Functional MR Imaging or Wada Test: Which Is the Better Predictor of Individual Postoperative Memory Outcome?1

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Purpose: To retrospectively determine whether blood oxygen level–dependent functional magnetic resonance (MR) imaging can aid prediction of postoperative memory changes in epileptic patients after temporal lobe surgery.

Materials and Methods: This study was approved by the local ethics committee, and informed consent was obtained from all patients. Data were analyzed from 25 patients (12 women, 13 men; age range, 19–52 years) with refractory epilepsy in whom temporal lobe surgery was performed after they underwent preoperative functional MR imaging, the Wada test, and neuropsychological testing. The functional MR imaging protocol included three different memory tasks (24-hour delayed recognition, encoding, and immediate recognition). Individual activations were measured in medial temporal lobe (MTL) regions of both hemispheres. The prognostic accuracy of functional MR imaging for prediction of postoperative memory changes was compared with the accuracy of the Wada test and preoperative neuropsychological testing by using a backward multiple regression analysis.

Results: An equation that was based on left functional MR imaging MTL activation during delayed recognition, side of the epileptic focus, and preoperative global verbal memory score was used to correctly predict worsening of verbal memory in 90% of patients. The right functional MR imaging MTL activation did not substantially correlate with the nonverbal memory outcome, which was only predicted by using the preoperative nonverbal global score. Wada test data were not good predictors of changes in either verbal or nonverbal memory.

Conclusion: Findings suggest that functional MR imaging activation during a delayed-recognition task is a better predictor of individual postoperative verbal memory outcome than is the Wada test.

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Anterior temporal lobectomy is an effective therapy for refractory medial temporal lobe (MTL) epilepsy (MTLE) (1) but may significantly damage memory (2). Obviously, patients with refractory epilepsy who may undergo temporal lobe surgery need precise information about their postoperative memory evolution. Currently, the prediction of potential postoperative memory deficits is based on neuropsychological measures and the Wada test, a procedure involving intracarotid injection of 140 mg of amobarbital sodium (Amytal Sodium; Ranbaxy Pharmaceuticals, Jacksonville, Fla). Neuropsychological testing assumes that an impairment of verbal memory is consistently associated with resections from the left dominant temporal lobe, whereas nonverbal memory deficits have been less reliably observed after resection from the right temporal lobe and, usually, preoperative memory ability is a consistent predictor of postoperative memory decline (3–5). The Wada test has been routinely used to assess and lateralize language and memory before epilepsy surgery (6). It remains the reference standard to predict postoperative memory impairment in patients with atypical neuropsychological profiles including the following: (i) absence of significant memory deficit, (ii) both verbal and nonverbal memory deficits (ie, bilateral memory deficit) in unilateral MTLE, and (iii) atypical unilateral deficit (lateralized verbal or nonverbal memory impairment noncongruent with electroclinical and neuroimaging data, such as verbal memory deficit in a patient with right MTLE). However, the indication for and reliability of the Wada test have been questioned (7,8).

Newer, sophisticated imaging techniques, such as blood oxygen level–dependent functional magnetic resonance (MR) imaging, have raised the hope that a noninvasive method available in all MR imaging centers could replace the Wada test and help to provide accurate predictions of memory outcome. Researchers in multiple studies have assessed the utility of functional MR imaging for the replacement of the Wada language test (9–11), but to date, the replacement of the Wada memory test has proved to be more difficult (12). Investigators in previous studies have compared results from functional MR imaging and of the Wada test, with variable results. Researchers in two studies (13,14) performed in small groups of patients found good agreement between the two techniques. Investigators in three other studies (15–17) found no clear correlation between results of functional MR imaging and the Wada test. Researchers in several functional neuroimaging studies have assessed the question of memory laterality, independently of the Wada procedure, and suggest that preoperative memory assessed with functional MR imaging could be a useful noninvasive predictor of postoperative memory change following surgery (18–22). However, it remains unclear whether functional MR imaging could replace the Wada test in patients with atypical preoperative neuropsychological assessment results, which typically is when a Wada test is performed. In this study, we therefore asked whether a dedicated functional MR imaging paradigm that included various and specific memory tasks provided a better prediction of postoperative memory outcome than the Wada test in patients with atypical neuropsychological preoperative profiles. We wanted to retrospectively determine whether blood oxygen level–dependent functional MR imaging could help predict postoperative memory changes in epileptic patients after temporal lobe surgery.

Materials and Methods

This retrospective study was approved by the local ethics committee, in agreement with the Declaration of Helsinki. Informed written consent was obtained from all patients.

Patients

The study population included 23 nonconsecutive MTLE patients (12 women, 13 men; mean age, 41 years ± 9 [standard deviation]; range, 19–52 years). These men (mean age, 43 years ± 4.7; range, 34–50) and women (mean age, 38 years ± 11; range, 19–52 years) underwent surgery in Salpêtrière Epileptology Unit, Paris, France, between January 1, 2002, and December 31, 2006. Fourteen patients had right MTLE, and 11 had left MTLE. Twenty-three patients exhibited MTL lesions.
ipsilateral to the seizure focus (mostly unilateral hippocampal sclerosis), one patient had bilateral lesions, and one patient had no lesions. Clinical and MR imaging data are reported in Appendix E1 in Table E1 (online).

Inclusion criteria were the following: (a) a well-explored unilateral MTLE (an extracranial video electroencephalogram and structural MR imaging were performed in all cases, an intracranial electroencephalogram was performed in five cases, subtraction ictal SPECT (single photon emission computed tomography) coregistered to MR imaging, or SISCOM, and/or positron emission tomography was performed in five cases), (b) preoperative neuropsychological assessment (Full Scale IQ test, digit span test, verbal memory test [Marilyn Jones-Gotman Verbal Learning Test] and/or Rey Auditory Verbal Learning Test) and nonverbal tests (Rey-Taylor Complex Figure test and/or Aggie Figure Learning test), and (c) an atypical preoperative neuropsychological profile requiring a Wada test. During the study period, 115 patients underwent surgery without the Wada test and thus were not included in this study. The exclusion criterion was a contraindication for functional MR imaging.

Pre- and postoperative neuropsychological testing 6 months after surgery were performed by one author (M.D., with 10 years of experience in neuropsychological testing). A preoperative neuropsychological evaluation was performed in all patients (Table E2 [online]). Results of the preoperative and postoperative memory tests in 24 patients are included in Table E3 (online).

We (S.D., S.S.) calculated pre- and postoperative verbal and nonverbal memory scores for the correlations with functional MR imaging and Wada test results (Table E3 [online]). Postoperative changes in verbal and nonverbal memory were expressed as the difference between post- and preoperative verbal and nonverbal scores. A significant postoperative change in memory was arbitrarily defined as ≥ 10% (Table E3 [online]).

**Wada Test Procedure**

After insertion of a catheter into the internal carotid artery by a neuroradiologist with 5 years experience, 140 mg of amobarbital sodium was injected first ipsilaterally to the suspected seizure focus, with continuous electroencephalographic monitoring.

Testing proceeded in three stages: (a) at baseline, during the drug effect, and after the effects of drugs had dissipated (23); (b) at assessment of hemispheric language dominance by using the presence of language disturbances (S.S., with 20 years of experience in the performance of Wada tests, V.N., and M.D.); and (c) at assessment of hemispheric memory dominance by presenting the patient with 24 different items (eight at baseline, eight during the drug effect, and eight during the stage after effects of the drug had dissipated) by three authors (S.S., V.N., M.D.). All 24 objects were later shown as a yes-no recognition test, so that errors in recognition of the eight objects presented during the drug effect could be measured.

**Functional MR Imaging Protocol**

Blood oxygen level–dependent functional MR imaging data were acquired with a 1.5-T system (GE Healthcare, Milwaukee, Wis) by two authors (C.D., E.V.) by using the standard quadrature head coil. Subjects were placed in a supine position in the MR imager. Their heads were immobilized with cushions and tape to reduce motion artifacts. The stimuli were projected onto a mirror located at the end of the imager bore. For each subject, a series of conventional structural three-dimensional T1-weighted MR images was first collected to provide detailed anatomic information. Following this acquisition, gradient-echo echo-planar functional MR imaging was performed by using 20 contiguous 5-mm axial sections (repetition time, 3 seconds; matrix, 64 × 80; field of view, 22 × 22 cm²) covering the whole brain. The entire session, including both structural and functional acquisitions, lasted 45 minutes.

**Functional MR Imaging Memory Tasks Procedures**

Memory tasks included episodic memory encoding and recognition tasks. Patients were tested on 2 consecutive days to create two recognition conditions that differed in relation to the delay of recognition: immediate recognition or 24-hour delayed recognition (24) (S.D., with 10 years of experience performing functional MR imaging). For each session, a sequential task-activation block paradigm was used, with alternation of an experimental condition and a control condition (Fig 1). Session 1 was performed outside the imager.

Session 1.—The task consisted of three blocks of 12 stimuli repeated over the three blocks, alternating with four blocks of 12 control stimuli. Stimuli consisted of color photographs of simple objects, such as fruit, flowers, or animals, which may be encoded by both verbal and nonverbal strategies. Control stimuli were obtained by degrading study stimuli with a random-rectiling algorithm (Photoshop 6.0; Adobe, San Jose, Calif). Patients were explicitly instructed to try to remember the studied stimuli for a later test.

After a delay of 60 seconds, patients were presented with 24 stimuli consisting of 12 unlearned stimuli and the 12 previously learned stimuli, displayed in blocks of eight stimuli (four unlearned and four study stimuli) alternating with four blocks of eight control stimuli. They were asked to respond by pressing a button: They were to press the right button when they recognized the stimulus and to push the left button when they did not. A button was also pressed during the control condition to control for motor and response preparation activation.

Session 2.—The following day, subjects began the functional MR imaging session by using a 24-hour delayed recognition of stimuli encountered the previous day, followed by new encoding and immediate-recognition tasks.

**Data Analysis**

Data analysis was performed by using analytic software (Matlab 6.1; Math-Works, Natick, Mass) and a statistical parametric mapping software package (SPM 99; Wellcome Department of Cognitive Neurology, London, England) (25). For each subject, we reoriented the images along the bicommissural line. Images were then coregistered and resliced to correct for head movements.
movement and were further spatially normalized to standard stereotactic Montreal Neurological Institute coordinates to correct for anatomic variance across subjects. Analysis of the translation and rotation movements across the images showed that these movements were similar for control subjects and patients. The resulting images were then convolved with a three-dimensional 5-mm Gaussian filter. The data were then analyzed statistically on a voxel-by-voxel basis by using a two- or four-dimensional basis functions model. We performed an individual analysis for each subject. Voxels were considered to be significantly activated in comparison with the reference task at \( P < .01 \), uncorrected for multiple comparisons.

This individual analysis focused on MTL activations (hippocampus proper and parahippocampal cortices [Brodmann areas 27, 28, and 34–36]). We did not perform a group analysis of our functional MR imaging activation data because side and type of lesions were not sufficiently homogeneous across the group.

**Comparison between the Wada Test and the Functional MR Imaging MTL Activations**

**Wada test lateralization.**—A lateralization index (LI) was calculated from Wada test data by dividing the difference in the number of correct memory test scores between the left and the right hemispheres by the maximal possible score (ie, eight), as previously described (17). The resulting Wada LI ranged from 1.0 (100% correct memory performance by using the left hemisphere and 0% correct memory performance by using the right hemisphere) to \(-1.0\) (100% correct memory performance by using the right hemisphere and 0% correct memory performance by using the left hemisphere).

**Functional MR imaging lateralization.**—We considered the number of activated voxels within a region of interest, including the left and right hippocampal and parahippocampal regions. Two activation measures were considered: (i) LI was calculated as the difference between the number of activated voxels in the left and right MTLs, divided by the sum of voxels in the left and right MTLs, as previously described (13–15). The functional MR imaging LI ranged between 1 and \(-1\), representing exclusive left MTL activation and exclusive right MTL activation, respectively. We calculated functional MR imaging LI for each individual memory condition and for all combinations of all memory conditions to determine the association that best correlated with the Wada test or postoperative outcome. (ii) The absolute number of activated voxels in left and right hippocampal regions.

**Statistical Analysis**

Statistical analysis was performed by two of the authors (S.D., Y.S.). A backward multiple regression was performed by using dedicated software (MedCalc 9.0.1.1; MedCalc Software, Mariakerke, Belgium) with the following variables: (a) The dependent variable was the post-versus preoperative verbal memory evolution. (b) Independent variables included clinical variables, such as age at functional MR imaging, duration of epilepsy, side of epileptic focus, and number of antiepileptic drugs; neuropsychological variables such as preoperative verbal and nonverbal memory scores and the Full Scale IQ test results; Wada LI; and functional MR imaging LI and absolute number of activated voxels.

Regression analysis (stepwise entry with \( P < .05 \) and \( .1 \) to exit) was used to determine which variables influenced postoperative memory outcome and build a model that could help correctly predict the patient’s postoperative memory outcome. A receiver operating characteristic (ROC) curve analysis was then performed to analyze the sensitivity and specificity of this model for the prediction of significant postoperative decline (worsening group) versus no change or a postoperative improvement.

A second model without functional MR imaging data was also built to assess how much additional information was garnered by using the functional MR imaging examination. An ROC curve analysis was also performed for this model and was compared with the ROC curve of the initial model with functional MR imaging data.

**Results**

**Functional MR Imaging Results**

**Memory tasks eliciting MTL activations.**—All patients exhibited hippocampal or parahippocampal activations during at least one of the memory tasks (Fig 2). Patients could exhibit MTL activations during one, two, or three tasks: The task that elicited the most activations was the delayed-recognition task (19 patients), followed by the immediate-recognition task (17 patients) and the encoding task (15 patients).

**Lateralization of the MTL global activations.**—MTL global activations over the three tasks were strictly unilateral in six patients, contralateral to the seizure focus in four patients, and ipsilateral to the seizure focus in two patients. Most patients \( n = 19 \) exhibited bilateral MTL activations.
The evolution of verbal and nonverbal memory scores according to the lateralizations of MTL activations is described in Table E3 (online).

**Wada Test Results**

In 19 patients, with the Wada test, memory was lateralized either strictly to the side contralateral to the seizure focus (one left temporal lobe epilepsy) or bilaterally but predominantly to the contralateral side (five left temporal lobe epilepsy, 13 right temporal lobe epilepsy). In six patients, the Wada test results were inconclusive, with no errors on stimuli presented during the two injections.

The evolution of verbal and nonverbal memory according to the lateralization provided by the Wada test is described in Table E3 (online).

**Comparison between Functional MR Imaging and the Wada Test**

Only 48% (12) of 25 patients had concordant functional MR imaging and Wada LI, on the basis of the global functional MR imaging LI calculated by using the association of the three memory conditions (Table E4 [online]). The concordance did not improve significantly when the memory conditions were separated. There was no correlation between functional MR imaging LI (individual tasks or global) and Wada LI (correlation coefficient, 0.152; \( P = .47 \)).

**Comparison with the Neuropsychological Postoperative Memory Outcome**

Postoperative verbal memory changes.—The post-versus preoperative evolution of verbal memory scores correlated with left functional MR imaging activation during delayed recognition (\( P = .009 \)), with the side of the epileptic focus (\( P = .036 \)) and the preoperative verbal memory score (\( P < .001 \)).

**Postoperative nonverbal memory changes.**—The post- versus preoperative evolution scores were only significantly correlated with the preoperative nonverbal score (\( P < .023 \)).

**Individual prediction of postoperative worsening.**—The regression analysis produced the following solution: \( VM_{\text{post}} = 7.62 + 7.23 \cdot \text{LDR} - 5.65 \cdot S - 0.38 \cdot VM_{\text{pre}} \), where \( VM_{\text{pre}} \) is postoperative verbal memory evolution, \( VM_{\text{pre}} \) is preoperative verbal memory evolution, \( \text{LDR} \) is left delayed recognition, and \( S \) is side. Including an \( S \cdot \text{LDR} \) interaction term in this final model produced no significant change in the results.

The estimated probabilities from this model (including left functional MR imaging activation during delayed recognition, side of the epileptic focus, and preoperative verbal score) provided an accurate determination of the evolution of verbal memory in 19 (79%) of 24 patients with postoperative neuropsychological impairment: (a) In nine (90%) of 10 patients who experienced a worsening of their verbal memory, the prediction of a risk of worsening was correct. (b) In 10 (83%) of 12 patients with no significant worsening or an improvement of verbal memory, the profiles were predicted to be stable. (c) In one (50%) of two patients who exhibited an improvement of verbal memory, the prediction of improvement was correct.

By using the ROC curve analysis, the specificity to predict a postoperative verbal memory change was 92.9% and the sensitivity was 90%, for a cutoff value of 14.13 (Fig 3). The area underneath the ROC was 0.943 (95% confidence limits: 0.766, 0.993; \( P < .001 \)). In comparison, the best model without functional MR imaging data only retained preoperative memory testing and had a significant lower area underneath the ROC of 0.721 (95% confidence limits: 0.5, 0.88; \( P = .009 \)).

**Discussion**

Epileptic patients who are candidates for surgery usually ask two questions: Will the surgery cure my epilepsy? Will I have aftereffects following surgery? The data presented in the current study may help improve our capacity to provide accurate information on probable postoperative memory evolution to patients who will undergo surgery. Although effects on seizure outcome may be excellent, there remains a high degree of variability in postoperative memory function (26). Here, we have shown that the combination of left functional MR imaging MTL activation during delayed recognition, side of the epileptic focus, and preoperative memory verbal score could help to correctly predict the occurrence of verbal memory worsening in 90% of patients. Furthermore, the prognostic accuracy of functional MR imaging to aid in prediction of postoperative memory changes was better than that of the Wada test.

The predictive value of lateralized MTL activations in temporal lobe epilepsy remains a debated subject. Interpretations of most reported functional neuroimaging studies have been divided between the hippocampal reserve and the functional adequacy theories (27). According to the hippocampal reserve theory, memory function will decline if the reserve capacity of the contralateral hippocampus is insufficient to support memory after surgery. In contrast, the functional adequacy hypothesis suggests that a postoperative decline in memory is, rather, inversely proportional to the effectiveness of the resected tissue. This adequacy model is a good convergence of data from multiple measures.
of both neurobehavioral function (baseline neuropsychological test scores and the procedure involving contralateral intracarotid artery injection of amobarbital sodium [Wada test] pertinent to the surgical hemisphere) and structure (hippocampal cell densities and MR imaging volumes). In fact, a recent study performed by Powell et al (28) showed that reorganization of the undamaged MTL was an inefficient process, incapable of preserving memory function. Functional studies in patients with stroke suggest that recruitment of contralateral structures cannot necessarily maintain performance (29) and also that recovery related to activation of an opposite hemisphere was associated with a poor recovery (30). Similarly, our study demonstrates that verbal memory is better subserved and predicted by the degree of left MTL activation. This datum therefore agrees with the functional hypothesis and suggests that the contralateral hippocampal reserve is poorly related to postoperative changes in verbal memory.

In this study, only the delayed-recognition task appeared to be pertinent for prediction of verbal memory outcome. This finding is supported by neuropsychological data on hippocampal consolidation. We have already shown in MTLE patients that activation of MTL regions was most reliably initiated by memory delayed-recognition tasks (24,31). This finding is supported by the growing body of data suggesting that sleep is involved in the consolidation of episodic memory. Experimental and imaging data suggest that sleep states contribute to the effectiveness of memory processing and facilitate memory retrieval in wakefulness (32,33). In addition, successful recollection of emotional stimuli elicits larger hippocampal activations in healthy volunteers after a full night of sleep than in subjects subjected to complete sleep deprivation (34).

The direct correlation between the Wada test and functional MR imaging was not conclusive when subjects were considered individually. This may be explained by methodological aspects. The Wada test is an inactivation test, thought to mimic the effect of surgical resection, and is based on performance failure during brain inactivation, whereas functional MR imaging is a test of activation, showing a cerebral network activated during a memory task.

The use of the Wada procedure has been debated recently (35), because it is an invasive procedure and several severe complications, such as carotid dissection or arterial spasm, have been reported. Furthermore, the validity of the test itself has been questioned (7), with the recognition of test failures (cases of patients who failed the memory Wada test but who underwent surgery without postoperative memory worsening) and false-negative cases (cases of patients who succeeded Wada test but exhibited significant memory deficits after temporal lobe surgery). The results of the present study confirm that the reliability of the Wada test may sometimes be uncertain. The only patient who experienced a bilateral memory impairment after surgery had positive results of the Wada test, but in this patient, the prediction was for high-risk verbal memory worsening by using functional MR imaging. Our data suggest that functional MR imaging may have a better prognostic accuracy than the Wada test for changes in memory function.

Our study had limitations. Postoperative verbal memory outcome was quite accurately predicted by using the combination of left functional MR imaging activation during delayed recognition, side of the epileptic focus, and preoperative verbal memory score. However, we failed to find any correlation between postoperative nonverbal memory outcome and right functional MR imaging activation during delayed recognition. Several factors could be involved: (i) our patient sample was small (the sample sizes were dependent on the number of subjects who had to undergo a Wada test; because the indications for the Wada test are limited for ethical reasons to those patients who have an atypical neuropsychological profile, we were not able to increase the sample size), (ii) patients' neuropsychological profiles were atypical, and (iii) the postoperative changes tested were limited to those involving verbal memory, except in one patient who exhibited bilateral memory impairment. Another limitation of the study is that estimates of accuracy, sensitivity, and specificity were derived from the same sample from which the model was created and, therefore, are clearly overestimations of these measures in the generalized population. We, thus, need to repeat the study in a new population for a true assessment of accuracy, sensitivity, and specificity.

All these limitations led us to plan systematic functional MR imaging studies in future TLE patients to validate our findings and to ask whether functional MR imaging may also help to predict nonverbal memory outcome after surgery.
In conclusion, functional MR imaging represents a useful and noninvasive technique to assess memory before surgery when neuropsychological test results are not conclusive and to accurately predict the postoperative verbal memory outcome. Combining left functional MR imaging activation during delayed recognition, side of the epileptic focus, and preoperative verbal memory score may help to predict exact verbal memory evolution after surgery, especially a postoperative worsening. These data are preliminary and need to be further verified in a larger sample.

References