Radiology

Lateralized Anterior Mesiotemporal Lobe Activation: Semirandom Functional MR Imaging Encoding Paradigm in Patients with Temporal Lobe Epilepsy—Initial Experience[1]

Karel Deblaere, MD
Walter H. Backes, MSc, PhD
Ann Tieleman, MD
Pieter Vandemaele, MSc
Luc Defreyne, MD
Kristl Vonck, MD, PhD
Paul Hofman, MD, PhD
Peter Boon, MSc, PhD
Jan Vermeulen, MSc, PhD
Jan Wilmink, MD, PhD
Albert Aldenkamp, MSc, PhD
Paul A. J. M. Boon, MD, PhD
Guy Vingerhoets, MSc, PhD
Eric Achten, MD, PhD

Published online
10.1148/radiol.2363040780
Radiology 2005; 236:996–1003

Abbreviations:
IAP = intracarotid amobarbital procedure
LI = lateralization index
MTL = mesiotemporal lobe
TLE = temporal lobe epilepsy

From the Depts of Neuroradiology (K.D., A.T., P.V., E.A.), Interventional Radiology (L.D.), and Neurology (K.V., P.A.J.M.B.), and Laboratory for Neuropsychology (G.V.), Ghent Univ Hosp, MR Dept 1 K12, De Pintelaan 185, 9000 Ghent, Belgium; Depts of Neuroradiology (W.H.B., P.H., J.W.) and Medical Psychology (P.B.), Maastricht Univ Hosp, Maastricht, the Netherlands; Kempenhaeghe Epilepsy Ctr, Heese, the Netherlands (J.V., A.A.); and Psychological Laboratory, S.E.I.N. Heemstede, the Netherlands (J.V.). Received Apr 30, 2004; revision requested Jul 12; revision received Oct 7; accepted Nov 5. Supported by grant 99-02 from the National Epilepsy Foundation of the Netherlands. K.D. supported by grant from Ghent University. **Address correspondence to** K.D. (e-mail: *karel.deblaere@ugent.be*).

Authors stated no financial relationship to disclose.

Author contributions:
Guarantor of integrity of entire study, K.D.; study concepts and design, K.D., W.H.B., A.T., P.V., K.V., P.H., P.B., J.V., J.W., A.A., P.A.J.M.B., G.V., E.A.; literature research, K.D., W.H.B.; clinical and experimental studies, K.D.; data acquisition, K.D., L.D., P.A.J.M.B., K.V., A.T.; data analysis/interpretation, K.D., W.H.B.; statistical analysis, K.D., W.H.B.; manuscript preparation and definition of intellectual content, K.D., W.H.B.; manuscript editing, K.D.; manuscript revision/review and final version approval, K.D., W.H.B., A.T., P.V., K.V., P.H., P.B., J.V., J.W., A.A., P.A.J.M.B., G.V., E.A.

PURPOSE: To prospectively demonstrate anterior mesiotemporal lobe (MTL) activation in healthy volunteers by using a semirandom memory-encoding paradigm and to prospectively compare lateralized functional magnetic resonance (MR) imaging activation with intracarotid amobarbital procedure (IAP) memory test results in patients with temporal lobe epilepsy (TLE) who were scheduled to undergo surgery.

MATERIALS AND METHODS: The study was approved by a local ethics committee, and written informed consent was obtained from all subjects. Eight healthy volunteers and 18 patients with TLE who were scheduled for surgery were included in the functional MR imaging study involving the use of a memory-encoding paradigm with variable epoch lengths. Subjects were instructed to memorize new pictures that were mixed among pictures that they had seen before. Data analysis entailed computations of the contrast between the MTL activation induced by the new pictures and the MTL activation induced by the old pictures and of the lateralization index, defined as the relative difference in the number of activated voxels between the left and right MTLs. Lateralization indexes were compared between the patients and the volunteers and statistically correlated with the patients' IAP memory test results. To study deviations from perfect correspondence between the functional MR imaging– and IAP-derived lateralization indexes, orthogonal regression analysis was applied. Proportional relations for the patients with left-sided TLE and for those with right-sided TLE were calculated separately.

RESULTS: The memory paradigm consistently activated the posterior and anterior MTL structures in both the healthy volunteers and the patients. Regression analysis revealed that functional MR imaging activation was stronger than the IAP results when it was lateralized to the contralateral MTL. This analysis also revealed a significant ($P < .001$) correlation between the functional MR imaging results and the IAP results in the patients with right-sided TLE but not in those with left-sided TLE ($P > .1$).

CONCLUSION: The functional MR imaging memory-encoding paradigm consistently yielded MTL activation in the volunteers and the patients with TLE, but lateralized functional MR imaging activation was in concordance with the IAP results in only those patients with right-sided TLE.

As many as 30% of patients with localization-related (ie, partial) temporal lobe epilepsy (TLE) have little or no seizure relief after anticonvulsant therapy. A surgical procedure known as anterior temporal lobectomy is an alternative therapy for these patients. During this intervention, the anterior temporal pole, anterior hippocampus, and part of the parahippocampal gyrus are resected, as they are usually involved in the generation of epileptiform activity. Thanks to careful candidate selection and thorough presurgical evaluation, 80%–90% of patients who undergo anterior temporal lobectomy become seizure free (1).

The results of multiple brain lesion and neuropsychologic studies have demonstrated that mesiotemporal lobe (MTL) activity is essential to memory formation (2,3). Presurgical evaluation of the memory function of the contralateral MTL is therefore necessary to avoid postsurgical amnesia. The current reference standard for such an evaluation is the intracarotid amobarbital procedure (IAP), or Wada test (4). This test was originally developed for the assessment of hemispheric language dominance in the presurgical evaluation of patients with TLE who were being considered for anterior temporal lobectomy. Later, the procedure was adapted for the presurgical evaluation of memory function of both MTL structures in patients with TLE (5).

Functional magnetic resonance (MR) imaging has been suggested many times as a possible noninvasive alternative for assessment of both the language-dominant hemisphere and memory redundancy in the contralateral MTL. The successful use of functional MR imaging in determining language dominance has been demonstrated in numerous studies during the past decade (6–10). Only a limited number of studies (11–13) addressing the assessment of memory function in patients with TLE have been published, however. Most studies, which have involved the use of classic block-related designs, have generally revealed more posterior MTL activation (11,14) in individual subjects. The more anterior MTL activations—particularly the hippocampal activations—have so far been reported as group-averaged results, especially when event-related designs were used (15). This does not mean that no individual anterior activation was found, but group averaging eliminates the variability in individual results. Developing a paradigm that consistently demonstrates memory-related activation in the anterior regions of the MTL would be an improvement because the paradigm would depict the activation in areas that *(a)* are more likely to be deactivated during the IAP and *(b)* are resected during anterior temporal lobectomy.

Event-related functional MR imaging examinations are generally considered to be more specifically focused on the brain processes of interest (ie, not only those processes that are constantly active during a task, which can also be demonstrated with a block design, but also those processes that are only active at the initiation of the task or that are sensitive to habituation). The drawback of event-related designs is that they are less powerful than block-designed approaches (16). The application of an event-related design for reliable anterior MTL activation would require very long imaging sequences that would render this approach not clinically applicable. Liu et al (16) suggested using a semirandom paradigm design to combine the accuracy of an event-related paradigm with the signal sensitivity of a block design. Moritz et al (17) applied such a design in the examination of five healthy subjects and observed anterior MTL activation in all of them.

With consideration of the above factors, the aims of the current study were to prospectively demonstrate anterior MTL activation in healthy volunteers by using a semirandomly designed memory-encoding paradigm and to prospectively compare the lateralization of functional MR imaging activation with the IAP memory test results for individual patients with TLE who were scheduled for surgery.

MATERIALS AND METHODS

Study Subjects

Eight healthy volunteers aged 23–47 years (mean, 28 years ± 7 [standard deviation]) served as control subjects in this study. Three volunteers were men aged 27–47 years (mean, 33 years), and five were women aged 23–28 years (mean, 25 years). These subjects were selected from an existing list of individuals who volunteered to participate in functional MR imaging experiments according to their availability at the time of imaging. Most of the subjects on this list were academic staff members, students, or hospital personnel, and none of them reported having a history of neurologic disorders or contraindications to MR imaging.

The number of patients to be included in this study was estimated by performing a power analysis with consideration of an expected positive correlation between the lateralization index (LI) derived at functional MR imaging and the LI derived at the IAP. Without any prior quantitative information, we assumed a correlation coefficient *(r)* of 0.7 to be feasible and considered *r* values of up to 0.5 to still be relevant. By using a confidence interval of 95%, a statistical power of 80%, and the Fisher *z* transformation of the correlation coefficient, one can estimate the sample size for the total number of patients with epilepsy to be at least 12.

Eighteen consecutive patients with TLE aged 13–55 years (mean, 38 ± 12) who were undergoing presurgical evaluation for anterior temporal lobectomy were prospectively selected to undergo the functional MR imaging experiment following the IAP within a period of 15 months (August 2002 to November 2003). Ten patients were male (mean age, 38 years; age range, 23–54 years), and eight were female (mean age, 33 years; age range, 13–55 years). No significant differences in age ($P > .05$) or sex ($P > .4$) between the volunteers and the patients were observed (independent samples *t* test). Seven patients had left-sided and nine had right-sided TLE, as determined at a comprehensive preoperative assessment that included continuous electroencephalographic video recording, dedicated MR imaging, and neuropsychologic testing. The side of the seizure focus in the remaining two patients (patients 6 and 8) suspected of having TLE was undetermined before the IAP and functional MR imaging; it was determined after the IAP and functional MR imaging with depth-recording electroencephalography. This study was approved by the local ethics committee of Ghent University Hospital. Written informed consent was obtained from all subjects.

IAP Protocol

All patients underwent bilateral diagnostic internal carotid angiography before the IAP and were found to have normal cerebral vasculature. Within 5 seconds after undergoing diagnostic angiography, the patients were manually injected with amobarbital (Sodium Amytal; Certa, Braine L'Alleud, Belgium) at a dose of 2 mg per kilogram of body weight. Diagnostic angiography and amobarbital injection were performed by a radiologist (L.D.) with 15 years of experience in performing this procedure. The side ipsilateral to the side of the suspected seizure focus was injected first. Immediately afterward, the patient experienced contralateral hemiparesis and hemianopia. The drug's effectiveness was determined on the basis of the patient's contralateral grip strength, as assessed by a neurologist (K.V.). Another neurologist (P.A.J.M.B., with 15 years of experience performing IAPs) assessed the hemispheric language dominance on the basis of the presence or absence of paraphasia and speech arrest, naming task capability, and comprehension of simple aural commands.

A neurologist (P.A.J.M.B.) assessed hemispheric memory performance by presenting each patient with 11 items: three written one-syllable words, two written two-syllable words, two line drawings of simple objects, three line drawings of action scenes, and one abstract item. Two sets of similar items were used, one for each side of the suspected seizure focus. During the IAP, special care was taken to present the test items within the visual hemifield that was not impaired. Twelve minutes after the injection, when the effect of the amobarbital had worn off, the patient was given a recognition task. The 11 previously presented items, as well as three distracters with each item, were shown again. The patient was judged to have passed the IAP memory test on the injected side (ie, for assessment of the noninjected side) if he or she could recognize at least seven of the 11 items out of a multiple-choice series of items (1,18). Guessing was not encouraged. In each patient, the functional MR imaging examination was performed exactly 2 days after the IAP.

Functional MR Imaging Paradigm

The patient and volunteer subjects viewed five images in the picture set of Snodgrass and Vanderwart (19) while they were outside of the MR imaging unit, approximately 15 minutes before the start of the MR imaging examination. At the start of the examination, during anatomic MR imaging, the subjects viewed the five pictures 25 times, each for 3 seconds. Two MR imaging examinations were performed while the subjects viewed variable-length epochs of new pictures (new condition) that were mixed among variable-length epochs of five pictures that they had seen before (old condition). The epoch length of the new condition varied between one and six picture stimuli. The stimuli were semirandomly mixed into two runs of 180 stimuli each. A total of 120 new pictures were shown in the new condition. Every 2.6 seconds, a picture was shown and the subjects had to decide whether it was old or new—that is, they pushed either the "OLD" or the "NEW" button. Their decisions (ie, correct hits, nonhits, and errors) and reaction times (ie, times to response) were automatically recorded.

MR Imaging Protocol

All subjects were imaged with a 1.5-T MR imaging system (Symphony Quantum Magnet; Siemens, Erlangen, Germany) by using a standard head coil. For anatomic reference, first a T1-weighted imaging sequence—three-dimensional magnetization-prepared rapid gradient echo—was performed with the following parameters: 11/3.5 (repetition time msec/echo time msec), a 90° flip angle, a 256 × 256 matrix, 128 contiguous sagittal sections, and a voxel size of 0.9 × 0.9 × 1.3 mm. The coronal sections were positioned orthogonal to the long axis of the hippocampus on these sagittal T1-weighted images. For functional MR imaging, a single-shot multisection T2*-weighted echo-planar sequence of 360 imaging volumes was subsequently performed twice with the following parameters: 50/1.3, 90° flip angle, a voxel size of 3 × 3 × 6 mm, a 64 × 64 matrix, and 13 coronal contiguous sections per volume. The total acquisition time for functional MR imaging was 15 minutes 6 seconds.

Data Collection and Statistical Analyses

Preprocessing.—The SPM99 software package (Wellcome Department of Cognitive Neurology, London, England; *www.fil.ion.ucl.ac.uk/spm*) was used for the first part of the data processing. The functional MR images were coregistered to the three-dimensional anatomic MR image and subsequently motion corrected by using rigid-body transformations and sinc interpolation. The high-spatial-resolution three-dimensional T1-weighted MR image obtained in each subject was normalized into the three-dimensional space by using the pertaining Montreal Neurological Institute image template embedded in the SPM99 software. The normalization parameters were then applied to the previously coregistered echo-planar images. The resultant functional MR images had a voxel size of 2 × 2 × 2 mm and were spatially smoothed with a 12 × 12 × 12-mm Gaussian kernel. The normalized time series was low-pass filtered in the time domain by using the hemodynamic response function.

Activation analysis.—With use of the general linear model approach (20), two regressors were created for the new and old conditions. These regressors modeled the hemodynamic brain response to each stimulus as an event. Partial derivatives for time and dispersion were added as additional regressors to allow corrections for slight differences in onset time and hemodynamic response width. The activation contrast, "new condition greater than old condition," was calculated in terms of the number of voxels in a region of interest in the MTL. The activation contrast is the difference in blood oxygen level–dependent response between the new and the old visual stimuli. It has been previously demonstrated that the hippocampus and related structures participate in novelty encoding; therefore, we calculated the contrast between the new stimuli and the previously learned stimuli (21,22). The region of interest included the hippocampus, the parahippocampus, and the part of the fusiform gyrus along the full length of the hippocampus. The region of interest was manually drawn on images of the averaged normalized brain of the healthy volunteers (by K.D.), and the volume of the region of interest in one MTL was 48 cm^3.

The statistical significance of the activation contrast was expressed in terms of statistical z and corresponding P values. Individual statistical thresholds for the patients were set at a z score of greater than 2.0 or a P value of less than .025 (uncorrected for multiple comparisons). The number of significantly ($z > 2.0$) activated voxels was counted for the left and right MTL regions. The LI at functional MR imaging was calculated as the difference between the number of activated voxels in the left MTL and the number of activated voxels in the right MTL, divided by the sum of voxels in the left and right MTLs. The functional MR imaging LI was calculated for a range of threshold values between 0.5 and 2.5 and ranged between +1 and −1, which represent exclusive left MTL activation and exclusive right MTL activation, respectively.

Functional MR imaging lateralization.—Functional MR imaging LIs ($P < .002$) for the right-sided TLE and left-sided TLE patient groups were averaged and statistically (with one-tailed Student t test) compared with zero. For the control subjects, the functional MR imaging LI was considered to represent bilateral activation when the value was not significantly different from zero. The functional MR imaging LI in the right-sided TLE group was considered to indicate dominant left-hemisphere MTL activation when the related functional MR imaging LI was sig-

Radiology

nificantly positive. Similarly, the functional MR imaging LI in the left-sided TLE group was considered to indicate dominant right-hemisphere MTL activation when the related functional MR imaging LI was significantly negative. In addition, the absolute LIs were statistically compared between the two patient groups (with two-tailed Student *t* test) to reveal possible asymmetric activation in the MTL. The difference was considered to be significant at $P < .05$. Individual subjects were considered to have lateralized MTL activation when their functional MR imaging LI deviated more than two times the standard deviation from the mean functional MR imaging LI for the control group.

IAP lateralization.—The LI at the IAP was calculated by dividing the difference in the number of correct memory test scores between the left and right hemispheres by the sum of these scores. The IAP LI can vary between +1 and −1, which represent a score of 0 for the right and left hemispheres, respectively. These indexes were calculated only to compare functional MR imaging with the IAP. In the clinical environment, the score for only the contralateral MTL is used. A score of 7 (indicating seven of 11 items were correctly recognized) is considered the minimum score needed to pass the test and indicates that surgery could be performed. The separate and summed scores for the ipsilateral and contralateral hemispheres were statistically compared between the patients with left-sided TLE and those with right-sided TLE by using the Wilcoxon rank sum test.

Functional MR imaging versus the IAP.—Finally, the relationship between the LIs obtained at functional MR imaging and those obtained at the IAP was statistically analyzed. With the assumption that the IAP results would be reproduced at functional MR imaging, the LI data points for both functional MR imaging and the IAP would lie scattered around the diagonal line through the origin with a slope of 1 (ie, the identity relation) on a plot of functional MR imaging LI versus IAP LI. To study the possible deviations from perfect correspondence between the functional MR imaging– and IAP-derived LIs, we performed an orthogonal regression analysis in which the proportional relationship (ie, ratio) between the functional MR imaging and IAP LIs was estimated (23,24). By using orthogonal regression analysis, one can assess the inaccuracies in both functional MR imaging LIs and IAP LIs and minimize the orthogonal distances between the data points (functional MR imaging LI, IAP LI) and the regression line through the origin. The proportional relationships in the left-sided TLE and right-sided TLE patient groups were calculated separately. In addition, for both patient groups, we calculated the orthogonal squared distance between the data points and the identity relation to quantify the deviation from perfect concordance between both evaluation methods.

Typically, one would expect a high IAP score and strong functional MR imaging activation in the contralateral side. The IAP LI and the functional MR imaging LI were therefore expected to be influenced mainly by the results for the ipsilateral side. To this end, graphs depicting the functional MR imaging LI as a function of the IAP memory score for the ipsilateral hemisphere were constructed for both patient groups. To identify possible deviations from this way of reasoning, we constructed a statistical contingency table in which the number of patients in the right-sided TLE group who passed the IAP test (ie, correctly recognized at least seven items) and the number of patients in the left-sided TLE group who passed the test were counted separately at evaluation of the ipsilateral side. This analysis was conducted with a cutoff value of 7 (ie, our clinical practice). Statistical analyses were performed by using the Fisher exact test (25), and significance was inferred when the *P* value was less than .05.

TABLE 1
Patient Characteristics and IAP Memory Results

Patient No./Sex/Age (y)	Total Intelligence Quotient	Focus Side*	IAP Score, Left	IAP Score, Right	IAP LI	Functional MR Imaging LI
1/F/35	84	L	ND	10	ND	0.00
2/F/35	85	L	7	10	−0.27	−1.00
3/M/29	89	L	11	10	0.09	−0.96
4/M/42	80	R	8	7	0.09	0.44
5/M/40	82	L	9	8	0.09	−0.81
6/M/39	112	R	9	5	0.36	0.91
7/F/55	94	R	9	3	0.55	0.87
8/M/50	97	L	8	10	−0.18	−0.45
9/M/23	107	R	11	6	0.45	0.34
10/M/48	88	R	11	7	0.36	−0.04
11/F/13	83	R	11	11	0.00	0.33
12/F/42	60	R	11	7	0.36	0.39
13/F/46	50	R	10	6	0.25	0.46
14/F/20	122	R	10	5	0.33	0.32
15/F/51	112	R	8	0	1.00	0.29
16/M/25	99	L	11	7	0.22	0.00
17/M/32	50	L	0	9	−1.00	−0.17
18/M/54	108	L	11	11	0.00	−0.62

Note.—All except four patients had sclerosis. In patients 6 and 8, no structural abnormalities were found, and the side of the seizure focus was determined after the IAP and functional MR imaging with depth-recording electroencephalography. Patient 7 had an MTL cystic lesion with gliosis. Patient 16 had a lesion in the amygdala. ND = not determined.
* L = left, R = right.

RESULTS

IAP Memory Testing

The patients' characteristics and IAP results are listed in Table 1. In one patient (patient 1), only the ipsilateral side (ie, the side of the seizure focus) was evaluated and a passing IAP score for the contralateral MTL (ie, the healthy side) was observed. After patient 18 was injected with amobarbital on the left side, there was only minimal loss of manual grip strength; hence, the IAP score for the right side, which was the contralateral side in this patient, was not fully reliable. In the remaining 16 patients, both sides were assessed. Seven of these 16 patients failed the IAP memory test for the side of the seizure focus, and the remaining nine passed the test for both sides. The mean IAP LIs for the patients with right-sided TLE and those with left-sided TLE were 0.38 ± 0.27 (standard deviation) and −0.15 ± 0.41, respectively. These results indicate that the right-sided TLE group exhibited significantly ($P < .001$) positive IAP LIs, while the left-sided group did not show significantly ($P > .2$) lateralized IAP LIs. No significant differences in contralateral ($P > .6$) or summed ($P > .19$) IAP scores between the right-sided TLE

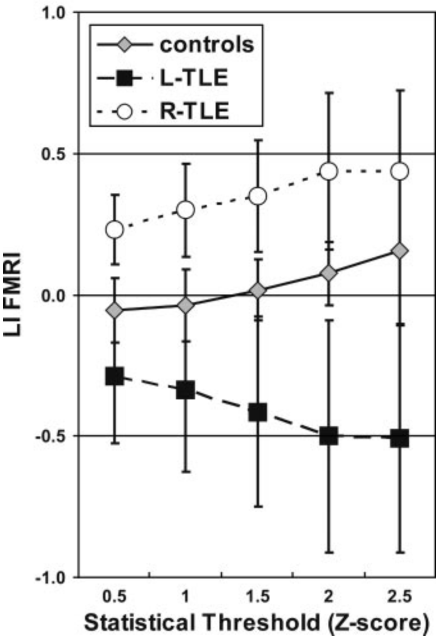

Figure 1. Graph of means and standard deviations of LIs for the healthy volunteers, the patients with right-sided TLE *(R-TLE),* and the patients with left-sided TLE *(L-TLE),* derived across a range of statistical thresholds (ie, *z* scores). Note that the mean LI for the healthy volunteers stays around zero, whereas the mean LI for the patient groups increases with increasing statistical threshold. *FMRI* = functional MR imaging.

and left-sided TLE patient groups were observed. The median score for the ipsilateral hemisphere was three points higher, with the scores in the right-sided TLE group being borderline significantly (P = .05) higher than those in the left-sided TLE group.

Functional MR imaging

A bilateral distribution of the activation foci across all threshold values, with increasing standard deviation toward higher thresholds, was observed in the control group (Fig 1). The mean functional MR imaging LI for the control group was 0.08 ± 0.11 at the $P < .025$ threshold; this value does not deviate significantly from zero and therefore indicates a bilateral activation pattern. Individual patients with TLE were considered to have lateralized MTL activation when the functional MR imaging LI was higher than 0.29 (indicating left MTL dominance) or lower than −0.14 (indicating right MTL dominance).

All control subjects exhibited bilateral posterior and anterior MTL activation. The activated areas included the hippocampus, parahippocampus, and fusiform gyrus. Additional whole-brain analysis revealed activated areas in the thalamus and the lateral temporal neocortical areas also. The same activation foci were observed in the patients, albeit more lateralized to the healthy hemisphere. The graph in Figure 1 depicts the functional MR imaging LIs obtained in not only the control subjects but also the left-sided and right-sided TLE patient groups. The control subjects had bilateral LIs, whereas the patients with right-sided TLE had left-lateralized (ie, positive) functional MR imaging LIs and the patients with left-sided TLE had right-lateralized (ie, negative) functional MR imaging LIs at all used thresholds.

Fifteen of the 18 patients, including the two patients in whom the side of the seizure focus was undetermined at the time of functional MR imaging, had lateralized functional MR imaging results (ie, functional MR imaging LI more than 2 standard deviations from the mean LI for the control subjects) that favored the contralateral MTL. The other three patients (patients 1, 10, and 16) had a bilateral activation pattern. The mean functional MR imaging LIs for the right-sided and left-sided TLE patient groups were 0.43 ± 0.28 and −0.57 ± 0.39, respectively. The right-sided TLE group had significantly (P = .004) left-lateralized (ie, positive) functional MR imaging LIs, whereas the left-sided TLE group had significantly (P = .004) right-lateralized (ie, negative) functional MR imaging LIs. The activation foci in the MTLs of two representative patients and two representative control subjects are shown in Figure 2.

The behavioral data recorded during the functional MR imaging measurements were group averaged (Table 2). Owing to technical problems, the data of one control subject and one patient were lost to further analysis. Multivariate analysis revealed no significant correlations between the groups (control subjects and patients) and the behavioral data (ie, numbers of hits [$P > .7$], errors [$P > .1$], and reaction times [$P > .9$]); these results indicate that group type had no significant effect on the behavioral data. The "NEW" button was pushed a mean of 102 msec later (±77) ($P < .001$, paired t test) than was the "OLD" button.

Functional MR Imaging versus IAP

Of the 15 patients who had lateralized MTL activation, seven (patients 6, 7, 9, 13, 14, 15, and 17) had ipsilateral memory failure at the IAP, two (patients 2 and 12) had a near-passing ipsilateral IAP score with a high contralateral score, three (patients 4, 5, and 8) had intermediate but symmetric scores, and three (patients 3, 10, and 18) had high scores bilaterally. Of the three patients with nonlateralized functional MR imaging results, two (patients 10 and 16) had a near-passing IAP score on the ipsilateral side, whereas in the other patient (patient 1), the IAP was not performed on the ipsilateral side.

The relationships between the functional MR imaging LIs and the IAP LIs observed at orthogonal regression analyses in both patient groups indicated that the mean slopes for the right-sided and left-sided TLE patient groups were 1.16 ± 0.06 and 5.7 ± 4.5, respectively (Fig 3). Statistical analysis revealed a significant ($P < .001$) relationship between the functional MR imaging and IAP results in the patients with right-sided TLE but not in those with left-sided TLE ($P > .1$). The mean orthogonal squared distance (d^2) between the data points and the identity line (ie, line indicating that the functional MR imaging LI equaled the IAP LI) in Figure 3 was four times larger (P = .006) for the patients with left-sided TLE (d^2 = 0.13) than for the patients with right-sided TLE (d^2 = 0.034).

Comparison of the ipsilateral IAP memory test scores revealed that when the cutoff score was set at 7, which is the value used in the clinical environment, six of 10 patients with right-sided TLE and only one of seven patients with left-sided TLE failed to pass the ipsilateral IAP memory test (Fig 4). However, Fisher exact testing revealed that with a cutoff score of 7, there were no significant ($P >$ .1) differences between the left-sided and right-sided TLE patient groups in terms of the number of patients who passed the test for the ipsilateral side.

DISCUSSION

In this study, it was demonstrated that the lateralized brain activation measured with functional MR imaging can be demonstrated by using a semirandom memory-encoding paradigm. To our knowledge, our study is the first in which the investigators reported the results of a functional MR imaging examination by using a semirandom memory-encoding paradigm in patients with TLE. Patients with right-sided TLE and those with left-sided TLE generally exhibit a functional MR imaging activation pattern in the MTL that lateralizes to the contralateral hemisphere stronger than the IAP result. It turns out that this lateralization is in agreement with IAP results in only those patients with right-sided TLE. On the contrary, in patients with left-sided TLE, the ipsilateral (ie, epileptic) MTL region is still able to mediate memory function during the IAP, while functional MR imaging yields an activation pattern that is lateralized to the contralateral hemisphere.

Correlations between Functional MR Imaging and IAP Results

In the current study, the patients with TLE, as compared with the healthy volunteers, generally had asymmetric MTL activation during novelty encoding favoring the contralateral side. This finding is consistent with the published results of Detre et al (11) and Golby et al (12), who also used encoding paradigms to evaluate memory function. Using a complex scene-encoding task in a classic block design in 10 patients with TLE, Detre et al observed activation asymmetry in posterior MTL regions in accordance with the IAP results of nine patients. Although the observed activation in individual patients was in the posterior MTL regions only, good correlation between the functional MR imaging and IAP results was reported.

Activation of the anterior MTL region was demonstrated when the functional MR imaging results were group averaged. This finding suggests that the task itself activates the anterior MTL to a level that is not detectable in individual subjects. Several suggestions to explain the failed detection of activation in the anterior MTL are reported. These suggestions include a lack of sensitivity of the blood oxygen level–dependent effect and field inhomogeneity disturbances in the MTL region. Our opinion is that block-designed encoding paradigms do not challenge the MTL as adequately as does the design that was used in this study. In a block design paradigm, subjects can anticipate a new block of stimuli, and this anticipation may reduce their attention and probably their memory-related MTL activity. Using a semirandom novelty encoding paradigm, we were able to reliably detect anterior MTL activation in every healthy volunteer and every patient (on the side contralateral to the epileptic focus).

Using the same stimuli that were used in this study, we previously reported symmetric MTL activation in healthy volunteers who underwent an overt picture-naming task (14). This bilateral memory-related activation was explained by the high visual input and the novelty component of the experimental task and by the fact that visual encoding also takes place during naming tasks, regardless of whether the subject is or is not instructed to memorize the items.

Dually (ie, visually and verbally) en-

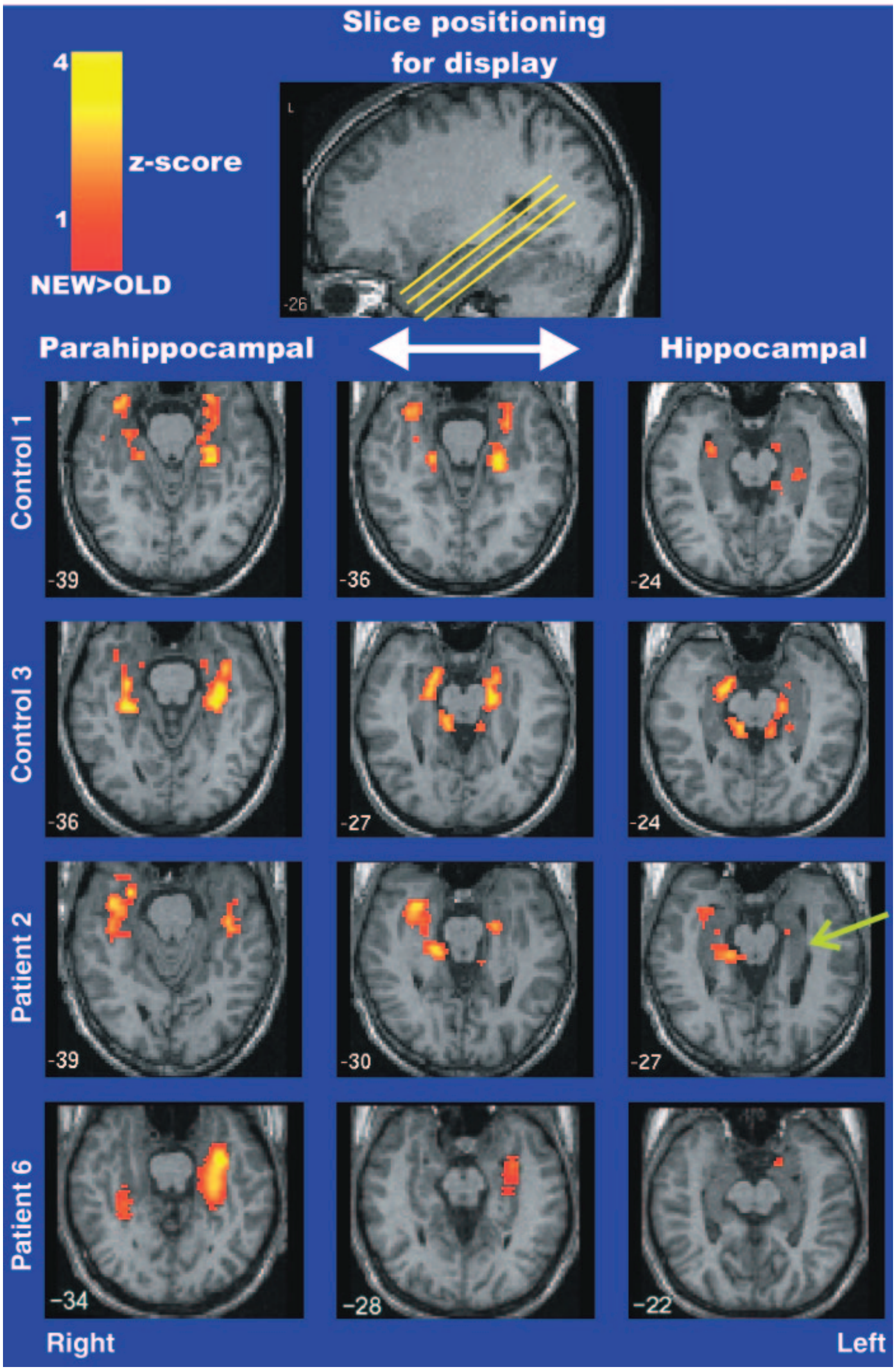

Figure 2. Activation patterns ($P < .025$, uncorrected) derived from a time series of T2*-weighted MR images (1300/50, 90° flip angle, voxel size of 3 × 3 × 6 mm, 64 × 64 matrix) of the MTL are displayed on a T1-weighted three-dimensional magnetization-prepared rapid gradient-echo MR image (11/3.5, voxel size of 0.9 × 0.9 × 1.3) obtained in control subjects 1 and 3 and patients 2 and 6. The plane of view is illustrated in the top right image. Note the bilateral distribution of activated foci in the MTL region in the healthy subjects. Patient 2 has right-lateralized activation in the MTL region; also note the left MTL sclerosis (arrow) in this patient. Patient 6 has left-lateralized activation; depth-recording electroencephalography revealed an onset of seizures in the right MTL region.

TABLE 2
Behavioral Data for Patients and Control Subjects

Subject Group	Correct Hits (%)	Nonhits (%)	Errors (%)	RT (msec)	RT, New (msec)	RT, Old (msec)
Control subjects (*n* = 7)	98.5 ± 1.3	0.6 ± 0.6	1.0 ± 1.0	985 ± 193	947 ± 189	1030 ± 192
Patients (*n* = 17)	96.44 ± 4.8	1.6 ± 2.2	2.0 ± 3.0	1006 ± 157	950 ± 132	1063 ± 171

Note.—Data are means ± standard deviations. RT = reaction time—that is, the time from seeing the picture to deciding whether it was old or new and pushing the corresponding button.

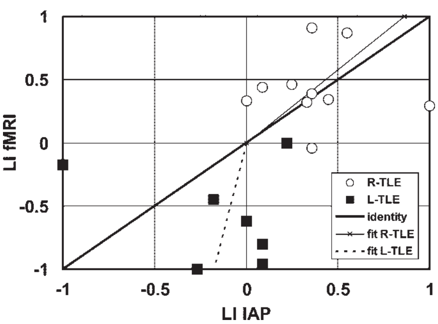

Figure 3. Graph depicts LIs derived at functional MR imaging *(fMRI)* and IAP measurements in all patients. The identity relation—that is, the relation when the functional MR imaging LI equals the IAP LI—is represented by the thick line through the origin with a slope of 1. The calculated lines derived at orthogonal regression analysis for the right-sided TLE *(R-TLE)* and the left-sided TLE *(L-TLE)* patient groups are indicated by the thin and hatched lines, respectively. Note that the functional MR imaging LIs are highly correlated with the IAP LIs in the patients with right-sided TLE, whereas the correlation between functional MR imaging LI and IAP LI is much smaller in the patients with left-sided TLE.

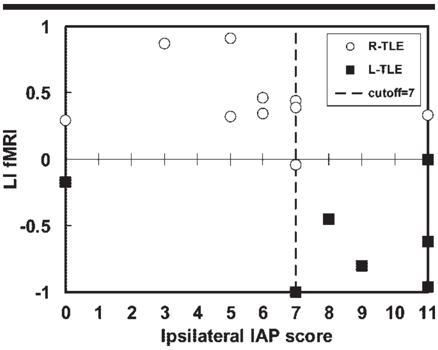

Figure 4. LIs derived at functional MR imaging *(fMRI)* plotted as a function of the IAP memory score for the ipsilateral (ie, epileptic) hemisphere. The vertical line represents the cutoff score, which is set at 7 (ie, seven of 11 items recognized), the minimal score for which the patient's hemisphere is considered to have passed the IAP memory test. Note the generally high scores for the patients with left-sided TLE *(L-TLE)* as compared with the broad range of scores for the patients with right-sided TLE *(R-TLE)*.

codable items, such as those of Snodgrass and Vanderwart (19), were used because this kind of material typically activates bilateral MTL regions and enables the detection of asymmetries (11,26). Golby et al (12,27) added stimuli that typically engage the left or right MTL (for verbal or nonverbal memory, respectively). They examined material-specific novelty encoding in healthy volunteers (27) and in nine patients with TLE (12) by using four kinds of stimuli: patterns, faces, scenes, and words. In eight of nine patients with TLE, the memory encoding–related activation measured by using functional MR imaging lateralization was concordant with the IAP results. Consistent with the concept of reorganization of memory function to the contralateral medial temporal region, the group results indicated right MTL activation for word encoding in the patients with left-sided TLE and left MTL activation for nonverbal encoding tasks in the patients with right-sided TLE.

Procedural Differences

Because IAP and functional MR imaging are two essentially different evaluation methods, differences in the results can be expected. The IAP involves attempts to mimic the effects of a future lesion, whereas functional MR imaging yields information about the natural situation before surgery. In general, we observed good correlation between functional MR imaging and IAP data when the lateralizations observed with the two methods were compared (11–13). Significant correlations between the functional MR imaging LIs and the IAP LIs were observed, but further exploration of the data revealed that this was true only for those patients who had right-sided TLE. The functional MR imaging results were clearly more lateralized in favor of the contralateral side than were the IAP results. Moreover, the correlation between functional MR imaging and the IAP in terms of memory lateralization in the patients with left-sided TLE was not significant because there seemed to be an overestimation of the memory capabilities on the ipsilateral (ie, epileptic) side. One explanation for this discordance in the patients with left-sided TLE might be the difference between the two procedures that was described earlier.

The supposed power of the ipsilateral IAP lies in the simulation of the unilateral resection, which gives one an idea of the extent of possible anterograde amnesia when memory redundancy in the contralateral MTL is absent. However, using the same procedure to assess memory function on the epileptic side—at least from a theoretic point of view—is not similarly effective. The contralateral IAP forces the epileptic side to work on its own and thus places demands on this brain structure that probably reflect an overestimation of its memory function compared with the memory function in the natural situation. This theory may explain why stronger lateralization results were found with functional MR imaging than with the IAP. This theory does not, however, explain why there were good correlations between functional MR imaging and IAP in the patients with right-sided TLE but not in those with left-sided TLE since the theory applies to results on both sides.

In typical cases, we would expect a high IAP memory test score for the contralateral side; this means that the lateralization of memory results with the IAP is most influenced by the score for the ipsilateral side. There was no difference in the contralateral IAP score; this means that the patients with lesions on the left side did not have more cognitive problems than the patients with lesions on the right side at testing of the contralateral hemisphere. However, the finding that the ipsilateral (ie, left) MTL yielded a somewhat higher IAP score in the patients with left-sided TLE than in the patients with right-sided TLE is consistent with the idea that the left MTL is biased toward verbal processing. Results of statistical analysis of the relationship between the side of the epileptic focus and the ipsilateral IAP memory test score (Fig 4) indicated that patients with left-sided TLE tend to rely on left MTL function more heavily than patients with right-sided TLE rely on right MTL function.

In our opinion, the stimulus items used in the IAP are clearly more verbally oriented than the material used in the functional MR imaging paradigm. When the items presented in the IAP are studied in greater detail, this imbalance becomes clear: The five words used are preferentially verbally encodable, the line drawings of objects and scenes are both verbally and nonverbally encodable, and the single abstract item is the only stimulus that is not verbally encodable. Another indication of this theory is that six of the seven patients who failed the IAP on the ipsilateral side had right-sided TLE. Although the theory that IAP materials are more verbally oriented needs to be confirmed in studies involving larger patient groups, these findings are worth considering when comparing the observed results.

Killgore et al (28) correlated the functional MR imaging and IAP results obtained in the Detre et al (11) study with seizure relief after surgery. In general, asymmetric MTL activation favoring the contralateral hemisphere was associated with a seizure-free status at 1-year follow-up. This means that 15 of the 18 patients in our present study would be considered to have a good prognosis, whereas in three patients (patients 1, 10, and 16), postoperative seizure relief could not be assured. However, Killgore et al concluded that functional MR imaging combined with the IAP yielded complementary data that enabled improved predictions of postoperative seizure control compared with the predictions made by using either procedure alone (28). The preliminary results of Casasanto et al (29) suggest that postsurgical amnesia correlates with functional MR imaging activation of the ipsilateral MTL and thus that functional MR imaging has a promising complementary role in the presurgical evaluation of patients with TLE. In general, one can expect a better outcome for patients with a high LI favoring the contralateral side.

This study was limited by the small number of patients, especially when the left-sided and right-sided TLE patient groups were compared. The results of this investigation need to be confirmed in a study with a larger patient group. In this study, we compared the functional MR imaging and IAP results only, but the results of both modalities need to be correlated with the outcomes of patients in terms of seizure relief after surgery and possible memory loss.

In conclusion, a memory-encoding paradigm that consistently yielded bilateral MTL activation in healthy volunteers and asymmetric activation in patients with TLE was applied by using functional MR imaging. Lateralization of functional MR imaging activation was in concordance with the IAP results in the patients with right-sided TLE but not in those with left-sided TLE. The disagreement between the functional MR imaging and IAP results in the patients with left-sided TLE indicates the dominant role of the left MTL for verbally encodable items and the intrinsic differences in brain conditions during functional MR imaging and IAP evaluation. In the future, it might be feasible—for at least a portion of patients with TLE—to replace the invasive IAP with noninvasive functional MR imaging for the presurgical evaluation of cerebral memory function.

References

1. Boon P, Vandekerckhove T, Achten E, et al. Epilepsy surgery in Belgium, the experience in Gent. Acta Neurol Belg 1999;99:256–265.
2. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions: 1957. J Neuropsychiatry Clin Neurosci 2000;12:103–113.
3. Bookheimer SY. Functional MRI applications in clinical epilepsy. Neuroimage 1996; 4(3 pt 3):S139–S146.
4. Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralisation of cerebral speech dominance: experimental and clinical observations. J Neurosurg 1960;17:226–282.
5. Milner B, Branch C, Rasmussen T. Study of short-term memory after intracarotid injection of sodium amytal. Trans Am Neurol Assoc 1962;8:224–226.
6. Desmond JE, Sum JM, Wagner AD, et al. Functional MRI measurement of language lateralization in Wada-tested patients. Brain 1995; 118(pt 6):1411–1419.
7. Binder JR, Swanson SJ, Hammeke TA, et al. Determination of language dominance using functional MRI: a comparison with the Wada test. Neurology 1996;46:978–984.
8. Worthington C, Vincent DJ, Bryant AE, et al. Comparison of functional magnetic resonance imaging for language localization and intracarotid speech amytal testing in presurgical evaluation for intractable epilepsy: preliminary results. Stereotact Funct Neurosurg 1997;69:197–201.
9. Benbadis SR, Binder JR, Swanson SJ, et al. Is speech arrest during Wada testing a valid method for determining hemispheric representation of language? Brain Lang 1998;65: 441–446.
10. Lehericy S, Cohen L, Bazin B, et al. Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. Neurology 2000;54:1625–1633.
11. Detre JA, Maccotta L, King D, et al. Functional MRI lateralization of memory in temporal lobe epilepsy. Neurology 1998;50:926–932.
12. Golby AJ, Poldrack RA, Illes J, Chen D, Desmond JE, Gabrieli JD. Memory lateralization in medial temporal lobe epilepsy assessed by functional MRI. Epilepsia 2002;43:855–863.
13. Jokeit H, Okujava M, Woermann FG. Memory fMRI lateralizes temporal lobe epilepsy. Neurology 2001;57:1786–1793.
14. Deblaere K, Backes WH, Hofman P, et al. Developing a comprehensive presurgical functional MRI protocol for patients with intractable temporal lobe epilepsy: a pilot study. Neuroradiology 2002;44:667–673.
15. Constable RT, Carpentier A, Pugh K, Westerveld M, Oszunar Y, Spencer DD. Investigation of the human hippocampal formation using a randomized event-related paradigm and Z-shimmed functional MRI. Neuroimage 2000;12:55–62.
16. Liu TT, Frank LR, Wong EC, Buxton RB. Detection power, estimation efficiency, and predictability in event-related fMRI. Neuroimage 2001;13:759–773.
17. Moritz CH, Johnson SJ, Meyerand ME. Variable-length block memory encoding paradigm demonstrates individual subject hippocampal fMRI response (abstr). In: Proceedings of the 10th Meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine, 2002.
18. Blume WT, Grabow JD, Darley FL, Aronson AE. Intracarotid amobarbital test of language and memory before temporal lobectomy for seizure control. Neurology 1973;23:812–819.
19. Snodgrass JG, Vanderwart M. A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. J Exp Psychol [Hum Learn] 1980;6:174–215.
20. Friston KJ, Holmes AP, Poline JB, et al. Analysis of fMRI time-series revisited. Neuroimage 1995;2:45–53.
21. Stern CE, Corkin S, Gonzalez RG, et al. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci U S A 1996;93:8660–8665.
22. Jessen F, Manka C, Scheef L, Granath DO, Schild HH, Heun R. Novelty detection and repetition suppression in a passive picture viewing task: a possible approach for the evaluation of neuropsychiatric disorders. Hum Brain Mapp 2002;17:230–236.
23. Zar JH. Simple linear regression, inverse prediction. In: Biostatistical analysis. 3rd ed. London, England: Prentice-Hall, 2000; 335–337.
24. Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Modeling of data. In: Numerical recipes in C: the art of scientific computing. 2nd ed. Cambridge, England: Cambridge University Press, 1996; 666–667.
25. Weiger M, Pruessmann KP, Osterbauer R, Bornert P, Boesiger P, Jezzard P. Sensitivity-encoded single-shot spiral imaging for reduced susceptibility artifacts in BOLD fMRI. Magn Reson Med 2002;48:860–866.
26. Binder JR, Achten E, Constable RT, et al. Functional MRI in epilepsy. Epilepsia 2002; 43(suppl):51–63.
27. Golby AJ, Poldrack RA, Brewer JB, et al. Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding. Brain 2001;124:1841–1854.
28. Killgore WD, Glosser G, Casasanto DJ, French JA, Alsop DC, Detre JA. Functional MRI and the Wada test provide complementary information for predicting post-operative seizure control. Seizure 1999;8:450–455.
29. Casasanto DJ, Glosser G, Killgore WDS, et al. Presurgical fMRI predicts memory outcome following anterior temporal lobectomy (abstr). J Int Neuropscychol Soc 2001; 183.