Cortical reorganization following anterior temporal lobectomy in patients with temporal lobe epilepsy

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ABSTRACT

Background: Functional MRI was used to study the impact of temporal lobe epilepsy (TLE) and anterior temporal lobectomy (ATL) on the cortical language network in patients with medically refractory TLE.

Methods: Nineteen patients with medically refractory TLE and 11 healthy control subjects were enrolled in this study. Ten patients underwent left ATL (mean age 35.2 ± 3.8 years), and 9 underwent right ATL (mean age 35.9 ± 2.6 years). The subjects silently generated verbs in response to a series of visually presented nouns inside the scanner. Correlation analysis was performed between the subjects' performance on the clinical language tests and their neural response in the a priori cortical regions.

Results: Preoperative data revealed that the patients with TLE showed increased neural activity in the right inferior frontal gyri (IFG) and middle frontal gyri (MFG). The right TLE patients demonstrated strong correlation between their language performance and the level of cortical activation within the typical language areas. However, such a correlation was absent in the left TLE patients. After the ATL surgery, the left TLE patients showed reduced activation in the left MFG and right IFG, whereas no difference was observed in the right TLE patients. In the right TLE patients, the correlation between language performance and neural response shifted from the typical language areas to the anterior cingulate cortex.

Conclusion: This study demonstrates that the cortical language network is affected differently by the left and right temporal lobe epilepsy and is reorganized after anterior temporal lobectomy.

Neurology® 2009;73:518–525

GLOSSARY

ACC = anterior cingulate cortex; **ATL** = anterior temporal lobectomy; **BDAE** = Boston Diagnostic Aphasia Examination; **BNT** = Boston Naming Test; **BOLD** = blood oxygenation level-dependent; **fMRI** = functional MRI; **FOV** = field of view; **IFG** = inferior frontal gyrus; **LHSC** = London Health Sciences Centre; **LQ** = Language Quotient; **MFG** = middle frontal gyrus; **MNI** = Montreal Neurological Institute; **ROI** = region of interest; **SFG** = superior frontal gyrus; **TE** = echo time; **TLE** = temporal lobe epilepsy; **TR** = repetition time; **WAB** = Western Aphasia Battery.

Temporal lobe epilepsy (TLE) is the most common cause of medically intractable partial epilepsy.¹ Anterior temporal lobectomy (ATL) has been used to treat patients with medically refractory TLE,² resulting in seizure freedom in approximately 60% of these patients.³ However, decline in language functioning has been reported in some of the patients with TLE who undergo ATL.^{4–9} Previous neuroimaging studies using functional MRI (fMRI) have shown that patients with TLE demonstrated atypical cortical representation of language processing,^{10–12} and ATL exerted differential impact on the language functions of the left and right TLE patients.^{10,13} Nevertheless, it is still unclear whether the distinct patterns observed in the left and right TLE patients is a consequence of the ATL alone or due to the cortical reorganization before the surgery.

Supplemental data at
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Supported by Lawson Health Research Institute, The Physicians' Services Incorporated Foundation, and The Summer Research Training Program from Schulich School of Medicine and Dentistry at The University of Western Ontario, London, Ontario, Canada.

Disclosure: The authors report no disclosures.

The present study has 2 major objectives: 1) to determine the differential impact of the left and right TLE on the cortical organization of language functioning in preoperative patients through comparing their fMRI response with that of a group of healthy control subjects; and 2) to determine the impact of ATL on the left and right TLE patients through comparing their preoperative and postoperative fMRI responses. Based on the previous data, we hypothesized that epilepsy on the left and right temporal lobe would elicit distinct impact on the cortical organization of language functioning. We also hypothesized that the pattern of cortical activation would change after the ATL, indicating cortical reorganization.

METHODS Patients. Twenty-three consecutive patients with medically refractory unilateral mesial TLE who were undergoing presurgical evaluation for ATL in the University Hospital at London Health Sciences Centre (LHSC) participated in this prospective study. The clinical profile of the patients, including neurologic examination, EEG findings, neuropsychological data, and anatomic MRI data, were reviewed for eligibility in this study. Inclusion criteria included MRI compatibility, unilateral mesial TLE of any cause except where a lesion extended to the posterior temporal neocortex or other adjacent brain regions apart from the anterior temporal neocortex, medically intractable epilepsy, surgical candidates, and no history of brain surgery. The handedness of the subjects was assessed using the Edinburgh Handedness Inventory.¹⁴ Eleven healthy right-handed subjects (mean age 26.9 ± 1.6 years) were recruited as normal controls for the study. English was the first language among all the subjects. This study was approved by the Research Ethics Board of the University of Western Ontario, with all subjects providing written informed consent upon recruitment.

Imaging methods. Anatomic and functional MRI scanning was performed on a 1.5-T GE Signa Excite MRI system (GE Healthcare, Waukesha, WI) with a full-volume head coil at the University Hospital of the LHSC (London, Ontario, Canada). Postoperative scans were completed in 6.4 ± 1.6 months in the left TLE patients and 7.8 ± 1.6 months in the right TLE patients. A high-resolution whole brain T1-weighted anatomic MRI (3-D) spoiled gradient recall echo pulse sequence, 120 slices, 1.5-mm slice thickness, 0 gap, field of view [FOV] $24 \text{ cm} \times 24 \text{ cm}$, 256×265 matrix, $0.75 \text{ mm} \times 0.75\text{-mm}$ in-plane resolution, repetition time [TR] = 6,000 msec, echo time [TE] = 1,500 msec, flip angle = 10°) was obtained. For fMRI, a T2*-weighted 1-shot spiral-in sequence^{14a} was used to measure the blood oxygenation level-dependent (BOLD) signal over time. A boxcar-designed verb-generation paradigm was used for testing, which consisted of 10 active states and 11 rest states of equal duration and required 7.5 minutes. Each active state consisted of covert generation of action verbs in response to 5 visually presented nouns and lasted 22 seconds. The same task incorporating a different set of words was used preoperatively and postoperatively to avoid any potential practice effect. The 2 sets of words were comparable with respect to frequency and length. The total acquired fMRI volumes

were 190 with each volume consisting of 30 slices (5-mm slice thickness, 0 gap, FOV $24 \text{ cm} \times 24 \text{ cm}$, 64×64 matrix, $3.75 \text{ mm} \times 3.75\text{-mm}$ in-plane resolution, TR = 2500 msec, TE = 40 msec, flip angle = 90°).

fMRI data analysis. SPM2 (www.fil.ion.ucl.ac.uk/spm) was used to preprocess the data and to perform statistical analyses based on the generalized linear model. The functional images were aligned and normalized into standardized space using the Montreal Neurological Institute (MNI) average-152 template brain. The first volume in each run was excluded to allow time to achieve magnetic steady state. Low-frequency noise was removed from the data with a high-pass filter (cutoff = 128 seconds), and the data were spatially smoothed with an 8-mm full-width at half-maximum gaussian filter. Series with motions greater than 5.0 mm were excluded from further analyses. A 1-sample *t* test was used for statistical analysis at the individual level. Whole brain group analysis was performed by using a mixed-design analysis of variance model (random effect) with $p \leq 0.001$ (uncorrected) and cluster size ≥ 10 voxels. Activation maps from the preoperative and postoperative sessions were overlaid on the 3-dimensional standard MNI brain. Anatomic regions of interest (ROIs), including the bilateral inferior frontal gyri (IFG), middle frontal gyri (MFG), superior frontal gyri (SFG), and anterior cingulate cortex (ACC), were selected based on previous language study¹⁵ and defined using the Automatic Anatomic Labeling package.¹⁶ Percent signal change was calculated from these a priori ROIs. To examine the relationship between language performance and the measured neural activities, correlation analysis was performed between the percent signal change of these ROIs and the language scores obtained from the clinical language testing.

Language assessment. The Boston Naming Test (BNT),¹⁷ a subtest of the Boston Diagnostic Aphasia Examination (BDAE),¹⁸ and the Western Aphasia Battery (WAB)¹⁹ were administered by a speech-language pathologist who was blinded to the fMRI results but not the status of the subjects. The Complex Ideational Material subtest from the BDAE was chosen to assess auditory processing skills in the context of short narratives. Only the language subtests of the WAB that examine the auditory and reading comprehensions plus oral and graphic expressions were administered to derive a Language Quotient (LQ).^{20,21} The reported reference value for WAB LQ in the healthy individuals was 93.8. Testing was completed at the time of fMRI study.

RESULTS All the patients were right-handed, with normal neurologic examination and EEG findings consistent with unilateral TLE. Among the 23 patients, 4 of them (3 left TLE and 1 right TLE) were excluded from further analysis because of severe head movement during the fMRI scanning. The clinical profile of the patients, including age, sex, age at the time of presurgical fMRI, age at onset of habitual seizures, MRI findings, antiepileptic drugs tried at the time of the fMRI studies, side of the ATL, pathology of the resected tissue, and seizure outcome based on Engel classification,² are presented in table e-1 on the *Neurology*[®] Web site at www.neurology.org. Left ATL was performed in 10 patients (patients 1–10), and right ATL was performed in 9 patients (patients 11–19). The mean age of the patients was 35.2 ± 3.8 years for the left TLE group and $35.9 \pm$

Figure 1 Activation maps before and after anterior temporal lobectomy

Activation maps for the left temporal lobe epilepsy (LTLE), right temporal lobe epilepsy (RTLE), and healthy control (CTRL) groups before (left) and after (right) the anterior temporal lobectomy ($p < 0.001$, uncorrected).

2.6 years for the right TLE group. The left TLE group was somewhat heterogeneous with respect to the etiology of TLE, whereas all the patients in the right TLE group except for one (patient 13) had mesial temporal sclerosis. The neuropsychological profile of the patients with respect to IQ, including verbal and performance IQs before surgery, is shown in table e-2. The surgical outcome was excellent (Engel class I) in 14 of 19 patients (74%), very good (Engel class II) in 4 of 19 patients (21%), and good (Engel class III) in 1 of 19 patients (5%) during the follow-up, which was at least approximately 1 year.

Language outcomes. The results of language assessments before and after the surgery are shown in figure e-1. Among the right TLE patients, 8 of them completed the preoperative language assessment, whereas 6 of them completed the postoperative assessment. All the left TLE patients completed the language assessments both before and after the surgery, and they showed a trend for reduction in their BNT scores after the surgery ($p < 0.086$), whereas the right TLE patients did not show any changes between their preoperative and postoperative BNT scores. In addition, the left and right TLE patients showed a trend for change in their presurgical and postsurgical BDAE scores (i.e., BDAE scores decreased in the left TLE patients but increased in the right TLE patients after the surgery), but these changes did not reach significance. Both left and

right TLE patients did not show any significant change in their WAB scores.

fMRI findings. Before the ATL surgery, the left and right TLE patients activated a similar cortical network as the control group did. As shown in the left panel of figure 1, the bilateral IFG, bilateral MFG, left SFG, left middle temporal gyrus, supplementary motor area, and right insular cortex were commonly activated in all 3 groups. Nevertheless, the ROI analysis revealed that the patient groups elicited stronger activity in the right IFG and MFG relative to the control group (figure 2). The major difference between the 2 patient groups is that the left TLE patients activated the left inferior and superior parietal gyri, which was not observed in the right TLE patients. In general, the verb-generation task elicited left hemisphere–dominated activation in both the patient and control groups, which is consistent with previous language studies.^{10,15}

After the surgery, the right TLE patients activated the same cortical network as they did before the surgery (right panel of figure 1). On the contrary, the left TLE patients elicited less activation after the surgery. A subtraction analysis between the preoperative and postoperative BOLD response confirmed that the right IFG and the left MFG were less activated postoperatively in the left TLE patients (figure 3). In the ROIs analysis, the left TLE patients showed a trend for decreased activation across the subdivisions of the right IFG (i.e., the pars opercularis, par triangularis, and par orbitalis) and the right MFG (figure 2).

Figure 2 Percent signal change at the predefined regions of interest

CTRL = healthy control subjects; LTLE = left temporal lobe epilepsy; pre = before anterior temporal lobectomy; post = after anterior temporal lobectomy; RTLE = right temporal lobe epilepsy; oper = pars opercularis of inferior frontal gyrus; tri = pars triangularis of inferior frontal gyrus; orb = pars orbitalis of inferior frontal gyrus; LMFG = left middle frontal gyrus; RMFG = right middle frontal gyrus.

To determine the relationship between the subjects' language performance and level of neural activity, cross-subjects correlation analyses between the language assessment scores and the percent signal change in the a priori ROIs were performed. Before the surgery, the right TLE patients ($n = 8$) showed stronger correlation between their BNT scores and the percent signal change in the left IFG ($R^2 = 0.867$ vs 0.016) and the right IFG ($R^2 = 0.485$ vs 0.258) than the left TLE patients ($n = 10$) did (figure 4). The correlation coefficients were decreased in both the left and right TLE patients after the surgery. Although the right TLE patients ($n = 6$) still exhibited a stronger correlation between their BNT scores and their postoperative BOLD response than the left TLE patients ($n = 10$) did, the correlation coefficients

in both patient groups became negligible after the surgery.

We further expanded the correlation analyses to various language scores and ROIs and plotted the correlation coefficients as contour maps (figure 5). As shown in figure 5B, before the surgery, the right TLE patients exhibited robust correlation between various language scores (i.e., BNT, WAB LQ, and WAB subtests) and the BOLD responses at the bilateral IFG, MFG, and SFG. Consistently across ROIs, stronger correlations were observed in the left hemisphere. Indeed, the strongest correlation coefficient was the one between the BNT score and BOLD response within the left MFG ($R^2 = 0.92$). After the surgery, the correlation coefficients within the bilateral IFG (including pars triangularis, pars opercularis, and pars orbitalis) were reduced, whereas stronger correlation was revealed within the bilateral ACC. The strongest correlation was observed between the left ACC activity and the BNT ($R^2 = 0.884$) and WAB naming scores ($R^2 = 0.932$) and between the left SFG activity and WAB writing ($R^2 = 0.982$) (figure 5D). Relative to the right TLE patients, the left TLE patients exhibited much weaker correlation between their language scores and BOLD responses both before and after the surgery (figure 5, A and C). Before the surgery, the strongest correlation was observed between the BDAE scores and the BOLD response within the left MFG ($R^2 =$

Figure 3 Decreased activation after anterior temporal lobectomy in the left temporal lobe epilepsy group

Before anterior temporal lobectomy, left temporal lobe epilepsy (LTLE) patients showed stronger activation in the right inferior frontal gyrus, left middle frontal gyrus, and left inferior and superior parietal gyri ($p < 0.001$, uncorrected).

Figure 4 Correlation between blood oxygenation level-dependent signal and language score before and after ipsilateral anterior lobectomy

Correlation between blood oxygenation level-dependent signal and language score in the left temporal lobe epilepsy (LTLE) patients and the right temporal lobe epilepsy (RTLE) patients before and after an ipsilateral anterior lobectomy (ATL). Postoperative language scores were obtained from 6 of the RTLE patients, and the language score of an RTLE patient was classified as an outlier and excluded from the correlation analysis. LIFG = left inferior frontal gyrus; BNT = Boston Naming Test; RIFG = right inferior frontal gyrus.

0.656) and SFG ($R^2 = 0.623$) (figure 5A). After the surgery, the strongest correlation was the one between the WAB naming score and the right MFG ($R^2 = 0.481$) (figure 5C). A post hoc analysis was performed to clarify whether the absence of correlation in the left TLE patients related to the different outcomes of the ATL within the group. The left TLE patients were further divided into 2 subgroups based on the change in their BNT scores after the ATL. Of the 10 patients, 4 of them showed a >15 decline in their postoperative BNT scores, whereas the others had little or no change (i.e., change in BNT score <5). Correlation analysis between the language scores and BOLD signal was conducted separately in these 2 subgroups. Strong left-lateralized correlations were observed in the group that showed an apparent decline in postoperative BNT scores (figure e-2).

DISCUSSION The present fMRI study examined the impact of TLE and ATL on the cortical organization of language processing using a verb-generation task. The healthy control subjects activated the typical language areas (i.e., IFG and MFG) on the left hemisphere, whereas the left and right TLE patients elicited bilateral activation in the IFG and MFG. These findings suggest that epilepsy affected the cor-

tical organization of language processing in both the left and right TLE patients. For the right TLE patients, the level of neural activity within the bilateral IFG and MFG correlated closely with the patients' performances in the clinical language tests. However, such a correlation was absent in the left TLE patients, suggestive of reallocation of language processing away from the typical language areas in these patients as a result of their epilepsy. Cortical reorganization is also present after the ATL, as suggested by decreased activation in the right IFG and left MFG of the left TLE patients and the attenuated correlation between the language scores and the postoperative BOLD response within the IFG and MFG in both patient groups. These findings support our hypotheses that the cortical organization of language processing is affected differently by left and right TLE and is reorganized after ATL.

Before the ATL, we observed both interhemispheric and intrahemispheric shift of cortical activation in the patients with TLE. The anterior temporal lobe has been associated with the processing of semantic information.²² Epilepsy within the temporal lobe may hence disrupt the semantic retrieval network that is involved in various language processing, including the verb-generation task of the present

Figure 5 Average correlation coefficient (R^2) between percent signal change at different predefined regions of interest and language scores across participants

LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; WAB = Western Aphasia Battery; LQ = Language Quotient; BDAE = Boston Diagnostic Aphasia Examination; BNT = Boston Naming Test; LIFG orb = pars orbitalis of left inferior frontal gyrus; LIFG oper = pars opercularis of left inferior frontal gyrus; LIFG tri = pars triangularis of left inferior frontal gyrus; LMFG = left middle frontal gyrus; LSFG = left superior frontal gyrus; LACC = left anterior cingulate cortex; RACC = right anterior cingulate cortex; RSFG = right superior frontal gyrus; RMFG = right middle frontal gyrus; RIFG tri = pars triangularis of right inferior frontal gyrus; RIFG oper = pars opercularis of right inferior frontal gyrus; RIFG orb = pars orbitalis of right inferior frontal gyrus.

study. Indeed, previous study has reported that TLE affected verbal but not nonverbal memory and increased right prefrontal cortex activation during a verbal memory task.¹⁰ In the present study, the increased activation in the right IFG and MFG of the patients with TLE therefore indicated cortical reorganization, which may play an important role in compensating the disturbed semantic retrieval network due to the epilepsy. In addition to the inter-hemispheric shift of activation, the left TLE patients also demonstrated increased activation in the left inferior and superior parietal cortex. Compared with the right TLE patients, the left TLE patients demonstrated a much weaker correlation between their language scores and the neural activity of the typical language areas. These findings revealed that the left TLE patients do not simply shift their language rep-

resentation to the homotopic area on the right hemisphere, but also shift their language processing away from the typical language area. The lateral parietal cortex has been identified together with the dorsolateral frontal cortex as an "task-activation ensemble," which is frequently activated by demanding cognitive tasks.²³ The augmented parietal cortex activation therefore indicated that epilepsy in the left temporal lobe may exert a stronger impact to the semantic retrieval network and hence increased the activation of the task-activation ensemble relative to the right TLE patients.

After the ATL, the left TLE patients showed an attenuated activation within the left MFG and the right IFG, which is consistent with the previous findings of a verbal memory study.¹⁰ The attenuated activities may be associated with the trend of reduced

BNT scores after the surgery. In fact, our post hoc analysis indicated that the left TLE patients who showed clear decrease in their postoperative BNT scores exhibited a strong correlation between their preoperative language scores and the BOLD signal within the typical language areas. This strong correlation may reflect a lack of cortical reorganization in this group of patients and make them more susceptible to decline in language functioning after ATL. Recent studies have indeed shown that it is possible to predict postoperative verbal memory outcome in ATL patients based on their preoperative fMRI signal.^{24,25} In particular, a left dominance of preoperative fMRI activation predicted verbal memory decline after ATL in the left TLE patients,²⁴ which is consistent with our present findings. However, the small sample size in our post hoc analysis limited further interpretation of the data. In contrast, the right TLE patients shifted the correlation between their language scores and BOLD signals from the typical language areas (i.e., IFG and MFG) to the ACC after ATL. The shift of correlation to the ACC may indicate an increase reliance on a more general cognitive control and response selection network within the ACC²⁶⁻²⁸ in completing the verb-generation task.

Relative to the previous studies, the present study had the advantage in comparing the clinical language test scores and neuroimaging data of the same patient groups before and after ATL. This within-group repeated-measures design reduces the intersubject variability in examining the effect of surgery to the cortical reorganization. The covert language task used in the present study helped us to minimize subjects' head movement inside the scanner but, at the same time, limited us in monitoring the performance of the subjects. Future study using a sparse scanning protocol may enable us to employ an overt language task. Also, the present study does not address reproducibility of language fMRI in healthy and patient populations; we suggest that a larger scale longitudinal study should be performed in the future with repeated fMRI measures in both the preoperative and postoperative conditions to examine whether cortical reorganization changes over time in patients with TLE, especially after ATL.

Received October 4, 2008. Accepted in final form May 6, 2009.

REFERENCES

- Engel J Jr. Etiology as a risk factor for medically refractory epilepsy: a case for early surgical intervention. *Neurology* 1998;51:1243-1244.
- Engel J Jr, Van Ness P, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press; 1993:609-621.
- Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345:311-318.
- Katz A, Awad IA, Kong AK, et al. Extent of resection in temporal lobectomy for epilepsy, II: memory changes and neurologic complications. *Epilepsia* 1989;30:763-771.
- Hermann BP, Perrine K, Chelune GJ, et al. Visual confrontation naming following left anterior temporal lobectomy: a comparison of surgical approaches. *Neuropsychology* 1999;13:3-9.
- Langfitt JT, Rausch R. Word-finding deficits persist after left anterotemporal lobectomy. *Arch Neurol* 1996;53:72-76.
- Seidenberg M, Hermann B, Wyler AR, Davies K, Dohan FC Jr, Leveroni C. Neuropsychological outcome following anterior temporal lobectomy in patients with and without the syndrome of mesial temporal lobe epilepsy. *Neuropsychology* 1998;12:303-316.
- Davies KG, Bell BD, Bush AJ, Hermann BP, Dohan FC Jr, Jaap AS. Naming decline after left anterior temporal lobectomy correlates with pathological status of resected hippocampus. *Epilepsia* 1998;39:407-419.
- Davies KG, Risse GL, Gates JR. Naming ability after tailored left temporal resection with extraoperative language mapping: increased risk of decline with later epilepsy onset age. *Epilepsy Behav* 2005;7:273-278.
- Maccotta L, Buckner RL, Gilliam FG, Ojemann JG. Changing frontal contributions to memory before and after medial temporal lobectomy. *Cereb Cortex* 2007;17:443-456.
- Carpentier A, Pugh KR, Westerveld M, et al. Functional MRI of language processing: dependence on input modality and temporal lobe epilepsy. *Epilepsia* 2001;42:1241-1254.
- Billingsley RL, McAndrews MP, Crawley AP, Mikulis DJ. Functional MRI of phonological and semantic processing in temporal lobe epilepsy. *Brain* 2001;124:1218-1227.
- Backes WH, Deblaere K, Vonck K, et al. Language activation distributions revealed by fMRI in post-operative epilepsy patients: differences between left- and right-sided resections. *Epilepsy Res* 2005;66:1-12.
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97-113.
- Li TQ, Takahashi A, Wang Y, Mathews V, Glover GH. Dual-echo spiral in/in acquisition method for reducing magnetic susceptibility artifacts in blood-oxygen-level-dependent functional magnetic resonance imaging. *Magn Reson Med* 2006;55:325-334.
- Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci* 2002;25:151-188.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002;15:273-289.
- Kaplan E, Goodglass H, Weintraub S. *The Boston Naming Test*. Philadelphia: Lea and Febiger; 1983.
- Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders*. 2nd ed. Philadelphia: Lea and Febiger; 1983.

19. Kertesz A. Classification of aphasic phenomena. *Can J Neurol Sci* 1976;3:135–139.
20. Kertesz A, Poole E. The aphasia quotient: the taxonomic approach to measurement of aphasic disability. *Can J Neurol Sci* 1974;1:7–16.
21. Shewan CM. The Language Quotient (LQ): a new measure for the Western Aphasia Battery. *J Commun Disord* 1986;19:427–439.
22. Nobre AC, McCarthy G. Language-related field potentials in the anterior-medial temporal lobe, II: effects of word type and semantic priming. *J Neurosci* 1995;15:1090–1098.
23. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 2007;27:2349–2356.
24. Binder JR, Sabsevitz DS, Swanson SJ, Hammeke TA, Raghavan M, Mueller WM. Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery. *Epilepsia* 2008;49:1377–1394.
25. Richardson MP, Strange BA, Duncan JS, Dolan RJ. Memory fMRI in left hippocampal sclerosis: optimizing the approach to predicting postsurgical memory. *Neurology* 2006;66:699–705.
26. Posner MI, Dehaene S. Attentional networks. *Trends Neurosci* 1994;17:75–79.
27. Raichle ME, Fiez JA, Videen TO, et al. Practice-related changes in human brain functional anatomy during non-motor learning. *Cereb Cortex* 1994;4:8–26.
28. Buckner RL, Petersen SE, Ojemann JG, Miezin FM, Squire LR, Raichle ME. Functional anatomical studies of explicit and implicit memory retrieval tasks. *J Neurosci* 1995;15:12–29.

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REFERENCES

1. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. *Neurology* 2008;71:1634–1638.
2. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. *Neurology* 2008;71:1639–1643.
3. Gross RA, Johnston KC. Levels of evidence: taking *Neurology*® to the next level. *Neurology* 2008;72:8–10.

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