 93% of the cases.

Research is ongoing to improve the identification of seizure focus with simultaneous EEG-fMRI, including occasions without intrascanner interictal epileptic discharges.

**Section Summary: Localization of Seizure Focus With Simultaneous Electroencephalography and fMRI**

Several small studies identified have evaluated seizure focus with simultaneous EEG-fMRI. This is a relatively recent area of research, which has followed the development of MRI-compatible EEG electrodes. Current research is attempting to improve the identification of seizure focus with this technique, particularly when there are no interictal epileptic discharges during the fMRI session. There are very few data on the effect of this procedure on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table 1.

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<td>Multi-modality Localization of Eloquent Brain Function-A Comparison of Technologies for Improved Applicability</td>
<td>80</td>
<td>Oct 2021</td>
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Practice Guidelines and Position Statements

The American College of Radiology, American Society of Neuroradiology, and Society for Pediatric Radiology jointly published a 2014 guideline stating that “fMRI using blood oxygen level-dependent response 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.” (21) The guideline’s primary indications for fMRI include presurgical planning and operative risk assessment, assessment of the eloquent cortex in relation to tumor or seizure focus, surgical planning for biopsy or resection, evaluation of preserved eloquent cortex, and therapeutic follow-up.

U.S. Preventive Services Task Force Recommendations

Not applicable

Summary of Evidence

For individuals who have epilepsy or brain tumors who are undergoing presurgical mapping of the eloquent cortex who receive functional magnetic resonance imaging (fMRI), the evidence includes studies on diagnostic accuracy and clinical utility. Relevant outcomes are test accuracy, morbid events, functional outcomes, and quality of life. The diagnostic accuracy of fMRI has been compared to the Wada test and intracortical mapping to evaluate postoperative language changes. Sensitivity and specificity depend on the specific task, but have been shown to be predictive of hemispheric dominance in a substantial percentage of patients. Evidence on health outcomes has indicated that fMRI in patients who are to undergo neurosurgery for seizures or brain tumors may help to define eloquent areas (eg, controlling verbal or motor function), reduce surgical time, and alter treatment decisions. Because of the highly detrimental impact of resecting the eloquent cortex, fMRI may be considered complementary to the Wada test and direct electrical stimulation when the lesion is in close proximity to an eloquent area of the brain. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have epilepsy who are being evaluated for localization of seizure focus who receive simultaneous electroencephalography and fMRI, the evidence includes a limited number of small studies. Relevant outcomes are test accuracy, morbid events, functional outcomes, and quality of life. The objective of current research is to improve the identification of seizure focus with this technique, particularly when there are no interictal epileptic discharges during an fMRI session. There are very few data on the effect of this procedure on health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare National Coverage

There is no national coverage decision (NCD) specifically for functional MRI. The NCD 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. (22) 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


Policy History

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<td>December 2011</td>
<td>New Policy</td>
<td>Policy updated with literature review. Rationale significantly revised. References 4, 9, 10, 14, and 16 added. Other references reordered. No change to policy statements.</td>
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<td>September 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review, reference 19 added; policy statements unchanged.</td>
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<tr>
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Keywords

MRI, Functional

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 2, 2016 and is effective January 15, 2017.

Signature on file

Deborah M. Smith, MD, MPH