Aetna considers functional magnetic resonance imaging (fMRI) medically necessary to identify the eloquent cortex in pre-surgical evaluation of persons with brain tumors, epilepsy, or vascular malformations.

Aetna considers fMRI experimental and investigational for the diagnosis, monitoring, prognosis, or surgical management of all other indications, including any of the following conditions/diseases (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Alzheimer's disease
- Anoxic-ischemic brain injury
- Attention-deficit hyperactivity disorder
- Bipolar disorder
- Chronic pain (including fibromyalgia)
- Disorders of consciousness (e.g., locked-in syndrome, minimally conscious state (subacute/chronic; traumatic/non-traumatic), and coma/vegetative state)
Multiple sclerosis  
Parkinson's disease  
Psychotic depression  
Schizophrenia  
Stroke/stroke rehabilitation  
Trauma (e.g., head injury).

See also CPB 0279 - Magnetic Source Imaging/Magnetoencephalography (../200_299/0279.html).

Background

Functional magnetic resonance imaging (fMRI) is a type of functional brain imaging technology. It localizes regions of activity in the brain by measuring blood flow and/or metabolism following task activation, and is generally used to identify areas of language (e.g., Broca's area, Wernicke's area) and sensorimotor function (e.g., sensorimotor cortex). Functional MRI has been employed for the diagnosis, monitoring, prognosis, or surgical management of many diseases/conditions (e.g., Alzheimer's disease, brain tumors, epilepsy, multiple sclerosis (MS), Parkinson's disease, stroke, trauma, vascular malformations, and vegetative state/coma).

The bulk of published evidence concerning the clinical applications of fMRI centers on its use in pre-surgical planning. In particular, studies involving language fMRI mainly address its use in pre-surgical planning for epilepsy, arterio-venous malformations (AVMs), and brain tumors (Bookheimer, 2007). It has been suggested that fMRI of the brain reduces the need for invasive testing of seizure disorder patients being considered for surgical treatment. Woermann et al (2003) compared the determination of language dominance using fMRI with results of the Wada test in 100 patients with different localization-related epilepsies. These investigators found 91% concordance between both tests. The overall rate of false categorization by fMRI was 9%, ranging from 3% in left sided temporal lobe epilepsy (TLE) to 25% in left sided extra-temporal epilepsy. The authors noted that language fMRI might reduce the necessity of the Wada test for language
lateralization, especially in TLE.

Sabsevitz and colleagues (2003) examined whether pre-operative fMRI predicts language deficits in patients with epilepsy undergoing left anterior temporal lobectomy (L-ATL). A total of 24 patients with L-ATL underwent pre-operative language mapping with fMRI, pre-operative intra-carotid sodium amobarbital (Amytal)/Wada testing for language dominance, as well as pre- and post-operative neuropsychological testing. Functional MRI laterality indexes (LIs), reflecting the inter-hemispheric difference between activated volumes in left and right homologous regions of interest, were calculated for each patient. Relationships between the fMRI LI, Wada language dominance, and naming outcome were examined. Both the fMRI LI (p < 0.001) and the Wada test (p < 0.05) were predictive of naming outcome. Functional MRI showed 100 % sensitivity and 73 % specificity in predicting significant naming decline. Both fMRI and the Wada test were more predictive than age at seizure onset or pre-operative naming performance. The authors concluded that pre-operative fMRI predicted naming decline in patients undergoing L-ATL surgery.

Medina et al (2005) prospectively evaluated effect of fMRI on diagnostic work-up and treatment planning in patients with seizure disorders who are candidates for surgical treatment. A total of 60 consecutively enrolled patients (27 females and 33 males; mean age of 15.8 +/- 8.7 years; range of 6.8 to 44.2 years) were examined. Forty-five (75 %) patients were right-handed, 9 (15 %) were left handed, and 6 (10 %) had indeterminate hand dominance. Prospective questionnaires were used to evaluate diagnostic work-up, counseling, and treatment plans of the seizure team before and after fMRI. Confidence level scales were used to determine effect of fMRI on diagnostic and therapeutic thinking. Paired-t test and 95 % confidence interval analyses were performed. In 53 patients, language mapping was performed; in 33, motor mapping; and in 7, visual mapping. The study revealed change in anatomical location or lateralization of language-receptive area --
(Wernicke's area) (28% of patients) as well as language-expressive area (Broca's area) (21% of patients). Statistically significant increases were found in confidence levels after fMRI in regard to motor and visual cortical function evaluation. In 35 (58%) of 60 patients, the seizure team thought that fMRI results altered patient and family counseling. In 38 (63%) of 60 patients, fMRI results helped to avoid further studies, including the Wada test. In 31 (52%) and 25 (42%) of 60 patients, intra-operative mapping and surgical plans, respectively, were altered because of fMRI results. In 5 (8%) patients, two-stage surgery with extra-operative direct electrocortical stimulation mapping (ESM) was averted, and resection was accomplished in one-stage. In 4 (7%) patients, extent of surgical resection was altered because eloquent areas were identified close to seizure focus. The authors concluded that fMRI results influenced diagnostic and therapeutic decision making of the seizure team; results indicated a change in language dominance, an increase in confidence level in identification of critical brain function areas, alterations in patient and family counseling as well as intra-operative mapping and surgical approach.

Functional MRI has been used in pre-surgical planning for patients with brain tumors as well as vascular malformations. Pouratian and colleagues (2002) evaluated the utility of pre-operative fMRI to predict if a given cortical area would be deemed essential for language processing by ESM. These investigators studied patients with vascular malformations, specifically AVMs and cavernous angiomas, in whom blood-flow patterns are abnormal and in whom a perfusion-dependent mapping signal may be questionable. A total of 10 patients were studied (7 with AVMs and 3 with cavernous angiomas). These researchers used a battery of linguistic tasks, including visual object naming, word generation, auditory responsive naming, visual responsive naming, and sentence comprehension, to identify brain regions that were consistently activated across expression and comprehension linguistic tasks. In a comparison of ESM and fMRI activations, the researchers varied the matching criteria (overlapping activations, adjacent activations, and deep activations) and the radii of influence of
ESM (2.5, 5, and 10 mm) to determine the effects of these factors on the sensitivity and specificity of fMRI. The sensitivity and specificity of fMRI were dependent on the task, lobe, and matching criterion. For the population studied, the sensitivity and specificity of fMRI activations during expressive linguistic tasks were found to be up to 100% and 66.7%, respectively, in the frontal lobe, and during comprehension linguistic tasks up to 96.2% and 69.8%, respectively, in the temporal and parietal lobes. The sensitivity and specificity of each disease population (AVMs and cavernous angiomas) and of individuals were consistent with those values reported for the entire population studied. The authors concluded that pre-operative fMRI is a highly sensitive pre-operative planning tool for identifying cortical areas that are essential for language; and that this imaging modality may play a future role in pre-surgical planning for patients with vascular malformations.

Anderson et al (2006) examined the utility of fMRI as a determinant of lateralization of expressive language in children with cerebral lesions. Functional MRI language lateralization was attempted in 35 children (29 with epilepsy) aged 8 to 18 years with frontal or temporal lobe lesions (28 left hemisphere, 5 right hemisphere, and 2 bilateral). Axial and coronal fMRI scans through the frontal and temporal lobes were acquired at 1.5 Tesla (T) by using a block-design, covert word-generation paradigm. Activation maps were lateralized by blinded visual inspection and quantitative asymmetry indices (hemispheric and inferior frontal regions of interest, at p < 0.001 uncorrected and p < 0.05 Bonferroni corrected). A total of 30 children showed significant activation in the inferior frontal gyrus. Lateralization by visual inspection was left in 21, right in 6, and bilateral in 3, and concordant with hemispheric and inferior frontal quantitative lateralization in 93% of cases. Developmental tumors and dysplasias involving the inferior left frontal lobe had activation overlying or abutting the lesion in 5 of 6 cases. Functional MRI language lateralization was corroborated in 6 children by frontal cortex stimulation or intra-carotid Amytal testing (IAT) and indirectly supported by aphasiology in a further 6 cases. In 2 children, fMRI language
lateralization was bilateral, and corroborative methods of language lateralization were left. Neither lesion lateralization, patient handedness, nor developmental versus acquired nature of the lesion was associated with language lateralization. Involvement of the left inferior or middle frontal gyri increased the likelihood of atypical language lateralization. The authors concluded that this study suggests that fMRI lateralizes language in children with cerebral lesions.

Stancanello et al (2007) attempted to validate a method to exploit functional information for the identification of functional organs at risk (fOARs) in CyberKnife radiosurgery treatment planning. Five patients affected by AVMs and scheduled to undergo radiosurgery were scanned prior to treatment using computed tomography (CT), three-dimensional rotational angiography (3D-RA), T2 weighted and blood oxygenation level dependent echo planar imaging MRI. Tasks were chosen on the basis of lesion location by considering those areas which could be potentially close to treatment targets. Functional data were superimposed on 3D-RA and CT used for treatment planning. The procedure for the localization of fMRI areas was validated by direct ESM on 38 AVM and tumor patients undergoing conventional surgery. Treatment plans studied with and without considering fOARs were significantly different, in particular with respect to both maximum dose and dose volume histograms; consideration of the fOARs allowed quality indices of treatment plans to remain almost constant or to improve in 4 out of 5 cases compared to plans with no consideration of fOARs. The authors concluded that the presented method provides an accurate tool for the integration of functional information into AVM radiosurgery, which might help to minimize undesirable side effects and to make radiosurgery less invasive.

Stippich and colleagues (2007) prospectively evaluated the feasibility of standardized pre-surgical fMRI for localizing the Broca and Wernicke areas as well as for lateralizing language function. A total of 81 patients (36 females, 45 males; aged 7 to 75 years) with different brain tumors underwent blood oxygen
level-dependent fMRI at 1.5 T with two paradigms: (i) sentence 
generation (SG), and (ii) word generation (WG). Functional MRI 
measurements, data processing, and evaluation were fully 
standardized by using dedicated software. Four regions of 
interest were evaluated in each patient: the Broca and 
Wernicke areas and their anatomical homologs in the right 
hemisphere. The SG and WG paradigms were successfully 
completed by all (100 %) and 70 (86 %) patients, respectively. 
Success rates in localizing and lateralizing language were 96 % 
for the Broca and Wernicke areas with the SG paradigm, 81 % 
for the Broca area and 80 % for the Wernicke area with the WG 
paradigm, and 98 % for both areas when the SG and WG 
paradigms were used in combination. Functional localizations 
were consistent for SG and WG paradigms in the inferior frontal 
gyrus (Broca area) and the superior temporal, supra-marginal, 
and angular gyri (Wernicke area). Surgery was not performed 
in 7 patients (9 %) and was modified in 2 patients (2 %) because 
of fMRI findings. The authors concluded that fMRI proved to be 
feasible during routine diagnostic neuro-imaging for localizing 
and lateralizing language function pre-operatively.

There is evidence for the use of fMRI in pre-surgical planning 
for epilepsy and monitoring of language function during tumor 
resection.

Roux et al (2003) analyzed the usefulness of pre-operative 
language fMRI by correlating fMRI data with intra-operative 
ESM results for patients with brain tumors. Naming and verb 
generation tasks were used, separately or in combination, for 
14 right-handed patients with tumors in the left hemisphere. 
Acquired fMRI data were analyzed with statistical parametric 
mapping software, with two standard analysis thresholds (p < 
0.005 and then p < 0.05). The fMRI data were then registered in 
a frameless stereotactic neuro-navigational device and 
correlated with direct brain mapping results. These 
researchers used a statistical model with the fMRI information 
as a predictor, spatially correlating each intra-operatively 
mapped cortical site with fMRI data integrated in the neuro-
navigational system (site-by-site correlation). Eight patients
were also studied with language fMRI post-operatively, with the same acquisition protocol. These investigators observed high variability in signal extents and locations among patients with both tasks. The activated areas were located mainly in the left hemisphere in the middle and inferior frontal gyri (F2 and F3), the superior and middle temporal gyri (T1 and T2), and the supra-marginal and angular gyri. A total of 426 cortical sites were tested for each task among the 14 patients. In frontal and temporo-parietal areas, poor sensitivity of the fMRI technique was observed for the naming and verb generation tasks (22 % and 36 %, respectively) with p < 0.005 as the analysis threshold. Although not perfect, the specificity of the fMRI technique was good in all conditions (97 % for the naming task and 98 % for the verb generation task). Better correlation (sensitivity, 59 %; specificity, 97 %) was achieved by combining the two fMRI tasks. Variation of the analysis threshold to p < 0.05 increased the sensitivity to 66 % while decreasing the specificity to 91 %. Post-operative fMRI data (for the cortical brain areas studied intra-operatively) were in accordance with brain mapping results for 6 of 8 patients. Complete agreement between pre- and post-operative fMRI studies and direct brain mapping results was observed for only 3 of 8 patients. The authors concluded that with the paradigms and analysis thresholds used in this study, language fMRI data obtained with naming or verb generation tasks, before and after surgery, were imperfectly correlated with intra-operative brain mapping results. A better correlation could be obtained by combining the fMRI tasks. The overall results of this study showed that language fMRI could not be used to make critical surgical decisions in the absence of direct brain mapping. Other acquisition protocols are needed for evaluation of the potential role of language fMRI in the accurate detection of essential cortical language areas.

Benke and associates (2006) noted that recent studies have claimed that language fMRI can identify language lateralization in patients with TLE and that fMRI-based findings are highly concordant with the conventional assessment procedure of speech dominance, the IAT. These researchers attempted to
establish the power of language fMRI to detect language lateralization during pre-surgical assessment and compared the findings of a semantic decision paradigm with the results of a standard IAT in 68 patients with chronic intractable right and left TLE (rTLE, n = 28; lTLE, n = 40) who consecutively underwent a pre-surgical evaluation program. The patient group also included 14 (20.6 %) subjects with atypical (bilateral or right hemisphere) speech. Four raters used a visual analysis procedure to determine the laterality of speech-related activation individually for each patient. Overall congruence between fMRI-based laterality and the laterality quotient of the IAT was 89.3 % in rTLE and 72.5 % in lTLE patients. Concordance was best in rTLE patients with left speech. In lTLE patients, language fMRI identified atypical, right hemisphere speech dominance in every case, but missed left hemisphere speech dominance in 17.2 %. Frontal activations had higher concordance with the IAT than did activations in temporo-parietal or combined regions of interest. Because of methodological problems, recognition of bilateral speech was difficult. The authors concluded that these data provide evidence that language fMRI as used in the present study has limited correlation with the IAT, especially in patients with lTLE and with mixed speech dominance. They noted that further refinements regarding the paradigms and analysis procedures will be needed to improve the contribution of language fMRI for pre-surgical assessment.

Petrella and colleagues (2006) prospectively evaluated the effect of pre-operative fMRI localization of language and motor areas on therapeutic decision making in patients with potentially resectable brain tumors. A total of 39 consecutive patients (19 men, 20 women; mean age of 42.2 years) referred for fMRI for possible tumor resection were evaluated. A pre-operative diagnosis of brain tumor was made in all patients. Sentence completion and bilateral hand squeeze tasks were used to map language and sensorimotor areas. Neurosurgeons completed questionnaires regarding the proposed treatment plan before and after fMRI and after surgery. They also gave confidence ratings for fMRI results and
estimated the effect on surgical time, extent of resection, and surgical approach. The effect of fMRI on changes in treatment plan was assessed with the Wilcoxon signed rank test. Differences in confidence ratings between altered and un-altered treatment plans were assessed with the Mann-Whitney U test. The estimated influence of fMRI on surgical time, extent of resection, and surgical approach was denoted with summary statistics. Treatment plans before and after fMRI differed in 19 patients (p < 0.05), with a more aggressive approach recommended after imaging in 18 patients. There were no significant differences in confidence ratings for fMRI between altered and un-altered plans. Functional MRI resulted in reduced surgical time (estimated reduction, 15 to 60 minutes) in 22 patients who underwent surgery, a more aggressive resection in 6, and a smaller craniotomy in 2. The authors concluded that fMRI enables the selection of a more aggressive therapeutic approach than might otherwise be considered because of functional risk. In certain patients, surgical time may be shortened, the extent of resection increased, and craniotomy size decreased.

Di et al (2007) assessed the differences in brain activation in response to presentation of the patient's own name spoken by a familiar voice (SON-FV) in patients with vegetative state (VS) and minimally conscious state (MCS). By using fMRI, these investigators prospectively studied residual cerebral activation to SON-FV in 7 patients with VS and 4 patients with MCS. Behavioral evaluation was performed by means of standardized testing up to 3 months post-fMRI. Two patients with VS failed to show any significant cerebral activation, while 3 patients with VS showed SON-FV induced activation within the primary auditory cortex. Finally, 2 patients with VS and all 4 patients with MCS not only showed activation in primary auditory cortex but also in hierarchically higher order associative temporal areas. The 2 patients with VS showing the most widespread activation subsequently showed clinical improvement to MCS observed 3 months after their fMRI scan. The authors concluded that cerebral responses to patient's own name spoken by a familiar voice as measured by fMRI might be a
useful tool to pre-clinically distinguish MCS-like cognitive processing in some patients behaviorally classified as vegetative.

The American College of Radiology (ACR)'s guideline on neurological imaging for patients with epilepsy (Karis et al, 2006) noted that the data provided by MRI are essential in the pre-surgical evaluation of patients with medically refractory epilepsy, but noted that structurally detectable abnormalities are absent in many patients. In these patients, functional studies provide useful information on localization of the seizure focus. In this regard, functional imaging techniques, including positron emission tomography, single-photon emission computed tomography, magnetic source imaging, and fMRI, have contributed to the pre-surgical evaluation of patients with epilepsy. The ACR guideline provided appropriateness ratings (1 = least appropriate; 9 = most appropriate) on fMRI for the following indications:

- Chronic epilepsy, poor therapeutic response. Surgery candidate (rating = 5; may be helpful in pre-surgical planning).
- New onset of seizure. Ethyl alcohol, and/or drug-related (rating = 2).
- New onset seizure. Aged 18 to 40 years (rating = 2).
- New onset seizure. Aged greater than 40 years (rating = 2).
- New onset seizure. Focal neurological deficit (rating = 2).

Additionally, the ACR's guideline on neurological imaging for patients with head trauma (Davis et al, 2006) provided an appropriateness rating of 2 for patients with sub-acute or chronic closed head injury with cognitive and/or neurological deficit(s).

The Ontario Ministry of Health and Long-Term Care's review on functioning brain imaging (2006) stated that there may be a role for fMRI in the identification of surgical candidates for tumor resection. The review also stated that there may be some clinical utility for fMRI in pre-surgical functional
The assessment by the Ontario Ministry of Health and Long-Term Care (2006) stated that there is limited clinical utility of functional brain imaging in the management of patients with MS at this time. This is in agreement with the European Federation of Neurological Societies' guideline on the use of neuro-imaging in the management of MS (Filippi et al, 2006), which stated that the use of non-conventional MRI techniques (e.g., fMRI, diffusion tensor MRI, magnetization transfer MRI, and MR spectroscopy) is not recommended.

Rocca and colleagues (2008) used fMRI to examine the properties of the mirror neuron system (MNS) in patients with MS. Using a 3 tesla scanner, these researchers acquired fMRI in 16 right-handed patients with relapsing-remitting MS and 14 controls. Two motor tasks were studied. The first consisted of repetitive flexion-extension of the last 4 fingers of the right hand (simple task) alternated to epochs of rest; the second (MNS task) consisted of observation of a movie showing the hand of another subject while performing the same task. During the simple task, compared to controls, patients with MS had more significant activations of the contralateral primary sensori-motor cortex and supplementary motor area. During the MNS task, both groups showed the activation of several visual areas, the infra-parietal sulcus, and the inferior frontal gyrus (IFG), bilaterally. The IFG and the visual areas were significantly more active in patients than controls. The between-group interaction analysis showed that in patients with MS, part of the regions of the MNS were more active also during the simple task. The authors concluded that the findings of this study suggested increased activation of the MNS in patients with MS with a normal level of function and widespread damage of the central nervous system. The potentialities of this system in facilitating clinical recovery in patients with MS and other neurological conditions should be investigated.

In an editorial that accompanied the afore-mentioned article,
Phillips (2008) stated that fMRI has tremendous potential for assessing and better understanding MS. He noted that it is important to remember that fMRI is an indirect measurement of neuronal activity. Also, it has been reported that there is altered brain perfusion in patients with MS. Changes in perfusion may alter the sensitivity and statistical characteristics of fMRI. Currently, it is unclear to what extent altered tissue perfusion complicates the interpretation of fMRI in MS. Furthermore, the enhanced activation patterns observed in MS have also been shown in other neurological conditions such as Alzheimer's disease, Parkinson's disease, and stroke.

In a randomized, double-blind, placebo-controlled study, Atri et al (2011) examined the feasibility and test-retest reliability of encoding-task fMRI in mild Alzheimer disease (AD). These investigators studied 12 patients with mild AD (mean [SEM] Mini-Mental State Examination score, 24.0 [0.7]; mean Clinical Dementia Rating score, 1.0) who had been taking donepezil hydrochloride for more than 6 months from the placebo-arm of a larger 24-week study (n = 24, 4 scans on weeks 0, 6, 12, and 24, respectively). They performed whole-brain t maps (p < 0.001, 5 contiguous voxels) and hippocampal regions-of-interest analyses of extent (percentage of active voxels) and magnitude (percentage of signal change) for novel-greater-than-repeated face-name contrasts. These researchers also calculated intra-class correlation coefficients and power estimates for hippocampal regions of interest. Task tolerability and data yield were high (95 of 96 scans yielded favorable-quality data). Whole-brain maps were stable. Right and left hippocampal regions-of-interest intraclass correlation coefficients were 0.59 to 0.87 and 0.67 to 0.74, respectively. To detect 25.0 % to 50.0 % changes in week-0 to week-12 hippocampal activity using left right extent or right magnitude with 80.0 % power (2-sided α = 0.05) requires 14 to 51 patients. Using left magnitude requires 125 patients because of relatively small signal to variance ratios. The authors concluded that encoding-task fMRI was successfully implemented in a single-site, 24-week, AD randomized controlled trial. Week 0 to 12 whole-brain t maps were stable, and test-retest reliability of hippocampal fMRI
measures ranged from moderate to substantial. Right hippocampal magnitude may be the most promising of these candidate measures in a leveraged context. These initial estimates of test-retest reliability and power justify evaluation of encoding-task fMRI as a potential biomarker for signal of effect in exploratory and proof-of-concept trials in mild AD. They stated that validation of these results with larger sample sizes and assessment in multi-site studies is warranted.

Burgmer and colleagues (2010) stated that studies with functional neuroimaging support the hypothesis of central pain augmentation in fibromyalgia syndrome (FMS) with functional differences in areas of the medial pain system. These investigators examined if these findings are unique to patients with FMS. BOLD-signal patterns during and before tonic experimental pain were compared to healthy controls and patients with rheumatoid arthritis (RA) as a chronic pain disorder of somatic origin. These researchers expected different BOLD-signal patterns in areas of the medial pain system that were most pronounced in patients with FMS. An fMRI-block design before, during and after an incision was performed in patients with FMS (n = 17), RA (n = 16) and in healthy controls (n = 17). A 2-factorial model of BOLD-signal changes was designed to explore significant differences of brain activation between the groups during the pain stimulus. Additionally, the correlation of brain activity during the anticipation of pain with the amount of the impending pain was determined. These researchers observed a FMS-unique temporal brain activation of the frontal cortex in patients with FMS. Moreover, areas of the motor cortex and the cingulate cortex presented a FMS-specific relation between brain activity during pain anticipation and the magnitude of the subsequent pain experience. The authors concluded that these findings support the hypothesis that central mechanisms of pain processing in the frontal cortex and cingulate cortex may play an important role in patients with FMS.

Tregellas et al (2010) noted that 3-(2,4-Dimethoxybenzylidene)-anabaseine (DMXB-A) is a partial agonist at alpha7-nicotinic
acetylcholine receptors and is now in early clinical development for treatment of deficits in neurocognition and sensory gating in schizophrenia. During its initial phase II test, fMRI studies were conducted to determine whether the drug had its intended effect on hippocampal inhibitory interneurons. Increased hemodynamic activity in the hippocampus in schizophrenia is found during many tasks, including smooth pursuit eye movements, and may reflect inhibitory dysfunction. Placebo and 2 doses of drug were administered in a random, double-blind cross-over design. After the morning drug/placebo ingestion, subjects underwent fMRI while performing a smooth pursuit eye movement task. Data were analyzed from 16 non-smoking patients, including 7 women and 9 men. The 150-mg dose of DMXB-A, compared with placebo, diminished the activity of the hippocampus during pursuit eye movements, but the 75-mg dose was ineffective. The effect at the 150-mg dose was negatively correlated with plasma drug levels. The findings are consistent with the previously established function of alpha7-nicotinic receptors on inhibitory interneurons in the hippocampus and with genetic evidence for deficits in these receptors in schizophrenia. Imaging of drug response is useful in planning future clinical tests of this compound and other nicotinic agonists for schizophrenia.

Whalley et al (2012) noted that although bipolar disorder (BD) and schizophrenia (SCZ) have a number of clinical features and certain susceptibility genes in common, they are considered separate disorders, and it is unclear which aspects of pathophysiology are specific to each condition. These researchers examined the fMRI literature to determine the evidence for diagnosis-specific patterns of brain activation in these 2 patient groups. A systematic search was performed to identify fMRI studies directly comparing BD and SCZ to examine evidence for diagnosis-specific activation patterns. Studies were categorized into (i) those investigating emotion, reward, or memory, (ii) those describing executive function or language tasks, and (iii) those looking at the resting state or default mode networks. Studies reporting estimates of sensitivity and specificity of classification were also summarized, followed by
studies reporting associations with symptom severity measures. A total of 21 studies were identified including patients (n = 729) and healthy subjects (n = 465). Relative over-activation in the medial temporal lobe and associated structures was found in BD versus SCZ in tasks involving emotion or memory. Evidence of differences between the disorders in pre-frontal regions was less consistent. Accuracy values for assignment of diagnosis were generally lower in BD than in SCZ. Few studies reported significant symptom associations; however, these generally implicated limbic regions in association with manic symptoms. The authors concluded that although there are a limited number of studies and a cautious approach is warranted, activation differences were found in the medial temporal lobe and associated limbic regions, suggesting the presence of differences in the neurobiological substrates of SCZ and BD. They stated that future studies examining symptom dimensions, risk-associated genes, and the effects of medication will aid clarification of the mechanisms behind these differences.

Astrakas et al (2012) stated that the number of individuals suffering from stroke is increasing daily, and its consequences are a major contributor to invalidity in today's society. Stroke rehabilitation is relatively new, having been hampered from the long-standing view that lost functions were not recoverable. Nowadays, robotic devices, which aid by stimulating brain plasticity, can assist in restoring movement compromised by stroke-induced pathological changes in the brain that can be monitored by MRI. Multi-parametric MRI of stroke patients participating in a training program with a novel Magnetic Resonance Compatible Hand-Induced Robotic Device (MR_CHIROD) could yield a promising biomarker that, ultimately, will enhance the ability to advance hand motor recovery following chronic stroke. Using state-of-the art MRI in conjunction with MR_CHIROD-assisted therapy can provide novel biomarkers for stroke patient rehabilitation extracted by a meta-analysis of data. Successful completion of such studies may provide a ground breaking method for the future evaluation of stroke rehabilitation therapies. Their results will
attest to the effectiveness of using MR-compatible hand devices with MRI to provide accurate monitoring during rehabilitative therapy. Furthermore, such results may identify biomarkers of brain plasticity that can be monitored during stroke patient rehabilitation. The potential benefit for chronic stroke patients is that rehabilitation may become possible for a longer period of time after stroke than previously thought, unveiling motor skill improvements possible even after 6 months due to retained brain plasticity.

Wager et al (2013) noted that persistent pain is measured by means of self-report, the sole reliance on which hampers diagnosis and treatment. Functional magnetic resonance imaging holds promise for identifying objective measures of pain, but brain measures that are sensitive and specific to physical pain have not yet been identified. In 4 studies involving a total of 114 participants, these researchers developed an fMRI-based measure that predicts pain intensity at the level of the individual person. In study 1, they used machine-learning analyses to identify a pattern of fMRI activity across brain regions -- a neurologic signature -- that was associated with heat-induced pain. The pattern included the thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the anterior cingulate cortex, the peri-aqueductal gray matter, and other regions. In study 2, these investigators tested the sensitivity and specificity of the signature to pain versus warmth in a new sample. In study 3, they assessed specificity relative to social pain, which activates many of the same brain regions as physical pain. In study 4, these researchers evaluated the responsiveness of the measure to the analgesic agent remifentanil. In study 1, the neurologic signature showed sensitivity and specificity of 94 % or more (95 % confidence interval [CI]: 89 to 98) in discriminating painful heat from non-painful warmth, pain anticipation, and pain recall. In study 2, the signature discriminated between painful heat and non-painful warmth with 93 % sensitivity and specificity (95 % CI: 84 to 100). In study 3, it discriminated between physical pain and social pain with 85 % sensitivity (95 % CI: 76 to 94) and 73 % specificity (95 % CI, 61 to 84) and with
95% sensitivity and specificity in a forced-choice test of which of 2 conditions was more painful. In study 4, the strength of the signature response was substantially reduced when remifentanil was administered. The authors concluded that it is possible to use fMRI to assess pain elicited by noxious heat in healthy persons. Moreover, they state that future studies are needed to assess whether the signature predicts clinical pain.

Magland and Childress (2014) stated that real-time fMRI is especially vulnerable to task-correlated movement artifacts because statistical methods normally available in conventional analyses to remove such signals cannot be used in the context of real-time fMRI. Multi-voxel classifier-based methods, although advantageous in many respects, are particularly sensitive. These researchers systematically studied various movements of the head and face to determine to what extent these can "masquerade" as signal in multi-voxel classifiers. A total of 10 subjects were instructed to move systematically (12 instructed movements) throughout fMRI exams and data from a previously published real-time study was also analyzed to determine the extent to which non-neural signals contributed to the high reported accuracy in classifier output. Of potential concern, whole-brain classifiers based solely on movements exhibited false positives in all cases (p < 0.05). Artifacts were also observed in the spatial activation maps for 2 of the 12 movement tasks. In the retrospective analysis, it was determined that the relatively high reported classification accuracies were (fortunately) mostly explainable by neural activity, but that in some cases performance was likely dominated by movements. The authors concluded that movement tasks of many types (including movements of the body, eyes, and face) can lead to false positives in classifier-based real-time fMRI paradigms.

The University of Michigan Health System's clinical guideline on “Attention-deficit hyperactivity disorder” (2013) listed functional magnetic resonance imaging as one of the search terms for the update of a previous version of this guideline. Moreover, the updated guideline stated that “Diagnosis is
based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) criteria. The three main types are primary hyperactive, primary inattentive, and combined. No specific test can make the diagnosis”.

Furthermore, UpToDate reviews on “Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation” (Krull, 2014) and “Adult attention deficit hyperactivity disorder in adults: Epidemiology, pathogenesis, clinical features, course, assessment, and diagnosis” (Bukstein, 2014) do not mention the use of fMRI as a diagnostic tool.

Wager and colleagues (2013) noted that persistent pain is measured by means of self-report, the sole reliance on which hampers diagnosis and treatment. Functional MRI holds promise for identifying objective measures of pain, but brain measures that are sensitive and specific to physical pain have not yet been identified. In 4 studies involving a total of 114 participants, these researchers developed an fMRI-based measure that predicts pain intensity at the level of the individual person. In study 1, they used machine-learning analyses to identify a pattern of fMRI activity across brain regions — a neurologic signature — that was associated with heat-induced pain. The pattern included the thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the anterior cingulate cortex, the periaqueductal gray matter, and other regions. In study 2, these researchers tested the sensitivity and specificity of the signature to pain versus warmth in a new sample. In study 3, they assessed specificity relative to social pain, which activates many of the same brain regions as physical pain. In study 4, these investigators assessed the responsiveness of the measure to the analgesic agent remifentanil. In study 1, the neurologic signature showed sensitivity and specificity of 94 % or more (95 % CI: 89 to 98) in discriminating painful heat from non-painful warmth, pain anticipation, and pain recall. In study 2, the signature discriminated between painful heat and non-painful warmth with 93 % sensitivity and specificity (95 % CI: 84 to 100). In
study 3, it discriminated between physical pain and social pain with 85% sensitivity (95% CI: 76 to 94) and 73% specificity (95% CI: 61 to 84) and with 95% sensitivity and specificity in a forced-choice test of which of 2 conditions was more painful. In study 4, the strength of the signature response was substantially reduced when remifentanil was administered. The authors concluded that it is possible to use fMRI to assess pain elicited by noxious heat in healthy persons. Moreover, they stated that future studies are needed to assess whether the signature predicts clinical pain.

Furthermore, the Work Loss Data Institute’s guideline on “Pain (chronic)” (2013) listed fMRI as one of the interventions that were considered, but are not recommended.

Stender et al (2014) stated that bedside clinical examinations can have high rates of misdiagnosis of unresponsive wakefulness syndrome (vegetative state) or minimally conscious state. The diagnostic and prognostic usefulness of neuroimaging-based approaches has not been established in a clinical setting. These researchers carried out a validation study of 2 neuroimaging-based diagnostic methods: (i) PET imaging and (ii) functional MRI (fMRI). For this clinical validation study, these investigators included patients referred to the University Hospital of Liege, Belgium, between January, 2008, and June, 2012, who were diagnosed by the authors’ unit with unresponsive wakefulness syndrome, locked-in syndrome, or minimally conscious state with traumatic or non-traumatic causes. They did repeated standardized clinical assessments with the Coma Recovery Scale-Revised (CRS-R), cerebral (18)F-fluorodeoxyglucose (FDG) PET, and fMRI during mental activation tasks. They calculated the diagnostic accuracy of both imaging methods with CRS-R diagnosis as reference. They assessed outcome after 12 months with the Glasgow Outcome Scale-Extended. The authors included 41 patients with unresponsive wakefulness syndrome, 4 with locked-in syndrome, and 81 in a minimally conscious state (48 = traumatic, 78 = non-traumatic; 110 = chronic, 16 = subacute). (18)F-FDG PET had high sensitivity for identification of patients
in a minimally conscious state (93 %, 95 % CI: 85 to 98) and high congruence (85 %, 77 to 90 %) with behavioral CRS-R scores. The active fMRI method was less sensitive at diagnosis of a minimally conscious state (45 %, 30 to 61 %) and had lower overall congruence with behavioral scores (63 %, 51 to 73 %) than PET imaging. (18)F-FDG PET correctly predicted outcome in 75 of 102 patients (74 %, 64 to 81 %), and fMRI in 36 of 65 patients (56 %, 43 to 67 %); 13 of 41 (32 %) of the behaviorally unresponsive patients (i.e., diagnosed as unresponsive with CRS-R) showed brain activity compatible with (minimal) consciousness (i.e., activity associated with consciousness, but diminished compared with fully conscious individuals) on at least 1 neuroimaging test; 69 % of these (9 of 13) patients subsequently recovered consciousness. The authors concluded that cerebral (18)F-FDG PET could be used to complement bedside examinations and predict long-term recovery of patients with unresponsive wakefulness syndrome. Moreover, they stated that active fMRI might also be useful for differential diagnosis, but seems to be less accurate.

UpToDate reviews on “Locked-in syndrome’ (Caplan, 2015) and “Stupor and coma in adults” (Young, 2015) do not mention functional MRI as a management tool.

Furthermore, an UpToDate review on “Treatment and prognosis of coma in children’ (Thompson and Williams, 2015) states that “Other neuroimaging modalities, MR spectroscopy, functional MRI, positron emission tomography are not useful in the evaluation of coma prognosis]. Studies, awaiting validation, suggest that these tools may help discriminate between persistent vegetative state, minimally conscious state and other states of impaired consciousness”.

**Anoxic-Ischemic Brain Injury:**

An UpToDate review on “Hypoxic-ischemic brain injury: Evaluation and prognosis” (Weinhouse and Young, 2016) states that “In the future, larger studies may find a role for standard MRI as well as functional neuroimaging, such as positron
emission tomography (PET) and functional MRI (fMRI), in the prognostic assessment of adults with anoxic-ischemic brain injury. fMRI studies have the potential to detect network processing of sensory and motor responses, showing some evidence of awareness in a small proportion of behaviorally unresponsive patients. However, the performance and interpretation of these studies remains complex and is still investigational. There are also ethical issues regarding quality of life in decision-making that need to be resolved, namely whether patients who can generate such binary responses can participate in a decision-making process”.

Psychotic Depression:

O'Connor and Agius (2015) stated that psychotic depression is widely accepted as a specific subtype of unipolar major depression. Magnetic resonance imaging studies have begun to investigate the neurobiological changes that differentiate this subtype of major depression from non-psychotic depression. Any differences may eventually be useful in aiding diagnosis patients for whom there is diagnostic uncertainty. This review collated the currently available evidence. These investigators performed a systematic search of the Medline, PubMed, Embase & Web of Science databases was used to identify all articles comparing structural grey matter or fMRI differences between adults (18 years or older) with previously diagnosed psychotic and non-psychotic depression in pre-defined regions of interest (hippocampus, amygdala, cingulate, insula and frontal cortices). The results were collated and organized according to brain region. There was a paucity of studies addressing structural and functional changes differentiating these 2 disorders and recommendations regarding use of these modalities in diagnosis cannot be made. From the available studies decreases in frontal cortex grey matter volumes may differentiate psychotic from non-psychotic depression while further studies are needed to confirm decreases in insula cortex volumes. Functional MRI studies showed associations between altered activity in these 2 regions and cognitive impairments in patients with psychotic depression. The volumes of putative
emotional processing regions including the amygdala, hippocampus and anterior cingulate showed no difference between psychotic and non-psychotic depression. The authors concluded that structural and functional changes in the higher associative regions of the frontal and insular cortices appeared to differentiate psychotic and non-psychotic depression to a greater degree than changes in putative emotional processing regions. The quality of the evidence both in terms of numbers of studies available and sample sizes involved was very poor; but in regard to directing future study, understanding the neurobiology of psychotic depression may benefit from a more detailed assessment of these 2 regions.

### CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

**ICD-10 codes will become effective as of October 1, 2015:**

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>70554</td>
<td>Magnetic resonance imaging, brain, functional MRI; including test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration</td>
</tr>
<tr>
<td>70555</td>
<td>requiring physician or psychologist administration of entire neurofunctional testing</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C71.0</td>
<td>Malignant neoplasm of brain</td>
</tr>
<tr>
<td>C71.9</td>
<td></td>
</tr>
<tr>
<td>C79.31</td>
<td>Secondary malignant neoplasm of brain and other parts of nervous system</td>
</tr>
<tr>
<td>C79.49</td>
<td></td>
</tr>
<tr>
<td>D33.0</td>
<td>Benign neoplasm of brain</td>
</tr>
<tr>
<td>D33.2</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>D43.0 - D43.2, D43.4</td>
<td>Neoplasm of uncertain behavior of brain and spinal cord</td>
</tr>
<tr>
<td>G40.001 - G40.919</td>
<td>Epilepsy and recurrent seizures</td>
</tr>
<tr>
<td>Q28.2 - Q28.3</td>
<td>Arteriovenous and other malformations of cerebral vessels</td>
</tr>
<tr>
<td>R56.1</td>
<td>Post traumatic seizures</td>
</tr>
<tr>
<td>R56.9</td>
<td>Unspecified convulsions</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F20.0 - F20.9</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>F25.0 - F25.9</td>
<td>Bipolar I disorder</td>
</tr>
<tr>
<td>F30.10 - F31.9</td>
<td>Attention-deficit hyperactivity disorder,</td>
</tr>
<tr>
<td>F90.1 - F90.9</td>
<td>Parkinson's disease and secondary parkinsonism</td>
</tr>
<tr>
<td>G20 - G21.9</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>G30.0 - G30.9</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>G35</td>
<td>Transient cerebral ischemic attacks and related syndromes</td>
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<tr>
<td>G89.21 - G89.29</td>
<td>Chronic pain</td>
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<tr>
<td>G93.81 - G93.89</td>
<td>Other specified disorders of brain [Locked-in syndrome]</td>
</tr>
<tr>
<td>I63.00 - I66.9</td>
<td>Cerebral infarction, occlusion and stenosis of cerebral and precerebral arteries not resulting in cerebral infarction</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>I67.1 - I69.998</td>
<td>Cerebrovascular diseases and disorders</td>
</tr>
<tr>
<td>M79.7</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>R40.20 - R40.236+</td>
<td>Coma</td>
</tr>
<tr>
<td>R40.3</td>
<td>Persistent vegetative state</td>
</tr>
<tr>
<td>S01.00x+ - S02.92x+</td>
<td>Open wound of head and fracture of skull and facial bones</td>
</tr>
<tr>
<td>S05.20x+ - S05.92x+</td>
<td>Injury of eye and orbit</td>
</tr>
<tr>
<td>S06.0x0+ - S06.9x9+</td>
<td>Intracranial injury</td>
</tr>
<tr>
<td>S08.0xx+ - S08.89x+</td>
<td>Avulsion and traumatic amputation of part of head</td>
</tr>
<tr>
<td>S09.20x+ - S09.90x+</td>
<td>Other and unspecified injuries of head</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

5. Roux FE, Boulanouar K, Lotterie JA, et al. Language...


37. Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Clinical features and evaluation. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2014.


41. Young CB. Stupor and coma in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2015.

42. Thompson L, Williams E. Treatment and prognosis of coma in children. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2015.


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Amendment to
Aetna Clinical Policy Bulletin Number: 0739
Functional Magnetic Resonance Imaging

There are no amendments for Medicaid.

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