Seizure 1999; **8**: 450–455
Article No. seiz.1999.0339, available online at http://www.idealibrary.com on IDEAL

Functional MRI and the Wada test provide complementary information for predicting post-operative seizure control

WILLIAM D. S. KILLGORE[*], GUILA GLOSSER[*], DANIEL J. CASASANTO[*], JACQUELINE A. FRENCH[*], DAVID C. ALSOP[†] & JOHN A. DETRE[*†]

[*] *Department of Neurology, University of Pennsylvania Medical Center;* [†] *Department of Radiology, University of Pennsylvania Medical Center*

Correspondence to: Dr. William D. S. Killgore, Brain Imaging Center, McLean Hospital, 115 Mill Street, Belmont, MA 02478-9106, USA

Prediction of post-surgical seizure relief and potential cognitive deficits secondary to anterior temporal lobectomy (ATL) are important to pre-surgical planning. Although the intracarotid amobarbital test (IAT) is predictive of post-ATL seizure outcome, development of non-invasive and more precise means for determining post-ATL seizure relief are needed. We previously reported on a technique utilizing functional MRI (fMRI) to evaluate the relative functional adequacy of mesial temporal lobe structures in preparation for ATL[1]. In the present study, we report follow-up outcome data on eight temporal lobe epilepsy (TLE) patients 1-year post-ATL who were evaluated pre-surgically using IAT and fMRI. Functional memory lateralization using fMRI predicted post-ATL seizure outcome as effectively as the IAT. In general, asymmetry of functional mTL activation favouring the non-epileptic hemisphere was associated with seizure-free status at 1-year follow-up. Moreover, when combined, fMRI and IAT provided complementary data that resulted in improved prediction of post-operative seizure control compared with either procedure alone.

Key words: FMRI; IAT; seizures; outcome; neuroimaging; Wada test.

INTRODUCTION

Despite a wide range of available anticonvulsant medications that are effective in controlling epileptic seizures, as many as 25–30% of patients with partial epilepsy may never experience complete seizure relief[2]. A relatively common and effective treatment for many patients with medically refractory complex partial epilepsy involves unilateral resection of the anterior hippocampus and portions of the parahippocampal gyrus, a procedure known as anterior temporal lobectomy (ATL)[3–5]. Whereas approximately 68% of patients who undergo ATL will achieve complete seizure relief, nearly one-third may continue to have at least some continued seizure activity post-surgically, and a very small minority may show little, if any, meaningful improvement[3]. Furthermore, the process of ATL candidacy and treatment represents a substantial investment of time and resources for both the patient and medical establishment. To ensure the best chance of treatment success and the most effective utilization of finite medical resources, it is important to identify those surgical candidates who are most likely to benefit from ATL.

Successful ATL is associated with the extent of hippocampal resection and the absence of functional tissue within the resected region[6,7]. Because successful ATL correlates with resection of dysfunctional tissue while sparing intact brain regions, pre-surgical techniques that localize the seizure focus and identify damaged tissue can improve the selection of candidates who are likely to achieve complete post-operative seizure control. Although specific protocols differ among epilepsy centres, pre-surgical evaluation often includes data from a number of sources including electroencephalography (EEG), single photon emission tomography (SPECT), positron emission tomography (PET) structural magnetic resonance

imaging (MRI), intracarotid amobarbital testing (IAT), and neuropsychological assessment[3, 7–9]. These techniques are useful for predicting post-ATL seizure relief to the extent that a discrete region of focal dysfunction and epileptogenesis can be localized. Because structures within the mesial temporal lobe (mTL) including the hippocampus and surrounding subcortical regions are common sites of epileptogenesis, techniques that measure the functional adequacy of these structures are capable of identifying dysfunctional mTL tissue[10, 11]. The functional adequacy of the mTL can be indirectly assessed through performance on cognitive tasks because these structures are critical for the formation and encoding of new memories[12, 13]. The intracarotid sodium amytal test (IAT), which selectively inactivates the anterior regions of a single hemisphere via unilateral injection of a short-acting anaesthetic, can serve as a controlled 'temporary lesion' to evaluate the functional adequacy of brain structures that are involved in long-term memory formation, including the hippocampus and surrounding tissue[10, 11, 14, 15]. Such assessment is important because resection of healthy mTL tissue may produce memory deficits post-ATL without cessation of seizure activity, whereas removal of damaged tissue may leave memory capacities unaffected, while significantly reducing the likelihood of future seizures[16]. Because functional memory performance mirrors underlying hippocampal integrity, functional deficits identified by the IAT have successfully predicted post-operative seizure control following removal of diseased tissue[6, 7, 17, 18].

While the IAT has remained the 'gold standard' for evaluating the functional integrity of mTL structures in preparation for ATL, newly emerging technologies, such as PET and functional MRI (fMRI) hold the promise of providing less invasive methods of assessment with potentially higher spatial resolution for detecting functional deficits. Asymmetries in functional activation within the mTL using event-related potentials (ERPs), SPECT[19, 20], and PET[21–23] also appear to be predictive of post-operative seizure control. In comparison with PET, however, the newly emerging technology of fMRI may provide a more widely available and potentially more cost-effective method of measuring functional brain activity. Recently, fMRI techniques reliably demonstrated asymmetrical mTL activation patterns during memory encoding in patients with temporal lobe epilepsy (TLE)[1, 24]. Moreover, these fMRI asymmetries accurately discriminated the side of epileptic focus[24] and were lateralized in the same direction as IAT performance[1].

As a potential measure of functional adequacy of the mTL, fMRI asymmetries during encoding should show similar capabilities for predicting post-operative seizure control as other functional assessment techniques. In an earlier study[1], we implemented a nonverbal scenic encoding task that produced robust bilateral mTL activation within healthy normal subjects during fMRI, but which showed asymmetrical activation consistent with IAT memory performance in a sample of 10 ATL surgery candidates. For the present study, we report follow-up data on the same cohort of patients from our earlier study, now 1-year post-ATL. We examined whether asymmetry in mTL activation determined by pre-surgical fMRI was predictive of post-operative seizure outcome at 12-month follow-up.

MATERIALS AND METHODS

Subjects

Ten consecutively recruited patients with TLE consented to participate in the fMRI and IAT phases of the study while undergoing pre-operative evaluation for anterior temporal lobectomy (ATL) for control of medically refractory seizures. One patient was excluded from the present study because his IAT data were uninterpretable due to significant cross-filling and resulting obtundation. Of the remaining nine patients who completed fMRI and IAT, eight (3 males, 5 females) eventually underwent resective surgery (3 right ATL; 5 left ATL). The average age at the time of fMRI was 27.3 (SD = 8.3) years and ranged from 17 to 37. The patients had a mean WAIS-R Full Scale IQ of 93.4 (SD = 10.1). Two of the patients were left-handed. Table 1 presents further demographic on the patients who underwent ATL. Detailed information regarding this patient sample were presented in a previous paper[1].

Imaging methods

Imaging data were collected as previously described[1] on a 1.5 Tesla GE Signa MRI scanner equipped with a standard quadrature RF head coil and a prototype fast gradient echoplanar imaging system using gradient echo, echoplanar images with BOLD contrast (TR = 2 s, TE = 50 ms) for functional imaging. Functional activation data were collected over two 160 scan runs, each consisting of four alternating control/task cycles of 80 s duration.

Activation task

Functional activation of brain regions involved in visual scene encoding was accomplished by presenting patients with a series of visually complex photographs to remember. Scene encoding was conducted in 40 s

Table 1: Patient demographics and outcome data.

Patient	Age/sex	Hand	Sz type	EEG	IAT memory asymmetry	fMRI asymmetry	Seizure outcome	Discriminant function	Probability of seizure-free status
1	33/F	R	CPS	LmTL	0.500	0.567	seizure-free	0.035	0.7595
2	17/M	R	CPS	LTL	0.056	0.833	seizure-free	2.730	0.9999
3	22/F	L	CPS	LmTL	0.222	0.522	seizure-free	0.758	0.9625
4	33/M	L	CPS, GTC	LTL	0.167	0.318	seizure-free	0.015	0.7488
5	36/F	R	CPS, GTC	LmTL	0.111	0.690	seizure-free	1.894	0.9986
6	37/F	R	CPS, GTC	RTL	0.722	0.333	seizures	−1.772	0.0165
7	18/M	R	CPS	RmTL	0.500	0.240	seizures	−1.453	0.0407
8	22/F	R	CPS, GTC	RTL	−0.056	−0.333	seizures	−2.206	0.0048

epochs which alternated with an equal length matched control condition throughout the duration of functional imaging. During the scene encoding condition, each photograph was presented for 2 s, with a blank screen ISI of 0.5 s. In the control condition, a single pixelated image matched for luminosity with the scene photographs was presented repeatedly at the same rate and in the same manner as the scene encoding condition. Patients were instructed to attempt to memorize the scene photographs but not the control image, and were informed that memory for the scenes would be tested after completion of the scan.

Image processing and analysis

As described in detail in our previous study[1], imaging data were corrected for static susceptibility-induced distortions and motion artefacts and convolved into three-dimensional space using a nonisotropic Gaussian kernel (full width half maximum [FWHM] = $11.25 \times 11.25 \times 15$ mm). A statistical parametric map was generated for each patient by making a voxelwise application of a linear model for autocorrelated observations. A multi-subject SPM ($\alpha = 0.01$, mapwise corrected for multiple comparisons) was constructed in Talairach space[25] and a mesial temporal region of interest was generated to evaluate the volume of activation near the boundary of the hippocampal formation and the lingual gyrus. The number of active voxels within each lateralized search region exceeding a threshold of statistical significance ($\alpha = 0.01$) was determined and an asymmetry ratio calculated for each hemisphere.

Whereas in our previous paper the asymmetry ratio indicated the relative activation in the left and right mTL, for the present study the asymmetry ratio was based on the proportion of activation in the mTL ipsilateral to the epileptic focus vs. activation in the mTL contralateral to the epileptic focus, thus controlling for the disproportionate number of left ATL patients in our sample. This index, [(contralateral mTL activation − ipsilateral mTL activation)/(contralateral mTL activation + ipsilateral mTL activation], which ranged from −1.0 (ipsilateral activation only) to +1.0 (contralateral activation only) indicated the degree of relative functional activation of hippocampal and parahippocampal regions within the epileptic and non-epileptic hemispheres.

Intracarotid amobarbital testing

Memory and language functioning were evaluated according to a standard IAT protocol[7,26]. To evaluate memory, nine visual stimuli were presented in a standard order for all patients. Stimuli consisted of visual confrontation naming of three common objects, oral reading of three low-imagery words, and visual inspection of three abstract line drawings. Initial presentation of the stimuli occurred during hemispheric anaesthetization, and recognition memory was evaluated following return to baseline as determined by neurological examination. As outlined by[7], recognition scores were calculated for each hemisphere and corrected for guessing. By subtracting the recognition memory performance of the epileptic hemisphere from that of the non-epileptic hemisphere[7] an index of the relative performance of each hemisphere was calculated. For the purposes of the present study, IAT data were converted to an asymmetry index similar to that used for the fMRI data. This IAT asymmetry ratio was calculated by dividing the obtained IAT difference score by the maximum possible score (i.e. 9), which yielded an IAT laterality index that ranged from +1.0 (100% correct memory performance using the non-epileptic hemisphere and 0% correct with the epileptic hemisphere) to −1.0 (100% correct memory performance using the epileptic hemisphere and 0% correct with the non-epileptic hemisphere).

Post-operative data analysis

Patients were classified as either seizure-free (Engel Class I)[3] or not seizure-free at 12-month follow-up

during a clinical interview with a physician naive to the hypothesis of the present study. A discriminant function analysis with post-operative seizure classification as the dependent variable and fMRI asymmetry ratio as the independent variable was performed using SPSS 6.1 (SPSS Inc., 1994). Prior odds were used in all analyses, assuming a base rate of 68% seizure-free status across epilepsy centres[3]. Discriminant function analysis was also used to evaluate seizure outcome using the asymmetry score derived from the pre-operative IAT as the independent variable.

RESULTS

The discriminant function analysis demonstrated that pre-operative asymmetries in mesial temporal activation, as measured by fMRI, significantly predicted seizure outcome following ATL regardless of side of lesion ($F[1, 6] = 7.05$, $P < 0.05$), with positive outcome associated with relatively greater functional activation of the mesial temporal region contralateral to the seizure focus ($M = 0.59$, $SD = 0.19$). In contrast, persistent seizure status was associated with an asymmetry index close to zero ($M = 0.08$, $SD = 0.36$), suggesting little difference in functional mTL activation between the epileptic and non-epileptic hemispheres. Discriminant function analysis on the transformed indices correctly classified 75% of the patients according to seizure outcome (see Table 2).

The data from the IAT were also analysed using discriminant function analysis to predict post-surgical seizure status. The IAT laterality agreement index was used as the independent variable with seizure outcome as the dependent variable. Although the IAT achieved the same proportion of correct seizure outcome classifications (75%) as the fMRI asymmetry index, the effect failed to reach statistical significance ($F[1, 6] = 0.81$, $P = 0.40$) due to variability in the magnitude of IAT performances across subjects. Table 2 summarizes the performance data for the IAT and fMRI asymmetry indices, while Table 3 presents data for hit rate, sensitivity, specificity, and predictive values of each method. As Table 3 shows, there is a trend for greater sensitivity to post-operative seizures when using IAT relative to fMRI, whereas a trend towards greater specificity was evident for fMRI relative to IAT.

The asymmetry ratios for the fMRI and IAT were found to be uncorrelated ($r = 0.11$), suggesting that each index may have accounted for unique variance in predicting post-surgical seizure status and that a combination of the two indices may prove more predictive than either method alone. Therefore, the asymmetry data from both the fMRI and IAT were entered together to determine their combined effectiveness at predicting post-surgical seizure outcome. Although the IAT did not contribute statistically significant predictive power above that provided by fMRI alone within our small sample, the combined data accurately classified all eight of the post-surgical seizure outcomes (see Fig. 1). The accuracy of classification when data from both the fMRI and IAT were combined was statistically reliable ($\chi^2 = 6.44$, $P < 0.05$). In our sample, the post-surgical status of patients was correctly classified in every case with the following unstandardized canonical discriminant function equation: {discriminant function $=$ [(fMRI index) $\times$ (4.55)] + [(IAT index) $\times$ (-3.34)] $-$ 0.88}. The obtained discriminant functions for each patient, along with the predicted probability of membership in the seizure-free group are also presented in Table 1.

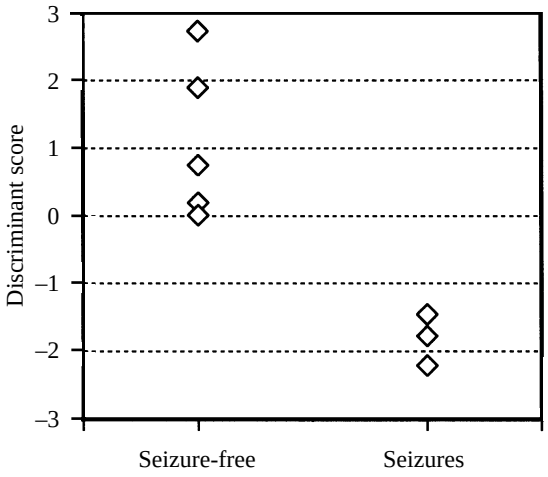

Fig. 1: Combined entry of asymmetry scores from the fMRI and IAT into a discriminant function analysis significantly predicted seizure control at 1-year follow-up.

DISCUSSION

Despite the small sample size and limited power to detect effects, our results suggest that fMRI can contribute meaningfully to the prediction of post-operative seizure control. In our sample, asymmetry of mTL activation measured by fMRI resulted in the same accuracy of outcome classification as IAT and significantly predicted seizure-free status at 1-year follow-up. These findings are consistent with other studies using alternate methodologies suggesting that the presence of functional deficits or abnormal functional asymmetry is associated with a favourable outcome following ATL[6, 7, 19–21]. We found that when the asymmetry of mTL activation during encoding favoured the side contralateral to the eventual surgical resection, there was a higher probability of seizure-free outcomes, suggesting that the resected tissue was functionally less adequate. In contrast, continued post-

Table 2: Frequencies of discriminant function analysis outcome classification for FMRI, IAT, and combined methods.

Prognostic technique	Actual group membership			
	Seizure-free ($n = 5$)		Not seizure-free ($n = 3$)	
	True negatives	False positives	True positives	False negatives
FMRI	5	0	1	2
IAT	4	1	2	1
FMRI + IAT	5	0	3	0

Table 3: Sensitivity, specificity, and predictive values for FMRI, IAT, and combined methods.

Performance standard	Prediction method		
	FMRI	IAT	Combined
Hit rate = (TN + TP)/N	0.75	0.75	1.00
Sensitivity = TP/(TP + FN)	0.33	0.67	1.00
Specificity = TN/(TN + FP)	1.00	0.80	1.00
Positive predictive value = TP/(TP + FP)	1.00	0.67	1.00
Negative predictive value = TN/(TN + FN)	0.71	0.80	1.00

Note. $n = 8$. TP = true positives; TN = true negatives; FP = false positives; FN = false negatives.

ATL seizure activity was associated with less asymmetry on fMRI, suggesting the possibility of intact tissue on the ipsilateral side, or potentially dysfunctional tissue on the contralateral side. Previous studies have similarly demonstrated that poor seizure outcome is associated with reduced asymmetry on IAT[27,28]. Recent ERP data also suggest that poor functional performance within the hippocampus contralateral to the side of resection is a negative prognostic indicator of post-ATL seizure control[19]. Our findings suggest that with further refinement, fMRI of mTL regions during memory encoding may emerge as a clinically useful tool for evaluating functional adequacy without invasive procedures, and which may potentially contribute to the selection of patients for ATL by predicting post-operative seizure control.

While the potential usefulness of fMRI as an independently prognostic tool is intriguing, our results further suggest that functional imaging may prove most useful when used in conjunction with IAT. Although fMRI and IAT both predicted outcome with the same overall degree of accuracy, each method contributed unique information to the classification of post-ATL seizure control. Surprisingly, the asymmetry scores of fMRI and IAT were essentially uncorrelated, suggesting that they each accounted for non-overlapping unique variance in predicting outcome. The complementary nature of these two methods was further demonstrated when they were entered together in a discriminant function analysis. In combination, fMRI and IAT correctly classified the outcome of all eight patients at 1-year follow-up. These findings provide preliminary evidence suggesting that functional memory assessment using fMRI and the IAT may contribute unique and complementary information, that when considered together, may further enhance the prediction of post-operative seizure status.

Obviously these results are preliminary and will require considerable cross-validation with other larger patient samples over longer follow-up periods. While our results were statistically significant, in practical terms the difference in outcome classification was small, a change of only one or two subjects among the three prediction methods. Furthermore, the generalizability and reliability of the findings are also severely limited by the small sample size, and the data cannot be extended beyond the present sample. Finally, the disproportionate number of left ATL patients limits the ability to make firm conclusions regarding the relationship between functional asymmetry and seizure outcome. Replication with larger samples including adequate numbers of left and right TLE patients may eventually lead to the development of clinically useful prediction equations. However, despite these limitations, the present findings are encouraging and warrant additional research to determine the potential clinical usefulness of these or similar fMRI techniques for predicting post-operative seizure control.

REFERENCES

1. Detre, J. A., Maccotta, L., King, D. *et al.* Functional MRI lateralization of memory in temporal lobe epilepsy. *Neurology* 1998; **50**: 926–932.
2. Engel, J. Surgery for seizures. *New England Journal of Medicine* 1996; **334**: 647–652.

3. Engel, J. (Ed.) *Surgical Treatment of the Epilepsies*. New York, Raven Press, 1993.
4. Primrose, D. C. and Ojemann, G. A. Outcome of resective surgery for temporal lobe epilepsy. In: *Epilepsy Surgery* (Ed. H. O. Luders). New York, Raven Press, 1992: pp. 181–190.
5. Spencer, S. S. and Spencer, D. D. Outcome: data, dogma, directions. In: *Surgery for Epilepsy* (Eds D. D. Spencer and S. S. Spencer). Blackwell, Cambridge, 1991: pp. 181–190.
6. Loring, D. W., Meador, M. J., Lee, G. P. *et al.* Wada memory performance predicts seizure outcome following anterior temporal lobectomy. *Neurology* 1994; **44**: 2322–2324.
7. Sperling, M. R., Saykin, A. J., Glosser, G. *et al.* Predictors of outcome after anterior temporal lobectomy: the intracarotid amobarbital test. *Neurology* 1994; **44**: 2325–2330.
8. Dodrill, C. B., Wilkus, R. J., Ojemann, G. A. *et al.* Multidisciplinary prediction of seizure relief from cortical resection surgery. *Annals of Neurology* 1986; **20**: 2–12.
9. Sperling, M. R. Neuroimaging in epilepsy: recent developments in MR Imaging, positron-emission tomography, and single-photon emission tomography. *Neurology Clinics* 1993; **11**: 883–894.
10. O'Rourke, D. M., Saykin, A. J., Gilhool, J. J., Harley, R., O'Connor, M. J. and Sperling, M. R. Unilateral hemispheric memory and hippocampal neuronal density in temporal lobe epilepsy. *Neurosurgery* 1993; **32**: 574–580.
11. Sass, K. J., Lencz, T., Westerveld, M., Novelly, R. A., Spencer, D. D. and Kim, J. H. The neural substrate of memory impairment demonstrated by the intracarotid amobarbital procedure. *Archives of Neurology* 1991; **48**: 48–52.
12. Squire, L. R. Memory and the hippocampus: a synthesis from finding with rats, monkeys and humans. *Psychological Review* 1992; **99**: 195–231.
13. Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O. and Raichle, M. E. Activation of the hippocampus in normal humans: a functional anatomical study of memory. *Proceedings of the National Academy of Science USA* 1992; **89**: 1837–1841.
14. Loring, D. W., Murro, A. M., Meador, K. J. *et al.* Wada memory testing and the hippocampal volume measurements in the evaluation for temporal lobectomy. *Neurology* 1993; **43**: 1789–1793.
15. Rauch, R. and Langfitt, J. T. Memory evaluation during the intracartoid sodium amobarbital procedure. In: *Epilepsy Surgery* (Ed. H. O. Luders). New York, Raven Press, 1991: pp. 507–514.
16. Chelune, G. J. Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology* 1995; **10**: 413–432.
17. Lancman, M. E., Benbadis, S., Geller, E. and Morris, H. H. Sensitivity and specificity of asymmetric recall on WADA test to predict outcome after temporal lobectomy. *Neurology* 1998; **50**: 455–459.
18. Perrine, K., Westerveld, M., Sass, K. J. *et al.* Wada memory disparities predict seizure laterality and postoperative seizure control. *Epilepsia* 1995; **36**: 851–856.
19. Grunwald, T., Lehnertz, K., Pezer, N. *et al.* Prediction of postoperative seizure control by hippocampal event-related potentials. *Epilepsia* 1999; **40**: 303–306.
20. Weinand, M. E. and Carter, L. P. Surface cortical cerebral blood flow monitoring and single photon emission computed tomography: prognostic factors for selecting temporal lobectomy candidates. *Seizure* 1994; **3**: 55–59.
21. Manno, E. M., Sperling, M. R., Ding, X. *et al.* Predictors of outcome after anterior temporal lobectomy: positron emission tomography. *Neurology* 1994; **44**: 2331–2336.
22. Salanova, V., Markand, O., Worth, R. *et al.* FDG-PET and MRI in temporal lobe epilepsy: relationship to febrile seizures, hippocampal sclerosis and outcome. *Acta Neurologica Scandinavica* 1998; **97**: 146–153.
23. Theodore, W. H., Sato, S., Kufta, C. V., Gaillard, W. D. and Kelly, K. FDG positron emission tomography and invasive EEG: seizure focus detection and surgical outcome. *Epilepsia* 1997; **38**: 81–86.
24. Bellgowan, P. S. F., Binder, J. R., Swanson, S. J. *et al.* Side of seizure focus predicts left medial temporal activation during verbal encoding. *Neurology* 1998; **51**: 479–484.
25. Talairach, J. and Tournoux, P. *Co-planar Stereotaxic Atlas of the Human Brain*. Stuttgart, Thieme, 1988.
26. Glosser, G., Saykin, A. J., Deutsch, G. K., O'Connor, M. J. and Sperling, M. R. Neural organization of material-specific memory functions in temporal lobe epilepsy patients as assessed by the intracarotid amobarbital test. *Neuropsychology* 1995; **9**: 449–456.
27. Kneebone, A. C., Chelune, G. J., Dinner, D. S., Naugle, R. I. and Awad, I. A. Intracarotid amobarbital procedure as a predictor of material-specific memory change after anterior temporal lobectomy. *Epilepsia* 1995; **36**: 857–865.
28. Loring, D. W., Meador, K. J., Lee, G. P. *et al.* Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy. *Neurology* 1995; **45**: 1329–1333.