Practice guideline: Use of fMRI in the presurgical evaluation of patients with epilepsy

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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DISCLOSURE

Dr. Szaflarski has served, in the past 2 years, as a consultant for GW Pharmaceuticals, Inc., Upsher-Smith Laboratories, Inc., Sage Pharmaceuticals, Inc., and Biomedical Systems, Inc.; has served or serves on the editorial boards of *Epilepsy & Behavior*, *Epilepsy Currents* (contributing editor), *Journal of Epileptology* (associate editor), *Journal of Medical Science, Folia Medica Copernicana, Restorative Neurology and Neuroscience* (associate editor), and *Conference Papers in Medicine*; has received funding for research from the US Department of Defense (DOD), US Food and Drug Administration, American Epilepsy Society, SAGE Pharmaceuticals, Inc., Eisai, Inc., UCB Pharmaceuticals, the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH, the State of Alabama ("Carly's Law"), and the University of Alabama at Birmingham; and has served as an expert witness in legal proceedings.

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Dr. Gaillard reports support from Research Triangle International and grant support from the NIH, the Centers for Disease Control and Prevention, the DOD, the National Science Foundation (NSF), Citizens United for Research in Epilepsy, Pediatric Epilepsy Research Foundation, and BAND; and serves on the editorial boards for *Epilepsia* and *Epilepsy Research*.

Dr. Golby serves on the editorial boards of *Brain Imaging and Behavior*, the *Journal of Neuroimaging*, the *Journal of Cancer Translational Medicine*, and *NeuroImage: Clinical*; serves as an associate editor of *Neurosurgery*; and has received research funding from the NIH, Harvard Catalyst, and Koh-Young Technology, Inc.

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Dr. Ojemann is a board member of Therma Neuroscience, Inc., receives funding from the NIH and the NSF; is a member of the Epilepsy Foundation Northwest professional advisory board; and serves on the editorial boards of *Neurosurgery* and *Journal of Neurosurgery*.

Dr. Spencer has served as an editor for *Neurology* and the *Neurology* patient page; has received research support from NeuroPace, Inc.; and has given a deposition in a legal proceeding.

Dr. Swanson has received support from the Epilepsy Foundation of America and the NIH; and has served as an expert witness in civil and criminal legal proceedings.

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ABBREVIATIONS

AAN: American Academy of Neurology

ATL: anterior temporal lobe

fMRI: functional MRI

IAP: intracarotid amobarbital procedure

LI: laterality index

MTL: medial temporal lobe

MTLE: medial temporal lobe epilepsy

ROI: region of interest

TLE: temporal lobe epilepsy

ABSTRACT

Objective: To assess the diagnostic accuracy of functional MRI (fMRI) in determining functional lateralization and the prognostic value of fMRI in predicting postsurgical language and memory outcomes.

Methods: An 11-member panel evaluated and rated available evidence according to the 2004 American Academy of Neurology process. The panel reviewed abstracts from 2,636 identified articles and deemed 172 to be possibly relevant. At least 2 panelists working independently of one another reviewed the full text of each article and selected 37 for full data extraction. Case reports, reports with <15 cases, meta-analyses, and editorials were excluded.

Results and recommendations: The use of fMRI may be considered an option for lateralizing language functions in place of the intracarotid amobarbital procedure (IAP) in patients with medial temporal lobe epilepsy (MTLE; Level C), temporal epilepsy in general (Level C), or extratemporal epilepsy (Level C). For patients with temporal neocortical epilepsy or temporal tumors, the evidence is insufficient (Level U). FMRI may also be used to predict postsurgical language deficits after anterior temporal lobe resection (Level C). For memory assessments, the use of fMRI may be considered as an option to lateralize memory functions in place of IAP in patients with MTLE (Level C) but is of unclear utility in other epilepsy types (Level U). FMRI of verbal memory or of language encoding should be considered as an option for predicting verbal memory outcome (Level B). FMRI using nonverbal memory encoding may be considered for predicting visuospatial memory outcomes (Level C). Presurgical fMRI could be an adequate alternative to IAP memory testing for prediction of verbal memory outcome (Level C). Clinicians should carefully advise patients of the risks and benefits of fMRI vs IAP during discussions concerning choice of specific modality in each case.

INTRODUCTION

Functional MRI (fMRI), introduced more than 20 years ago as a technique for localization of brain functions,[e1] has undergone substantial research and clinical development and has been used increasingly for presurgical mapping. FMRI is properly described as an image acquisition technique that has come to mean imaging brain activity. In most fMRI studies performed for research purposes, the initial analysis is conducted using a standard image analysis package such as Statistical Parametric Mapping (www.fil.ion.ucl.ac.uk/spm) or Analysis of Functional NeuroImages.[e2] Although fMRI tasks and postprocessing methods have not yet been universally standardized, standard practices are beginning to emerge and the Organization for Human Brain Mapping recently released a report describing its recommendations for best practices for fMRI data analysis.[e3] In clinical applications, several software packages have been approved by the US Food and Drug Administration for analysis, review, and reporting of fMRI results. Many clinical factors can affect fMRI results, including type of task contrast used or medications administered at the time of the procedure.[e4–e6] Typically, the number of "activated" voxels within predetermined anatomic regions, based on the chosen statistical threshold, is used to calculate a "laterality index (LI)" for comparison with values obtained from healthy volunteers and/or with LIs obtained from the intracarotid amobarbital procedure (IAP); results of such analyses are operator and method dependent.[e7] One study found comparable results for LI calculation and visual interpretation of activation maps.[e8] With few exceptions, the articles discussed herein use either LI or post-resection outcomes for the reporting of the fMRI results.

The IAP language or memory testing is also not standardized, and the reviewed studies varied widely with regard to the procedure used for comparison. The injected dose of sodium amobarbital varied from 75–150 mg, both across and within studies. One study comparing methohexital sodium indirectly with sodium amobarbital historical controls found the latter had better correlation with neuropsychological memory test results.[e9] It is not clear how the differences between IAP performed with sodium amobarbital affect the results of studies that compare the results of fMRI with those of IAP with methohexital sodium. The rate of administration has varied, as has the interval between injections when both hemispheres were studied. Some studies used formal scoring procedures to calculate an IAP LI that could be compared with fMRI LI. Others assessed function laterality by qualitative clinical observation. IAP results may be "inconclusive" in a substantial proportion of patients, and data on healthy volunteers are not available for the IAP. The IAP is associated with potentially serious complications, including carotid artery dissection, allergic reaction to contrast, and, in one series, strokes or TIAs occurring in 0.6% of patients.[e10]

The choice of performing IAP or fMRI for presurgical language and memory assessment depends on multiple factors, which include the clinician's previous training and clinical experience, availability of appropriate fMRI tasks and trained staff to process and interpret the data, ability of the patient to undergo the procedure (e.g., presence of metallic artifacts or claustrophobia may preclude fMRI, or an unusual vascular anatomy may make IAP difficult or impossible to perform), age, and local practice pattern. In general, clinicians need to consider whether determination of language lateralization is needed before choosing fMRI instead of IAP (e.g., in planning nondominant temporal lobe surgery) in patients with atypical handedness,

whether the neuropsychological testing indicates a high chance of post-resection deficits, or when preoperative assessment of memory lateralization is indicated (e.g., in planning dominant temporal lobe surgery). The efficacy of fMRI for cortical mapping and prediction of postsurgical outcome has been examined in many studies; thus, the goal of this practice guideline is to review the available evidence and provide practitioners with evidence-based recommendations for fMRI epilepsy surgical evaluation and postsurgical outcome prediction. The guideline authors used the American Academy of Neurology (AAN) diagnostic and prognostic schemes for rating evidence.

This practice guideline seeks to answer the following clinical questions:

1. Is fMRI comparable with the current standard (IAP) for measuring language lateralization?

2. Can fMRI predict postsurgical language outcomes in patients with epilepsy undergoing brain surgery?

3. Is fMRI comparable with the current standard (IAP) for measuring memory lateralization?

4. Can fMRI predict postsurgical verbal memory outcomes in patients with epilepsy undergoing temporal lobectomy?

5. Can fMRI predict postsurgical nonverbal (visuospatial) memory outcomes in patients with epilepsy undergoing temporal lobectomy?

6. Is there sufficient evidence in terms of diagnostic accuracy and outcome prediction for fMRI to replace the IAP (Wada test) in presurgical evaluation for epilepsy surgery?

DESCRIPTION OF THE ANALYTIC PROCESS

In 2009, the Guideline Development, Dissemination, and Implementation Subcommittee of the AAN (see appendices e-1 and e-2) appointed an 11-member panel that included neurologists, neurosurgeons, neuroscientists, a physicist, and a neuropsychologist with special expertise in neuroimaging or epilepsy, or both, and with experience in AAN guideline development. The panel followed the methods described in the 2004 AAN process manual[e11] to develop this practice guideline. A medical librarian searched MEDLINE, Embase, and Science Citation Index (using Web of Science) for relevant articles published from 1990 to April 2015. The key text and index words used in the search were "epilepsy," "epilepsy surgery," "brain tumor(s)," "brain malformation(s)," "cortical malformation(s)," "Wada test," "intracarotid amobarbital procedure," "electro-cortical mapping," "fMRI," "functional MRI," "outcomes," "memory," and "language." The guideline panel included only peer-reviewed studies in humans that addressed diagnosis and prognosis. Appendix e-3 provides the complete search strategy.

The original search yielded 2,636 abstracts. Each abstract was reviewed for relevance by at least 2 panel members, who then deemed 172 abstracts possibly relevant; the corresponding articles were obtained for full-text review. Two panelists working independently of each other reviewed each article and selected 37 articles for full data extraction on the basis of the following criteria: number of epilepsy patients included per study $n \geq 15$ (this a priori decision was made to eliminate as many underpowered studies as possible from the review process), relevance to the clinical questions previously listed, clearly described methods of data collection and analysis,

original data presented, and comparison data with IAP, electrocortical mapping, or postoperative outcome measures presented. The guideline panel excluded case reports, meta-analyses, and editorials. In a few cases, articles appeared to include subsets of patients who were incorporated in previous publications.[e12–e14] Where this appeared to be the case, only data from the most recent publication were examined, except when the earlier report included analyses not performed in the later report. Two panelists working independently of each other rated each of these articles according to the AAN diagnostic and prognostic classification of evidence schemes (appendix e-4). Differences in ratings were arbitrated by a third panel member (J.P.S.) until a consensus among the 3 reviewers was achieved. Additional review of all included articles was performed by the study methodologist (D.G.) to confirm adherence to the classification scheme. Because it is unclear whether the results of fMRI studies can be combined for seizure foci in different brain localizations (owing to possible function reorganization), the articles were also reviewed to determine whether the results could be analyzed separately for patients with medial and lateral temporal (temporal neocortical), temporal (if not divided into medial and lateral), and extratemporal epilepsies. Table e-1 presents the evidence. The guideline panel linked the strength of recommendations (A, B, C, and U; appendix e-5) to the strength of the evidence on the basis of the number of Class I, II, and III studies.

ANALYSIS OF EVIDENCE

Is fMRI comparable with the current standard (IAP) for measuring language lateralization?

In regard to medial, lateral, and extratemporal foci, 2 Class I, 8 Class II, and 12 Class III studies addressed this question. Because Class I and II data are available, Class III data are not discussed, as they are not applicable for powering recommendations. The guideline panel performed an individual patient data meta-analysis on the Class I and II studies[e15–e18] in order to address this question in patients with medial temporal lobe epilepsy (MTLE). An additional 18 studies were identified (6 Class II and 12 Class III) that did not specify medial or lateral temporal but did specify temporal.[e8,e19–e35]

Temporal lobe epilepsy

One Class I study was a large series of 229 patients with epilepsy, of whom 188 had temporal lobe epilepsy (TLE).[e17] There was concordance with IAP in 81 of 91 (89%) patients for the right and 82 of 97 (85%) for the left medial temporal foci. Medial and lateral temporal foci were not explicitly separated in the results, but the presence of "hippocampal atrophy" or "medial temporal sclerosis" did not affect concordance rate. In this study, the fMRI paradigm for language lateralization contrasted a semantic decision task with a tone decision task.[e17] One Class II study showed a concordance rate of 12 of 14 (86%) patients with MTLE and in 3 of 3 (100%) patients with medial temporal tumors.[e16] The fMRI paradigms for language lateralization included generating category words, answering questions, reading and listening to stories, and auditory response naming. Each patient performed at least the verbal task, 1 of the 2 reading comprehension tasks, and 1 of the 2 auditory comprehension tasks. In the second Class II study of 40 patients, when only the data on the reading task were evaluated, the concordance between fMRI and IAP was 26 of 31 for all patients and 9 of 13 when only those with medial temporal

seizure onset were analyzed.[e15] The last Class II study that compared concordance between fMRI and IAP showed excellent agreement for patients with MTLEs (17 of 17) and seizures related to medial temporal tumors (4 of 4).[e18] An additional Class I study did not separate medial from lateral temporal foci.[e24] All 17 patients with TLE showed concordance between IAP and LI for the frontal region of interest (ROI) but only 15 of 17 (88%) when hemispheric ROI analysis was conducted.

Extratemporal epilepsy

The data for patients with extratemporal epilepsies include the Class I study previously mentioned, which showed concordance between fMRI and IAP in 34 of 41 (83%) of the extratemporal cases.[e17] Of the Class II studies, 1 performed in 40 patients with epilepsy showed that in patients with extratemporal epilepsies the concordance was 8 of 11 for all IAP results and 8 of 10 if the patient with IAP bilateral language distribution was excluded.[e15] Another Class II study of 26 patients with epilepsy reported 100% concordance between fMRI and IAP in 5 of 5 patients with extratemporal lobe epilepsies.[e8]

Of the studies conducted in patients with mixed or unspecified location of seizure onset foci, one Class II study showed overall 86% correlation with IAP in 20 patients with epilepsy or brain tumors, or both, for the sentence task and 89% for the synonym task; individual patient data were not provided.[e26] A Class II study in 51 patients with epilepsy or brain tumors, or both, indicated moderate correlation ($r = 0.68$; $p < 0.0001$) between IAP and fMRI, but again, individual data were not provided to aid the combined analysis,[e27] which is similar to the other 2 Class II studies.[e30,e31] Finally, the last Class II study performed in 38 patients with epilepsy showed concordance in 1 of 2 extratemporal cases.[e18]

Meta-analysis of the previously discussed studies found the following concordance rates (considering only definitely right or left IAP results): 201 of 232 (87%) for medial temporal foci, 7 of 7 (100%) for medial temporal tumors, and 48 of 59 (81%) for extratemporal foci. Data from studies that included patients with mixed or unspecified foci are harder to interpret because some studies did not clearly specify the focus of seizure localization. We classified these meta-analysis data as Class II because they are composed of 2 Class I and 8 Class II studies.

Conclusions

FMRI possibly provides concordant language lateralization information to that of IAP in 87% of medial temporal cases (Class II meta-analysis of individual patient data) and in 81% of extratemporal cases (Class II meta-analysis of individual patient data). There are insufficient data for temporal tumors or lateral temporal cases.

Recommendations

The use of fMRI may be considered an option in lateralizing language functions in place of IAP in patients with MTLE (Level C), temporal epilepsy in general (Level C), or extratemporal

epilepsy (Level C), although patients should be carefully advised of the risks and benefits of fMRI vs IAP during discussions of modality choice in each individual case. The evidence is unclear for patients with temporal neocortical epilepsy or temporal tumors (Level U).

Can fMRI predict postsurgical language outcomes in patients with epilepsy undergoing brain surgery?

The purpose of measuring language lateralization preoperatively is to optimize and predict language outcomes. In contrast to the many studies comparing IAP and fMRI language lateralization results, relatively little information is available on the ability of either test to predict language change after surgery. The panel identified 1 Class II study of 44 patients with left or right TLE associated with hippocampal sclerosis[e36] and 1 Class III study of 56 patients with left or right MTLE (information regarding presence or absence of hippocampal sclerosis was not provided).[e34] In the Class II study, the authors showed that in patients with left TLE, strong left frontal activation predicted greater post-resection decline (sensitivity 100%, specificity 33%, positive predictive value 60%), and that the post-resection performance depended on greater right frontal language activation shift.[e36] The Class III study showed that stronger leftward lateralization in a temporal lobe ROI during a semantic decision task predicted greater postoperative naming decline (sensitivity of 100%, specificity of 73%, positive predictive value 81%; temporal lobe LI correlation to postoperative change on the Boston Naming Test: $r = -0.64$; $p < 0.001$).[e34] This study also assessed the ability of IAP language lateralization to predict naming outcome in the same patients. Accuracy of the IAP prediction (sensitivity 92%, specificity 45%, positive predictive value 67%) was lower than that of fMRI.

Conclusions

FMRI is possibly effective in aiding the prediction of postsurgical language deficits in patients undergoing presurgical evaluation for possible temporal lobectomy (1 Class II study and 1 Class III study). The high combined sensitivity and specificity of fMRI makes this an attractive target for an adequately powered study for creating a community standard.

Recommendation

The use of fMRI may be considered an option for predicting postsurgical language outcomes after anterior temporal lobe (ATL) resection for the control of TLE (Level C).

Is fMRI comparable with the current standard (IAP) for measuring memory lateralization?

Several strategies have been employed for memory activation in fMRI studies, such as scene/picture (with verbal and nonverbal elements), faces, semantic decision, and word encoding.[e12,e13,e22,e37–e40] IAP usually involves object or word presentation during hemiplegia, followed by post-recovery testing of the remembered items.

The usefulness of fMRI for memory lateralization has been assessed in 2 Class II and 2 Class III studies comparing medial temporal lobe (MTL) fMRI activation paradigms with IAP memory testing in patients with unilateral temporal lobe epilepsy (TLE). Of the Class II studies, 1 study of 67 patients with TLE, which employed an fMRI contrast between novel visual scenes and meaningless visual patterns, showed a significant correlation ($r = 0.31$; $p = 0.007$) between a hippocampal fMRI LI and IAP memory LI.[e22] The second Class II study found no significant correlation ($r = 0.152$; $p = 0.47$) between an IAP memory asymmetry measure and medial temporal fMRI LI in 25 patients with TLE.[e41]

Of the Class III studies, one conducted in 18 patients with TLE used an fMRI paradigm contrasting novel pictures with previously studied pictures. An LI computed for the MTL region showed a significant correlation ($r = 0.49$; $p = 0.049$) with the IAP memory LI in patients with TLE.[e39] The second Class III study in 30 patients with TLE showed that the number of activated left MTL voxels in patients with left TLE was positively correlated with left IAP memory score (Spearman $r = 0.60$, $p < 0.01$).[e42]

Conclusions

In patients with MTLE, there is Class II evidence that fMRI is comparable with IAP in its ability to lateralize memory functions and may be used for this purpose in patients with MTLE. The conflicting data from one study may be related to a relatively high dose of sodium amobarbital used to perform the IAP.

Recommendation

The use of fMRI may be considered as an option to lateralize memory functions in place of IAP in patients with MTLE (Level C).

Can fMRI predict postsurgical verbal memory outcomes in patients with epilepsy undergoing temporal lobectomy?

There were 9 Class II and 3 Class III studies that provided data to address this question.[e12,e13,e22,e29,e38,e40,e41,e43–e47] Because there are Class II data regarding MTL epilepsy, the Class III studies are not discussed further.[e13,e29,e43] One Class II study of 122 patients with TLE (60 left) conducted preoperative language lateralization with a semantic decision fMRI task in patients who underwent anterior temporal lobectomy and compared the results with those from preoperative IAP and pre- and postoperative neuropsychological testing.[e44] In this study, 50% of the variance in postsurgical verbal memory outcome was explained by preoperative neuropsychological testing, whereas fMRI contributed an additional 10% of the variance ($p \leq 0.003$). Neither IAP memory asymmetry nor IAP language asymmetry contributed to the postsurgical memory outcome prediction.[e44] Another Class II study evaluated the ability of a language task (semantic decision) vs a picture encoding memory task to predict post-resection memory outcomes.[e22] These authors found that, in contrast to lateralization of activation in the language network, the lateralization of hippocampal activation during the picture encoding task was not predictive of post-resection verbal memory outcomes. Another Class II study examined

asymmetry of hippocampal activation and postsurgical memory outcomes in 29 patients with left TLE and 25 patients with right TLE, using a word encoding fMRI paradigm and stepwise linear regression to test associations between fMRI activation and postoperative memory changes after ATL.[e12] The degree of fMRI asymmetry toward the left was correlated with postsurgical verbal memory decline ($p = 0.028$). A model including fMRI memory and language asymmetry and preoperative verbal learning scores had sensitivity of 100% and specificity of 86% for predicting verbal postoperative memory change in patients with left TLE.[e11] Another study involved 25 patients with medial TLE.[e41] This study presented a model including left fMRI activation during delayed recognition, side of the epileptic focus, and preoperative verbal memory score that provided an accurate determination of the evolution of verbal memory in 19 of 24 (79%) patients with postoperative neuropsychological impairment. Activation in the left MTL, side of seizure onset, and preoperative verbal memory score correctly predicted worsening of postoperative verbal memory in 90% of patients. IAP data did not predict postoperative memory outcome.[e41] A recent Class II study conducted in 50 patients with TLE (23 with left) showed that increasing left lateralization in the frontotemporal verbal memory network pre-resection was associated with post-resection verbal memory decline in patients with left TLE ($r = 0.44$; $p = 0.037$); this effect was not observed in patients with right TLE.[e40] In additional Class II studies, postsurgical memory outcome was related to presurgical fMRI memory lateralization (Spearman $r = 0.62$, $p < 0.03$; after Bonferroni correction for left TLE, not significant for right TLE).[e45,e46] Finally, one Class II study showed in 21 patients with left or right TLE that greater functional connectivity between the hippocampus and Brodmann area 22 (superior temporal gyrus) before surgical resection was associated with decreased verbal memory function after surgery.[e47]

Conclusion

FMRI leftward activation asymmetry during encoding of verbal material, regardless of whether measured in the MTL or in the language network, probably predicts verbal memory decline after left MTL surgery (9 Class II studies that used different methods).

Recommendation

Presurgical fMRI of verbal memory or of language encoding should be considered as an option to predict verbal memory outcome in patients with epilepsy who are undergoing evaluation for left MTL surgery (Level B).

Can fMRI predict postsurgical nonverbal (visuospatial) memory outcomes in patients with epilepsy undergoing temporal lobectomy?

One Class II study examined this issue.[e12] In this study, 68 of 72 patients had unilateral hippocampal sclerosis, making this cohort >90% medial temporal with respect to seizure onset localization.[e12] The authors of this study found that asymmetry of face recognition–related activation was the best predictor of visual-spatial decline after surgery (greater right anterior MTLE activation for encoding faces correlates with greater visual memory decline after right ATL resection: $r = 0.47$; $p = 0.02$).

Conclusion

FMRI activation asymmetry during nonverbal (scene and face recognition) memory tasks is possibly predictive of nonverbal memory decline after MTL surgery (1 Class II study).

Recommendation

Presurgical fMRI using nonverbal memory encoding may be considered as a means to predict visuospatial memory outcomes in patients with epilepsy who are undergoing evaluation for temporal lobe surgery (Level C).

Is there sufficient evidence in terms of diagnostic accuracy and outcome prediction for fMRI to replace the IAP (Wada test) in presurgical evaluation for epilepsy surgery?

The IAP is used to assess risk to language and memory functions before brain surgery. FMRI has some inherent advantages over the IAP, including lower risk, greater potential for localization of function, and lower cost. Whether fMRI is a suitable replacement for the IAP, however, depends on whether it produces results that are concordant with those from the IAP and whether it can predict cognitive outcomes as accurately as the IAP.

Language

As discussed with regard to the first question, several studies address the issue of concordance between fMRI and IAP language lateralization. Concordance is generally high although not 100% (table e-2). As discussed with regard to the second question, evidence for the ability of fMRI to predict language outcome (i.e., risk to language function from surgery) is limited to 1 Class II study and 1 Class III study.[e34,e36] Of note, data on the ability of IAP to predict language outcome also are quite limited.

Conclusions

Based on data from 1 Class II study and 1 Class III study, fMRI is possibly an effective method of lateralizing language functions in patients undergoing presurgical evaluation and may be a suitable replacement for the IAP for this purpose. Data on the ability of fMRI to predict language outcomes are limited.

Recommendation

Presurgical fMRI may be used instead of the IAP for language lateralization in patients with epilepsy who are undergoing evaluation for brain surgery (Level C). However, when fMRI is used for this purpose, task design, data analysis methods, and epilepsy type (temporal vs extratemporal, lesional vs nonlesional) need to be considered. Of particular importance for patients with lesional epilepsy is the fact that only small numbers of participants with variable lesion size/location were included in the previously discussed studies.

Memory

The memory portion of the IAP has 2 main purposes. The first objective is to assess risk of global amnesia after ATL resection, although IAP reliability for this purpose has been questioned.[e48–e51] The second objective is to predict material-specific verbal memory deficits, although several studies show that IAP has limited value for this purpose, particularly when used in combination with other, less invasive measures such as preoperative memory score, age at onset, and hippocampal volumetry.[e52–e55]

As discussed with regard to the fourth question, concordance is modest between IAP memory asymmetry and fMRI MTL activation asymmetry. Because of this low concordance rate and the limited ability of the IAP to predict postoperative verbal memory outcome, a crucial clinical question is whether fMRI can predict memory outcome better than the IAP. In the Class II study of 60 patients who had undergone left ATL surgery (as discussed with regard to the fourth question), an fMRI language LI was more strongly correlated with verbal memory change on a standardized list learning measure ($r = 0.44$; $p < 0.001$) than was the IAP memory asymmetry ($r = 0.30$; $p < 0.05$). Moreover, a multivariate prediction model that included preoperative memory score, age at seizure onset, and fMRI LI was not improved by adding IAP asymmetry scores.[e44]

Conclusion

The correlations between fMRI and IAP memory asymmetry measures are modest, and the ability of the memory IAP to predict material-specific verbal memory change is relatively weak. On the basis of 9 Class II studies, including one study that showed that fMRI of language LI is possibly more accurate in predicting material-specific verbal memory change than was the memory IAP in patients undergoing left ATL resection, fMRI may be an alternative to IAP memory testing. The ability of fMRI to predict global amnesia has not been assessed.

Recommendation

FMRI of language and verbal memory lateralization may be an alternative to IAP memory testing for prediction of verbal memory outcome in MTLE (Level C). FMRI is not yet established as an alternative to the IAP for prediction of global amnesia in patients who have undergone ATL surgery.

Clinical context

Functional MRI has been used for almost 2 decades for presurgical evaluation of patients with epilepsy and for postsurgical outcome prediction. More than 10 years ago, an editorial in *Neurology* posed the question of whether it was time to replace the IAP with fMRI.[e56] The opinion expressed in that editorial was that perhaps the medical community was ready to substitute fMRI for the language portion of the IAP but not yet ready to take the step of replacing IAP for memory localization/lateralization. Since then, several Class I–III studies have provided further support for the use of fMRI for language mapping, although several caveats are warranted.

First, the data remain somewhat limited despite almost 2 decades of research. Much of the evidence reviewed here was derived from relatively small patient samples with heterogeneous characteristics. Some studies were underpowered or susceptible to random variation. Few studies have examined the ability of fMRI to predict language outcomes. No multicenter studies have been conducted, and there is no information about generalizability of findings across centers.

Second, the evidence reviewed here leaves many critical matters unresolved. As noted earlier, the imperfect concordance between fMRI and IAP language lateralization in most studies leaves open the question of which test is more accurate in discordant cases. Although the IAP has been in use for many decades and is often considered a reference standard, it is susceptible to a number of methodologic limitations resulting from individual variation in arterial anatomy (i.e., circle of Willis), variable effects of anesthesia, rate of amobarbital or methohexital injection, variation in patient cooperation, and variation in testing methods. Evidence concerning the relative accuracy of IAP and fMRI in predicting language outcomes is limited to a single study.[e57] Another important clinical question is the extent to which the published results apply to children and adolescents, patients with varying seizure focus location or lesion types, and patients with different levels of cognitive performance or ability to cooperate with the procedure. The vast majority of the available data are from adults with TLE and minimal structural lesions. A few studies suggest less reliable results in patients with extratemporal foci and larger lesions. Several studies included adolescents and children as young as 6 years. Although results appear similar to those in adults, there are no Class I or II studies that solely address fMRI in comparison with IAP or outcomes in the younger age ranges. The reviewed studies varied across a number of methodologic features, including the strength of the magnetic field used, expertise in the techniques used for analysis of the raw data, thresholding method (if any), ROI examined, and lateralization method. The extent to which these variables affect data quality and validity is currently unknown.

Finally, the present recommendations assume that published standards are followed for conducting clinical fMRI studies. As with the IAP, cognitive fMRI is a complex diagnostic procedure that requires both advanced technical expertise in imaging and expert interaction with patients to elicit adequate levels of task performance, select a set of activation tasks appropriate to the patient's ability and the clinical aims of the study, instruct the patient on the tasks, administer the tasks during scanning, and evaluate and provide corrective feedback on task performance during the scanning session.[e58] Compliance with the activation tasks is a prerequisite for eliciting the modulation of brain activity on which fMRI depends, and therefore the validity of an fMRI test is critically dependent on task compliance. Clinicians also need to have a thorough understanding of the cognitive processes (language and nonlanguage) elicited by the tasks and be mindful of the advantages and disadvantages of particular language and baseline or contrast tasks.

Ten years ago practitioners were not ready to address the matter of replacing the memory portion of the IAP with fMRI, and the evidence with regard to memory localization and lateralization

with fMRI is still not as clear or straightforward as with the language tasks. Two Class II studies with relatively large participant samples have now shown that fMRI can predict verbal memory outcome in left ATL surgery,[e12,e44] and fMRI may be more accurate than IAP for this purpose.[e44] Some practitioners, however, depend on the IAP to assess risk for global amnesia, which has been reported after bilateral MTL damage.[e59–e61] According to this theory, anesthetization of the to-be-resected MTL is necessary to discover whether the contralateral hemisphere is healthy enough to support memory on its own. Global amnesia is rare after unilateral temporal lobe surgery, however, and occurs mainly when there is preexisting contralateral MTL dysfunction.[e48,e51,e62,e63] One possible approach, therefore, is to reserve use of the IAP memory test for those patients at greatest risk for global amnesia, that is, patients undergoing unilateral ATL resection who have structural or functional evidence of damage to the contralateral MTL.

RECOMMENDATIONS FOR FUTURE RESEARCH

There is a great need for further research in a number of areas, including the following:

- Studies comparing fMRI and IAP with regard to their ability to predict language and memory outcomes
- Studies comparing the ability of fMRI to predict language and memory outcomes in patients receiving various surgical treatments, including standard anterior temporal lobectomy, amygdalo-hippocampectomy, and laser ablation
- Studies comparing various fMRI language and memory tasks in regard to their ability to lateralize functions, their level of agreement with IAP, and their ability to predict postsurgical outcomes
- Studies comparing various fMRI analysis methods, using level of agreement with IAP and ability to predict postsurgical outcomes as standards
- Multicenter studies assessing the replicability of particular fMRI methods across centers
- Studies specifically targeting patients with extratemporal epilepsy and lesional epilepsy
- Studies specifically targeting pediatric epilepsy populations

Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN GDDI members 2015–2017

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD; (Co-Vice-Chair); Eric J. Ashman, MD; Stephen Ashwal, MD; Brian Callaghan, MD; Jane Chan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Gary S. Gronseth, MD (senior evidence-based medicine methodology expert); Jeffrey Fletcher, MD; Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Jacqueline French, MD (Guideline Process Historian)

Appendix e-3. Complete search strategy

Original & Updated Searches

Executed: May 2010; February 2015
Databases: EMBASE

fMRI Brain Surgery - EMBASE 1980 to 2010 Week 18; January 2010 to February 2015

#	Searches	Results	Search Type
	fMRI Component		
1	nuclear magnetic resonance imaging/	244105	Advanced
2	functional magnetic resonance imaging/	13127	Advanced
3	echo planar imaging/	823	Advanced
4	diffusion weighted imaging/	7286	Advanced
5	interventional magnetic resonance imaging/	295	Advanced
6	nuclear magnetic resonance spectroscopy/	34569	Advanced
7	(function* adj2 MRI).mp.	4043	Advanced
8	f-MRI.mp.	47	Advanced
9	fMRI.mp.	12159	Advanced
10	(function* adj2 MR imag*).mp.	574	Advanced
11	(magnetic resonance adj2 imag*).mp.	269276	Advanced
12	(diffusion adj2 magnetic resonance adj2 imag*).mp.	1478	Advanced
13	(echo planar adj2 imag*).mp.	2007	Advanced
14	or/1-13	303698	Advanced
	Brain Mapping Component		
15	brain mapping/	10606	Advanced
16	((brain or cortical) adj2 mapping).mp.	11058	Advanced

17	or/15-16	11058	Advanced
	Combined Results (fMRI & Brain Mapping)		
18	14 and 17	4484	Advanced
	Brain Tumor Component		
19	brain tumor/	23857	Advanced
20	brain ventricle tumor/	576	Advanced
21	choroid plexus tumor/	504	Advanced
22	choroid plexus papilloma/	500	Advanced
23	cerebellum tumor/	1210	Advanced
24	brain stem tumor/	904	Advanced
25	neuroepithelioma/	1420	Advanced
26	pineal body tumor/	1191	Advanced
27	hypothalamus tumor/ or pallister hall syndrome/	524	Advanced
28	hypophysis tumor/	4715	Advanced
29	glioma/	15553	Advanced
30	choroid plexus/	3272	Advanced
31	neuroblastoma/	13161	Advanced
32	(brain adj2 (neoplasm? or tumo?r?)).mp.	33054	Advanced
33	(brain ventricle adj2 (neoplasm? or tumo?r?)).mp.	638	Advanced
34	(choroid plexus adj2 (neoplasm? or tumo?r?)).mp.	622	Advanced
35	(choroid plexus adj2 papilloma).mp.	598	Advanced
36	((cerebellum or infratentorial) adj2 (neoplasm? or tumo?r?)).mp.	1352	Advanced
37	(brain stem adj2 (neoplasm? or tumo?r?)).mp.	1009	Advanced
38	(cerebellar adj2 (neoplasm? or umo?r?)).mp.	28	Advanced
39	((neurocystoma or neuroepithelioma) adj2 (neoplasm? or tumo?r?)).mp.	26	Advanced

40	((pinealoma or pineal body) adj2 (neoplasm? or tumo?r?)).mp.	1209	Advanced
41	(supratentorial adj2 (neoplasm? or tumo?r?)).mp.	521	Advanced
42	(hypothalam* adj2 (neoplasm? or tumo?r?)).mp.	605	Advanced
43	(pallister hall adj2 syndrome?).mp.	131	Advanced
44	((hypophysis or pituitary) adj2 (neoplasm? or tumo?r?)).mp.	7396	Advanced
45	((brain or cortical) adj2 malformation?).mp.	8161	Advanced
46	or/19-45	76983	Advanced
	Language Component		
47	language/	18104	Advanced
48	language*.tw.	46427	Advanced
49	speech/	11298	Advanced
50	speech intelligibility/	2127	Advanced
51	speech*.tw.	31306	Advanced
52	speech disorder/	7867	Advanced
53	aphasia/ or ataxic aphasia/ or conduction aphasia/ or cortical sensory aphasia/ or landau kleffner syndrome/ or primary progressive aphasia/	9144	Advanced
54	dysarthria/	4608	Advanced
55	echolalia/	202	Advanced
56	mutism/	921	Advanced
57	stuttering/	1773	Advanced
58	(aphasia* or (articulat* adj2 disorder?)).tw.	6909	Advanced
59	dysarthria?.tw.	2796	Advanced
60	echolalia?.tw.	124	Advanced
61	mutism.tw.	984	Advanced
62	stutter*.ti.	1454	Advanced

63	stutter*.tw.	1886	Advanced
64	language disability/ or agraphia/ or alexia/ or dysgraphia/ or dyslexia/ or dysphasia/	11941	Advanced
65	anomia/	601	Advanced
66	agraphia?.tw.	456	Advanced
67	alexia*.tw.	511	Advanced
68	dyslexia*.tw.	2153	Advanced
69	dysgraphia?.tw.	211	Advanced
70	dyslexia*.tw.	2153	Advanced
71	dysphasia?.tw.	759	Advanced
72	(landau kleffner adj2 syndrome?).tw.	319	Advanced
73	or/47-72	100352	Advanced
	Brain Surgery Component		
74	exp neurosurgery/	104069	Advanced
75	exp brain surgery/	23228	Advanced
76	(neurosurg* adj2 procedure?).mp.	1669	Advanced
77	(brain adj2 surger*).tw.	976	Advanced
78	or/74-77	104961	Advanced
	Combined Results (fMRI & Brain Tumour & Language & Brain Surgery)		
79	14 and 46 and 73 and 78	207	Advanced
	Combined Results (fMRI & Brain Mapping & Language & Brain Surgery)		
80	18 and 73 and 78	107	Advanced
	Memory Component		
81	exp memory/	82529	Advanced
82	deja vu/	109	Advanced
83	(memory or memories).mp.	115430	Advanced
84	deja vu.mp.	335	Advanced

85	(mental adj2 recall).mp.	28	Advanced
86	(recognition or retention).mp.	246732	Advanced
87	or/81-86	348017	Advanced
	Combined Results (fMRI & Brain Mapping & Brain Surgery & Memory)		
88	18 and 78 and 87	22	Advanced
	Combined results (fMRI & Brain Tumour & Brain Surgery & Memory)		
89	14 and 46 and 78 and 87	136	Advanced
	Combined all combined results limited to 1990- Current, human, and removed editorial, letter, note and reviews		
90	79 or 80 or 88 or 89	374	Advanced
91	exp animals/ not (exp animals/ and exp humans/)	31153	Advanced
92	90 not 91	374	Advanced
93	limit 92 to yr="1990 -Current"	374	Advanced
94	limit 93 to (editorial or letter or note or "review")	64	Advanced
95	93 not 94	310	Advanced

Original & Updated Searches

Executed: July 2010; February 2015

Databases: EMBASE

fMRI Epilepsy - EMBASE 1980 to 2010 Week 26; January 2010 to February 2015

#	Searches	Results	Search Type
	fMRI Component		
1	functional magnetic resonance imaging/	13621	Advanced
2	(function* adj2 imag*).mp.	11527	Advanced
3	(function* adj2 MR imag*).mp.	581	Advanced
4	(function* adj2 mri?).mp.	4133	Advanced

5	fmri.mp.	12459	Advanced
6	f-mri.mp.	49	Advanced
7	or/1-6	28178	Advanced
	Epilepsy Component		
8	epilepsy/	46005	Advanced
9	focal epilepsy/	8183	Advanced
10	temporal lobe epilepsy/	6729	Advanced
11	frontal lobe epilepsy/	1008	Advanced
12	rolandic epilepsy/	287	Advanced
13	traumatic epilepsy/	375	Advanced
14	epilep*.mp.	85734	Advanced
15	seizure/	50063	Advanced
16	seizur*.mp.	87588	Advanced
17	convulsion/	13924	Advanced
18	convuls*.mp.	26420	Advanced
19	"seizure, epilepsy and convulsion"/	68	Advanced
20	or/8-19	144760	Advanced
	Wada Test Component		
21	wada test/	309	Advanced
22	wada*.mp.	866	Advanced
23	amobarbital/	2080	Advanced
24	amobarbital*.mp.	2232	Advanced
25	amytal*.mp.	490	Advanced
26	neurologic examination/	24010	Advanced
27	(neurologic* adj2 examination*).mp.	28577	Advanced
28	neuropsychological test/	18026	Advanced

29	(neuropsychologic* adj2 test?).mp.	20320	Advanced
30	or/21-29	50718	Advanced
	Language Component		
31	language/	18434	Advanced
32	language disability/	6658	Advanced
33	agraphia/	462	Advanced
34	anomia/	608	Advanced
35	dyslexia/	3875	Advanced
36	alexia/	679	Advanced
37	language test/	1008	Advanced
38	(vocabulary adj2 test?).mp.	375	Advanced
39	language*.mp.	61430	Advanced
40	agraphia*.mp.	587	Advanced
41	anomia*.mp.	729	Advanced
42	dyslexia*.mp.	4057	Advanced
43	alexia*.mp.	805	Advanced
44	speech/	11461	Advanced
45	speech disorder/	8003	Advanced
46	speech analysis/	2606	Advanced
47	"speech and language assessment"/	216	Advanced
48	"speech and language"/	161	Advanced
49	speech*.mp.	47096	Advanced
50	aphasia/	7807	Advanced
51	ataxic aphasia/	867	Advanced
52	conduction aphasia/	154	Advanced
53	cortical sensory aphasia/	461	Advanced

54	primary progressive aphasia/	295	Advanced
55	progressive nonfluent aphasia/	67	Advanced
56	dysarthria/	4703	Advanced
57	echolalia/	206	Advanced
58	mutism/	925	Advanced
59	stuttering/	1782	Advanced
60	cluttering/	43	Advanced
61	dysphasia/	1077	Advanced
62	dysphonia/	3465	Advanced
63	fluency disorder/	290	Advanced
64	logorrhea/	73	Advanced
65	slurred speech/	995	Advanced
66	aphasia*.mp.	10249	Advanced
67	dysarthria*.mp.	5554	Advanced
68	echolalia*.mp.	258	Advanced
69	mutis*.mp.	1604	Advanced
70	stutter*.mp.	2138	Advanced
71	clutter*.mp.	481	Advanced
72	dysphasia*.mp.	1383	Advanced
73	dysphonia*.mp.	3920	Advanced
74	(fluency adj2 disorder?).mp.	331	Advanced
75	(articulat* adj2 disorder?).mp.	159	Advanced
76	(verbal adj2 disorder?).mp.	96	Advanced
77	logorrhea*.mp.	83	Advanced
78	slurred*.mp.	1172	Advanced
79	verbal behavior/	3977	Advanced

80	(verbal adj2 behavio?r?).mp.	4276	Advanced
81	or/31-80	117559	Advanced
	Memory Component		
82	memory/	40225	Advanced
83	short term memory/	4693	Advanced
84	recall/	9801	Advanced
85	recognition/	9518	Advanced
86	deja vu/	113	Advanced
87	(memory or memories).mp.	117635	Advanced
88	recall?.mp.	25605	Advanced
89	recognition?.mp.	164603	Advanced
90	or/82-89	283962	Advanced
91	30 or 81 or 90	420855	Advanced
	Combined Results limited to humans, 1990-Current, excluded Editorial, letter, and review		
92	7 and 20 and 91	534	Advanced
93	exp animals/ not (exp animals/ and exp humans/)	38451	Advanced
94	92 not 93	534	Advanced
95	limit 94 to (editorial or letter or "review")	134	Advanced
96	94 not 95	400	Advanced
97	limit 96 to yr="1990 -Current"	400	Advanced

Original & Updated Searches

Executed: April 2010; February 2015

Databases: Medline

fMRI Brain Surgery - 1950 to April Week 3 2010; January 2010 to February 2015

1 (function$ adj2 MRI).mp. (3928)
2 f-MRI.mp. (73)
3 fMRI.mp. (11948)
4 Magnetic Resonance Spectroscopy/ (109471)
5 limit 4 to yr="1966 - 1987" (25626)
6 (function$ adj2 MR imag$).mp. (581)
7 magnetic resonance imaging/ or diffusion magnetic resonance imaging/ or echo-planar imaging/ (212392)
8 ((magnetic resonance adj2 imag$) or (diffusion adj2 magnetic resonance adj2 imag$) or (echo-planar adj2 imag$)).mp. (238822)
9 1 or 2 or 3 or 5 or 6 or 7 or 8 (262730)
10 Brain Mapping/ (50362)
11 ((brain or cortical) adj2 mapping).mp. (50868)
12 10 or 11 (50868)
13 9 and 12 (15771)
14 brain neoplasms/ or cerebral ventricle neoplasms/ or choroid plexus neoplasms/ or papilloma, choroid plexus/ or infratentorial neoplasms/ or brain stem neoplasms/ or cerebellar neoplasms/ or neurocytoma/ or pinealoma/ or supratentorial neoplasms/ or hypothalamic neoplasms/ or pallister-hall syndrome/ or pituitary neoplasms/ (99357)
15 Glioma/ (23243)
16 limit 15 to yr="1994 - 1999" (4202)
17 choroid plexus/ (4065)
18 limit 17 to yr="1990 - 1991" (226)
19 neuroblastoma/ (20867)
20 limit 19 to yr="1990 - 1993" (2574)
21 ((brain adj2 neoplasm?) or (cerebral ventricle adj2 neoplasm?) or (choroid plexus adj2 neoplasm?) or (papilloma adj2 choroid plexus) or (infratentorial adj2 neoplasm?) or (brain stem adj2 neoplasm?) or (cerebellar adj2 neoplasm?) or neurocytoma? or pinealoma? or (supratentorial adj2 neoplasm?) or (hypothalamic adj2 neoplasm?) or (pallister hall adj2 syndrome?) or (pituitary adj2 neoplasm?)).tw. (2040)
22 ((brain adj2 tumour?) or (brain adj2 tumor?) or ((brain or cortical) adj2 malformation?)).mp. (23963)
23 14 or 16 or 18 or 20 or 21 or 22 (109952)
24 Language/ (20253)
25 language$.tw. (57226)
26 speech/ or speech acoustics/ or speech intelligibility/ (19173)
27 speech$.tw. (40130)
28 speech disorders/ or aphasia/ or aphasia, broca/ or aphasia, conduction/ or aphasia, primary progressive/ or primary progressive nonfluent aphasia/ or aphasia, wernicke/ or articulation disorders/ or dysarthria/ or echolalia/ or mutism/ or stuttering/ (22387)
29 (aphasia$ or (articulation adj2 disorder?) or dysarthria? or echolalia? or mutism or stuttering).tw. (13327)
30 language disorders/ or agraphia/ or anomia/ or dyslexia/ or dyslexia, acquired/ or alexia, pure/ or language development disorders/ (14725)
31 (agraphia? or anomia? or dyslexia? or (dyslexia adj2 acquired) or (alexia adj2 pure)).tw.

(3680)
32 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (129301)
33 exp Neurosurgical Procedures/ (122933)
34 (brain adj2 surger$).tw. (1256)
35 (neurosurgical adj2 procedure?).mp. (11803)
36 9 and 23 and 32 and 35 (70)
37 33 or 34 or 35 (124760)
38 9 and 23 and 32 and 37 (135)
39 13 and 32 and 37 (114)
40 memory/ or deja vu/ or memory, short-term/ or mental recall/ or "recognition (psychology)"/ or "retention (psychology)"/ (75451)
41 (memory or memories or deja vu or (short-term adj2 memory) or (short-term adj2 memories) or (mental adj2 recall) or recognition or retention).mp. (397726)
42 40 or 41 (397726)
43 13 and 37 and 42 (56)
44 9 and 23 and 37 and 42 (89)
45 38 or 39 or 43 or 44 (300)
46 limit 45 to (humans and yr="1990 -Current") (293)
47 limit 46 to (comment or editorial or letter or "review") (49)
48 46 not 47 (244)

Original & Updated Searches

Executed: April 2010; February 2015

Databases: Medline

fMRI Epilepsy - 1950 to April Week 3 2010; January 2010 to February 2015

1 (function$ adj2 MRI).mp. (3928)
2 f-MRI.mp. (73)
3 fMRI.mp. (11948)
4 Magnetic Resonance Spectroscopy/ (109471)
5 limit 4 to yr="1966 - 1987" (25626)
6 (function$ adj2 MR imag$).mp. (581)
7 magnetic resonance imaging/ or diffusion magnetic resonance imaging/ or echo-planar imaging/ (212392)
8 ((magnetic resonance adj2 imag$) or (diffusion adj2 magnetic resonance adj2 imag$) or (echo-planar adj2 imag$)).mp. (238822)
9 1 or 2 or 3 or 5 or 6 or 7 or 8 (262730)
10 eeg.mp. (42284)
11 electroencephalography/ (101558)
12 electroencephalogra$.mp. (106887)
13 or/10-12 (113028)
14 9 and 13 (8251)

15 epilepsy/ or epilepsies, partial/ or epilepsy, complex partial/ or epilepsy, frontal lobe/ or epilepsy, partial, motor/ or epilepsy, partial, sensory/ or epilepsy, rolandic/ or epilepsy, temporal lobe/ or epilepsy, post-traumatic/ or seizures/ (95830)
16 EPILEPSY, TRAUMATIC/ (936)
17 limit 16 to yr="1990 - 1991" (46)
18 (epileps$ or seizure$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (131025)
19 exp neurosurgical procedures/ (122933)
20 (neurosurgical adj2 procedure?).mp. (11803)
21 15 or 17 or 18 (131025)
22 (WADA adj2 test$).mp. (331)
23 (intracarotid adj2 amobarbital adj2 procedure?).mp. (152)
24 (intra-carotid adj2 amytal adj2 procedure?).mp. (1)
25 language/ (20253)
26 language$.tw. (57226)
27 speech/ or speech acoustics/ or speech intelligibility/ (19173)
28 speech$.tw. (40130)
29 speech disorders/ or aphasia/ or aphasia, broca/ or aphasia, conduction/ or aphasia, primary progressive/ or primary progressive nonfluent aphasia/ or aphasia, wernicke/ or articulation disorders/ or dysarthria/ or echolalia/ or mutism/ or stuttering/ (22387)
30 (aphasia$ or (articulation adj2 disorder?) or dysarthria? or echolalia? or mutism or stuttering).tw. (13327)
31 language disorders/ or agraphia/ or anomia/ or dyslexia/ or dyslexia, acquired/ or alexia, pure/ or language development disorders/ (14725)
32 (agraphia? or anomia? or dyslexia? or (dyslexia adj2 acquired) or (alexia adj2 pure)).tw. (3680)
33 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (129301)
34 22 or 23 or 24 (456)
35 9 and 21 and 33 and 34 (101)
36 memory/ or deja vu/ or memory, short-term/ or mental recall/ or "recognition (psychology)"/ or "retention (psychology)"/ (75451)
37 (memory or memories or deja vu or (short-term adj2 memory) or (short-term adj2 memories) or (mental adj2 recall) or recognition or retention).mp. (397726)
38 36 or 37 (397726)
39 9 and 21 and 34 and 38 (64)
40 14 and 21 and 33 (355)
41 35 or 39 or 40 (452)
42 limit 41 to (humans and yr="1990 -Current") (444)
43 limit 42 to (comment or editorial or letter or "review") (66)
44 42 not 43 (378)

Original & Updated Searches

Executed: April 2010; February 2015

Databases: Web of Science

fMRI Brain Surgery – 1990 to 2010; January 2010 to February 2015

		Combined all combined results limited to Journal Articles, 1990-2010
# 12	33	#10 OR #9 OR #8 OR #7 Refined by: [excluding] Conference Titles=(3RD INTERNATIONAL WORKSHOP ON MEDICAL IMAGING AND AUGMENTED REALITY (MIAR 2006) OR 55TH CONGRESS OF THE SOCIETE-DE-NEUROCHIRURGIE-DE-LANGUE-FRANCAISE OR XIITH MEETING OF THE WORLD SOCIETY FOR STEREOTACTIC AND FUNCTIONAL NEUROSURGERY OR 44TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-NEURORADIOLOGY) AND [excluding] Document Type=(REVIEW) Databases=SCI-EXPANDED Timespan=1990-2010
		Combined all combined results
# 11	43	#10 OR #9 OR #8 OR #7 Databases=SCI-EXPANDED Timespan=1990-2010
		Combined results (fMRI & Brain Tumour & Brain Surgery & Memory)
# 10	3	#6 AND #5 AND #2 AND #1 Databases=SCI-EXPANDED Timespan=1990-2010
		Combined Results (fMRI & Brain Mapping & Brain Surgery & Memory)
# 9	5	#6 AND #5 AND #3 AND #1 Databases=SCI-EXPANDED Timespan=1990-2010
		Combined Results (fMRI & Brain Mapping & Language & Brain Surgery)
#8	34	#5 AND #4 AND #2 AND #1 Databases=SCI-EXPANDED Timespan=1990-2010
		Combined Results (fMRI & Brain Tumour & Language & Brain Surgery)
# 7	23	#5 AND #4 AND #3 AND #1 Databases=SCI-EXPANDED Timespan=1990-2010
		Memory Component

# 6	>100,000	Topic=((memory OR memories OR deja vu OR (short-term SAME memory) OR (short-term SAME memories) OR (mental SAME recall) OR recognition OR retention)) Databases=SCI-EXPANDED Timespan=1990-2010
		Brain Surgery Component
# 5	4,4798	Topic=((brain SAME surger*) OR (neurosurgical SAME procedure?)) Databases=SCI-EXPANDED Timespan=1990-2010
		Language Component
# 4	>100,000	Topic=((aphasia* OR (articulation SAME disorder?)) OR dysarthria? OR echolalia? OR mutism OR stuttering OR agraphia? OR anomia? OR dyslexia? OR (dyslexia SAME acquired) OR (alexia SAME pure) OR speech* OR language*) Databases=SCI-EXPANDED Timespan=1990-2010
		Brain Tumour Component
# 3	29,472	Topic=((brain SAME (neoplasm? OR tumo$r?)) OR (cerebral ventricle SAME (neoplasm? OR tumo$r?)) OR (choroid plexus SAME (neoplasm? OR tumo$r?)) OR (papilloma SAME choroid plexus) OR (infratentORial SAME (neoplasm? OR tumo$r?)) OR (brain stem SAME (neoplasm? OR tumo$r?)) OR (cerebellar SAME (neoplasm? OR tumo$r?)) OR neurocytoma? OR pinealoma? OR (supratentORial SAME (neoplasm? OR tumo$r?)) OR (hypothalamic SAME (neoplasm? OR tumo$r?)) OR (pallister hall SAME syndrome?) OR (pituitary SAME (neoplasm? OR tumo$r?)) OR ((brain OR cortical) SAME malformation?)) Databases=SCI-EXPANDED Timespan=1990-2010
		Brain Mapping Component
# 2	4,459	Topic=(((brain or cortical) SAME mapping)) Databases=SCI-EXPANDED Timespan=1990-2010
		fMRI Component
# 1	>100,000	Topic=((function* SAME MRI) OR f-MRI OR fMRI OR (function* SAME MR imag*) OR (magnetic resonance SAME imag*) or (diffusion SAME magnetic resonance SAME imag*) OR (echo-planar SAME imag*)) Databases=SCI-EXPANDED Timespan=1990-2010

Original & Updated Searches

Executed: April 2010; February 2015

Databases: Web of Science

fMRI Epilepsy – 1990 to 2010; January 2010 to February 2015

Set	Results	
# 10	914	#8 AND #4 AND #3 Refined by: [excluding] Document Type=(PROCEEDINGS PAPER OR NOTE OR REVIEW OR MEETING ABSTRACT OR EDITORIAL MATERIAL) Databases=SCI-EXPANDED Timespan=1990-2010
# 9	1,185	#8 AND #4 AND #3 Databases=SCI-EXPANDED Timespan=1990-2010
# 8	>100,000	#7 OR #6 OR #5 Databases=SCI-EXPANDED Timespan=1990-2010
# 7	>100,000	Topic=(memory OR memories OR deja vu OR (mental SAME recall*) OR recognition? OR retention?) Databases=SCI-EXPANDED Timespan=1990-2010
# 6	>100,000	Topic=(language* OR agraphia* OR anomia* OR dyslexia* OR alexia* OR (vocabulary SAME test?) OR speech* OR aphasia* OR (articulat* SAME disorder?) OR (verbal SAME disorder?) OR dysarthria* OR echolalia* OR mutis* OR stutter* OR (verbal SAME behavio?r?)) Databases=SCI-EXPANDED Timespan=1990-2010
# 5	8,329	Topic=(wada* OR amobarbital* OR amytal* OR (diagnost* SAME neurologic*) OR (neuropsychologic* SAME test?)) Databases=SCI-EXPANDED Timespan=1990-2010
# 4	>100,000	Topic=(epilep* OR seizur* OR convuls*)

		Databases=SCI-EXPANDED Timespan=1990-2010
# 3	>100,000	#2 OR #1 Databases=SCI-EXPANDED Timespan=1990-2010
# 2	59,583	Topic=((echoplanar SAME imag*) OR (function* SAME imag*) OR (function* SAME MR imag*) OR (function* SAME mri?) OR fmri OR f-mri) Databases=SCI-EXPANDED Timespan=1990-2010
# 1	>100,000	Topic=((magnetic resonance SAME imag*) OR (diffusion SAME imag*) OR (diffusion SAME mri) OR (mr SAME tomograph*) OR (nmr SAME imag*) OR (echo planar SAME imag*)) Databases=SCI-EXPANDED Timespan=1990-2010

Appendix e-4. AAN rules for classification of evidence for risk of bias

Diagnostic accuracy scheme

Class I

A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II

A case-control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared with a broad spectrum of controls, or a cohort study with a broad spectrum of persons with the suspected condition where the data were collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III

A case-control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV

Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

Prognostic accuracy scheme

Class I

A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II

A case-control study of a broad spectrum of persons with the condition compared with a broad spectrum of controls, or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data were collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class III

A case-control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data were collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by

an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV

Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

Appendix e-5. Classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews and other guidance published by the American Academy of Neurology and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

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The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.[e11]

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