Seizure focus affects regional language networks assessed by fMRI

M.M. Berl, PhD; L.M. Balsamo, PhD; B. Xu, PhD; E.N. Moore, BS; S.L. Weinstein, MD; J.A. Conry, MD; P.L. Pearl, MD; B.C. Sachs, MA; C.B. Grandin, MD, PhD; C. Frattali, PhD†; F.J. Ritter, MD; S. Sato, MD; W.H. Theodore, MD; and W.D. Gaillard, MD

Abstract—*Objective:* To investigate the degree of language dominance in patients with left and right hemisphere seizure foci compared to normal volunteers using a fMRI reading comprehension task. *Methods:* Fifty patients with complex partial epilepsy, aged 8 to 56 years and 33 normal volunteers, aged 7 to 34 had fMRI (1.5 T) and neuropsychological testing. Participants silently named an object described by a sentence compared to a visual control. Data were analyzed with region of interest (ROI) analysis based on t maps for inferior frontal gyrus (IFG), midfrontal gyrus (MFG), and Wernicke area (WA). Regional asymmetry indices (AIs) were calculated [(L − R)/(L + R)]; AI >0.20 was deemed left dominant and AI <0.20 as atypical language. *Results:* Left hemisphere focus patients had a higher likelihood of atypical language than right hemisphere focus patients (21% vs 0%, $\chi^2 < 0.002$). Left hemisphere focus patients, excluding those with atypical language, had lower regional AI in IFG, MFG, and WA than controls. Right hemisphere focus patients were all left language dominant and had a lower AI than controls in WA and MFG, but not for IFG. AI in MFG and WA were similar between left hemisphere focus/left language patients and right hemisphere focus patients. Patients activated more voxels than healthy volunteers. Lower AIs were attributable to greater activation in right homologous regions. Less activation in the right-side WA correlated with better verbal memory performance in right focus/left hemisphere-dominant patients, whereas less strongly lateralized activation in IFG correlated better with Verbal IQ in left focus/left hemisphere-dominant patients. *Conclusions:* Patients had lower asymmetry indices than healthy controls, reflecting increased recruitment of homologous right hemisphere areas for language processing. Greater right hemisphere activation may reflect greater cognitive effort in patient populations, the effect of epilepsy, or its treatment. Regional activation patterns reflect adaptive efforts at recruiting more widespread language processing networks that are differentially affected based on hemisphere of seizure focus.

NEUROLOGY 2005;65:1604–1611

Patients with localization-related epilepsy may exhibit intra- or interhemispheric functional reorganization of language processing.[1,2] fMRI, an established method to identify language networks,[3,4] can measure regional language lateralization.[5,6] Studies in adults and children using reading comprehension,[5,7] listening comprehension,[8-10] and single-word lexical processing[11-14] identify a distributed network that is highly lateralized. The areas "activated" encompass "receptive" language processing along the left superior temporal sulcus extending to the supramarginal gyrus (Brodmann area [BA] 21,22, 39), and "expressive" language processing in the left inferior frontal gyrus (BA 44,45, 47) and left middle frontal gyrus (BA 9,46). fMRI studies stressing verbal fluency and semantic decision targeted at frontal language networks confirm that 94 to 96% of healthy right-handed adult volunteers are left dominant for language.[15,16]

Several of these language paradigms have been used to determine the dominant hemisphere for language in patients considered for epilepsy surgery, principally as a noninvasive version of the intracarotid amobarbital test. As a consequence, most prior fMRI studies in patients with epilepsy aimed to optimize paradigms and strategies for determining hemisphere dominance for language.[10,17-21] These studies also confirm a higher incidence of atypical language dominance, approximately 25%, in epilepsy populations compared to healthy control groups.[15,21-23] Relatively few studies, however, have examined the effect of localization-related epilepsy on regional brain activation patterns associated with language processing.[15,21,24,25]

Based on the hypothesis that a left-sided seizure focus disrupts the normal representation of language functions, we predicted that patients with a left seizure focus would (1) exhibit a higher likelihood of

†Deceased July 2004.

From the Department of Neurosciences (Drs. Berl, Balsamo, Weinstein, Conry, Pearl, and Gaillard, E.N. Moore and B.C. Sachs), Children's National Medical Center, George Washington University School of Medicine, Washington, DC; Clinical Epilepsy Section (Drs. Balsamo, Xu, Grandin, Sato, Theodore, and Gaillard), NINDS, and Speech-Language Pathology Section (Dr. Frattali), Rehabilitation Medicine Department, Clinical Center, NIH, Bethesda, MD; Minnesota Epilepsy Group (Dr. Ritter), St. Paul, MN.

Supported by NINDS KO8-NS1663, NINDS R01 NS44280, NICHD P30HD40677, the Clinical Epilepsy Section, NINDS, NIH.

Disclosure: The authors report no conflicts of interest.

Received January 21, 2005. Accepted in final form August 9, 2005.

Address correspondence and reprint requests to Dr. William Davis Gaillard, Neurology, Children's National Medical Center, 111 Michigan Avenue NW, Washington, DC 20010; e-mail: wgaillar@cnmc.org

atypical language representation than right hemisphere seizure focus patients and normal controls and (2) show greater right hemisphere activation and less marked hemisphere dominance. Furthermore, left hemisphere focus patients who were left hemisphere dominant for language would be less strongly lateralized for language dominance compared to healthy controls. In contrast, patients with a right hemisphere seizure focus would not exhibit atypical language dominance and would be as strongly lateralized for language dominance as healthy controls. Finally, we investigated the relationship between language lateralization and facility of cognitive skills by correlating brain activation with neuropsychological measures. Whereas prior studies primarily targeted frontal language networks, we performed our study using a task previously demonstrated to activate reliably both temporal lobe language processing areas and frontal lobe language-processing areas.[5,21]

Methods. *Subjects.* Patients. Fifty patients (26 adults, 24 children) with complex partial seizures ranging in age from 8 to 56 years (mean 22.9 years) were evaluated with an fMRI reading paradigm as approved by the institutional review board of the National Institute of Neurologic Disorders and Stroke, NIH. Informed consent was obtained from adult patients and from parents of pediatric patients. Assent was obtained from minors. Forty-nine patients were native English speakers; one was fluent in English that had been acquired before age 5. Twenty-three were male and 27 female. Mean seizure onset age was 10.2 years (range 0.5 to 36). Forty patients were right handed, eight left handed, and two ambidextrous. Seizure focus was based on ictal and interictal EEG, MRI, and clinical characteristics. Thirty-four patients had left hemisphere focus and 16 patients had a right hemisphere focus. A temporal lobe focus was identified in 43 patients, extratemporal neocortical focus in five patients (four frontal, one parietal), and a frontotemporal focus in one. One patient had independent frontal and temporal foci in the same hemisphere. Structural MRI (1.5 T, Signa, General Electric Medical Systems, Milwaukee, WI) was normal in 21 (one later found to have microscopic dysplasia following resection, two had transient T2 temporal neocortical signal changes following initial seizure presentation), 19 had mesial temporal sclerosis (MTS), five had a mesial temporal low-grade tumor, three had mesial temporal dysplasia, and two had temporal lobe vascular malformations.

Normal controls. Thirty-three volunteers (21 adults, 12 children) who had normal neurologic examinations and normal structural MRI were studied with the same fMRI paradigm. The mean age for all normal volunteers was 22 years (range 7 to 43). Seventeen were male and 16 were female. All normal volunteers were native English speakers and right handed as measured by the Edinburgh Handedness Inventory.[26] Data on 30 patients and the normal volunteers were reported previously.[21]

Neuropsychological testing. Neuropsychological testing results were obtained from a patient's referring medical center. Measures varied among referral sources. They were included in this analysis if data were recorded for at least 15 patients. Domains included intellectual functioning, memory, and language. Intellectual assessment was conducted with the age-appropriate Wechsler scale (Wechsler Adult Intelligence Scale, Third Edition or Wechsler Intelligence Scale for Children, Third Edition. The mean Full Scale IQ (FSIQ) for patients (n = 38) was in the average range (93 ± 18) but ranged from the mentally retarded to superior range (55 to 138). Immediate verbal memory was measured by the Wechsler Memory Scale, Third Edition for adults and the Wide Range Assessment of Memory and Learning for children. Immediate verbal memory was average (ss = 9) for the sample (n = 26), ranging from below average to above average (4 to 15). Both children and adults were given the Boston Naming Test and Controlled Oral Word Association. Raw scores were converted to age-normed standardized scores. Naming was low average for the group (n = 25) with a mean standard score of 82 (SD = 23). Fluency (n = 21) was also low average with a mean standard score of 82 (SD = 31). Overall, patients' cognitive functioning fell in the average range. Specific measures on the healthy volunteers are unavailable; however, all but one of the adult volunteers held a college degree, and most held graduate degrees. Children were likely comparable to our subsequent pediatric study populations where the mean IQ is 115.[26,27]

MRI scanning. Scanning parameters have been described previously and are briefly reviewed. Whole-brain fMRI was conducted on a conventional 1.5-T scanner (Signa, General Electric Medical Systems).[5] Gradient-recalled echo–planar images were collected using TE (echo time) = 40 milliseconds, FOV (field of view) = 22 × 22 cm, acquisition matrix = 64 × 64, and interscan interval (repetition time [TR]) = 4000 milliseconds. During each functional scan, a brain volume composed of 20 contiguous 5-mm thick axial slices was selected to provide coverage of the entire brain (voxel size 3.4375 × 3.4375 × 5 mm).

After functional imaging, anatomic images were collected using a three-dimensional fast spoiled gradient echo (SPGR) sequence (TE = 3.5 milliseconds, TR = 10.1 milliseconds, inversion time [TI] = 600, flip angle 20 degrees, number of excitations [NEX] = 1, slice thickness = 5 mm, FOV = 24 × 24, acquisition matrix = 256 × 256). Images were collected parallel to the anterior commissure–posterior commissure plane. Foam padding and an adjustable cotton strip were used to limit head motion within the coil.

Ninety-six sequential echo-planar volumes were collected during functional image data acquisition (total scanning duration = 6 minutes, 24 seconds). The functional study employed a block design composed of six epoch cycles; each cycle consisted of an experimental task (reading an object description) alternated with a visual control task (viewing letter-sized black boxes). The stimuli were presented through a MacIntosh computer using Superlab software onto a rear projection screen positioned at the end of the scanner bed.

Experimental paradigm. In the experimental condition, read response naming (RRN), study participants were instructed to read silently a sentence describing an object and think to themselves a single word matching the description (e.g., "What is a long yellow fruit?" Answer: "banana.") Stimuli have been described previously[5] and were selected from the Peabody Picture Vocabulary Test[28] and the One Word Expressive Picture Vocabulary Test.[29] There were eight sentences per epoch. Control stimuli consisted of eight different patterns of letter-sized squares that were displayed one at a time and were matched for sentence length and horizontal degree of visual angle subtended. Patients were instructed to perform the task silently and not to move. The same experimental paradigm was used for all patients without adjusting for individual ability. Item difficulty was designed so that 85% of task items could be readily answered by a 10 year old. Item difficulty was based on normative and pilot screening data.

Individual image processing and region of interest (ROI) analysis. Our data processing and ROI analysis methods have been reported in detail previously, including a description of our ROIs, choice of threshold, and criteria for activation and lateralization.[21,30] They are validated in relation to invasive methods of language lateralization and are comparable to other fMRI studies for determining language dominance in epilepsy populations.[5,10,19,21-23,31] The three ROIs included inferior frontal gyrus (IFG), midfrontal gyrus (MFG), and Wernicke area (broadly defined) (WA) in the temporal/inferior parietal lobe. Motion was assessed by measuring the signal change for all voxels across the experimental run.[21,32]

Further analysis was performed using an IDL-based automated program that generated individual t maps (t = 4.0) comparing control and task conditions on a voxel by voxel basis.[33] Voxels that exceeded the statistical threshold were deemed "activated." ROIs were drawn on individual participants maps based on anatomic landmarks while blinded to activation patterns; voxels exceeding the t threshold were automatically counted in the region previously described.[5] A minimum of four voxels in a region and at least a four-voxel difference between hemispheres were required as part of the lateralization criteria to guard against spurious activation as data were unfiltered and not clustered.[5,21] Regional asymmetry indices (AIs) were calculated from number of activated voxels, with AI = [(L − R)/(L + R)], and language dominance

Table 1 *Healthy volunteer and patient group regional results for asymmetry index (AI) and voxel counts (SD)*

	AI			No. of voxels in left hemisphere			No. of voxels in right hemisphere		
Subject	IFG	MFG	Wernicke	IFG	MFG	Wernicke	IFG	MFG	Wernicke
Patients, n = 50	0.48 (0.54)	0.41 (0.55)	0.55 (0.41)	13.62 (18.98)	15.38 (14.93)	22.8 (19.56)	3.62 (4.97)	5.32 (6.55)	5.74 (5.73)
Normals, n = 33	0.72 (0.40)	0.78 (0.78)	0.84 (0.22)	8.18 (7.29)	10.79 (8.69)	18.36 (11.86)	1.12 (3.55)	0.94 (1.64)	1.94 (3.14)
Adult normal, n = 21	0.69 (0.41)	0.78 (0.32)	0.79 (0.24)	8.38 (7.33)	12.48 (9.03)	17.81 (11.64)	1.48 (4.32)	1.19 (1.72)	2.42 (3.72)
Child normal, n = 12	0.79 (0.40)	0.79 (0.40)	0.91 (0.15)	7.83 (7.52)	7.83 (7.52)	19.33 (12.68)	0.50 (1.45)	0.50 (1.45)	1.08 (1.51)
Child patient, n = 24	0.49 (0.51)	0.44 (0.56)	0.52 (0.35)	10.92 (12.77)	12.25 (11.96)	23.33 (20.75)	3.04 (4.67)	4.67 (5.75)	6.58 (5.88)
Adult patient, n = 26	0.48 (0.59)	0.38 (0.55)	0.58 (0.45)	16.12 (23.29)	18.27 (16.94)	22.31 (18.80)	4.15 (5.26)	5.92 (7.27)	4.96 (5.58)
Left focus, n = 34	0.36 (0.59)	0.36 (0.52)	0.51 (0.44)	10.65 (11.66)	13.59 (13.22)	24.76 (21.74)	3.41 (4.05)	5.50 (6.47)	6.32 (6.07)
Right focus, n = 16	0.76 (0.27)	0.52 (0.54)	0.64 (0.32)	19.94(28.55)	19.19 (17.92)	18.63 (13.54)	4.06 (6.64)	4.94 (6.90)	4.50 (4.87)
Left focus/left language, n = 27	0.45 (0.48)	0.45 (0.45)	0.65 (0.28)	12.85 (12.13)	16.00 (13.57)	28.67 (21.10)	3.56 (4.25)	5.59 (6.26)	6.59 (6.50)
Left focus/atypical language, n = 7	−0.03 (0.84)	0.004 (0.83)	−0.04 (0.52)	2.14 (1.95)	4.29 (5.99)	9.71 (18.33)	2.86 (3.44)	5.14 (7.76)	5.28 (4.23)
Right focus/left language, n = 16	0.76 (0.27)	0.52 (0.54)	0.64 (0.32)	19.94 (28.55)	19.19 (17.92)	18.63 (13.54)	4.06 (6.64)	4.94 (6.90)	4.50 (4.87)
Normals, n = 33	0.72 (0.40)	0.78 (0.34)	0.84 (0.22)	8.18 (7.29)	10.79 (8.69)	18.36 (11.86)	1.12 (3.55)	0.94 (1.64)	1.94 (3.14)

IFG = inferior frontal gyrus; MFG = midfrontal gyrus.

defined as |AI| >0.20. An AI >0.20 shows left hemisphere language dominance. Laterality for a patient was considered present when one or more regions had an AI >0.20. An AI between 0.20 and −0.20 was deemed bilateral activation. A study was also considered bilateral if two regions had opposite AI laterality. Atypical language dominance included patients with bilateral or right language (AI< −0.20).

For the initial analysis, the following were performed. 1) Voxel counts and AIs among the three ROIs were compared between normal volunteers and patients using a multiple analysis of variance (MANOVA). 2) Further analysis was conducted taking into account location of hemisphere dominance for language and seizure focus. We divided the patient groups between right and left hemisphere seizure focus and determined the presence of atypical language dominance, regional AIs, and voxel counts. 3) Next, based on our fMRI criteria for atypical language and side of seizure focus, we placed patients into four groups: we divided the left focus patients between those with left focus left language dominance (LF/LL) and those with left focus but atypical language dominance (LF/AL) and separated the right seizure focus group between right focus and left language dominance (RF/LL) and right focus with atypical language dominance (RF/AL). We then compared the LF/LL group to the RF/LL group to determine whether a left hemisphere seizure focus has deleterious effects on language processing despite preservation of typical left language dominance. 4) Finally, we examined the effect of lobe of seizure origin on language laterality. Correlation analyses were conducted with voxel count and absolute AI values and neuropsychological data from patients.

Results. Mean regional AIs and voxel numbers are presented in table 1 for normal volunteer and patient data. Typical activation maps for the task in healthy adults and children have been previously reported.[5,21] Adult and child activation patterns were similar. There were no differences between adults and children ($F = 1.103$, $p > 0.05$) in number of voxels activated or AI; therefore, groups were not separated by age for subsequent analyses. There were no differences in motion measures between children and adults.

Normal/patient comparisons. All but one normal volunteer was left language dominant for all ROIs examined. This one subject was left language dominant for frontal regions but bilateral for WA. There were differences in number of voxels activated and AI between patient and normal volunteers ($p < 0.001$) (see table 1). Patients had lower AI for IFG ($p < 0.05$), MFG ($p < 0.001$), and WA ($p < 0.0001$). The number of activated voxels in left hemisphere regions were not different between patients and controls for IFG or WA, but there was a trend for MFG ($p = 0.08$). However, patients had more voxels activated than normal volunteers for right hemisphere regions in IFG ($p < 0.01$), MFG ($p < 0.001$), and WA ($p < 0.001$) (figure 1). Patients moved less (the mean, median, and SD of change in signal intensity during the experimental run) than normal volunteers for all motion parameters ($p < 0.0001$).

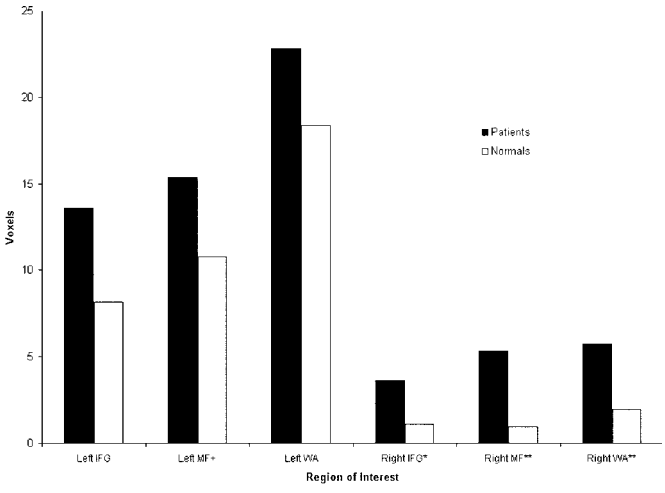

*Figure 1. Graphic comparison of voxel counts between patients (groups collapsed) and normal volunteers for left and right hemisphere regions of interest. IFG = inferior frontal gyrus; MF = midfrontal gyrus; WA = Wernicke area. +p = 0.08; *p < 0.01; **p < 0.001.*

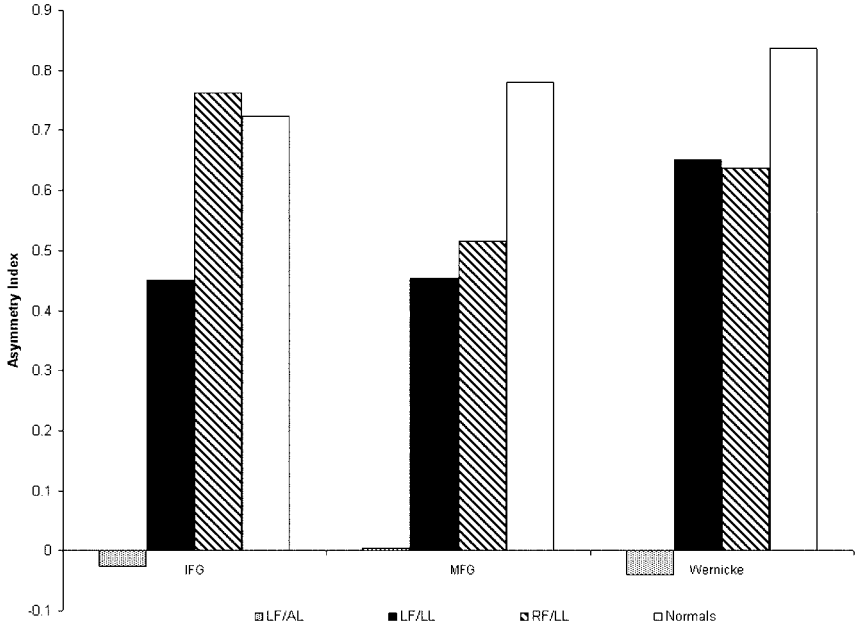

Figure 2. Graphic comparison of asymmetry index across normal volunteer and patient groups(LF/LL = left focus/left language; LF/AL = left focus/atypical language; RF/LL = right focus/left language) for region regions of interest. IFG = inferior frontal gyrus; MFG = midfrontal gyrus.

Seizure focus and language dominance comparisons. Experimental data were further examined based on side of focus and language dominance. Based on clinical evaluation and fMRI findings, patients fell into the following three groups: 27 patients were LF/LL dominant, seven patients were LF/AL, and 16 patients were RF/LL; only patients with a left hemisphere seizure focus had atypical language representation. Differences in regional AI and hemisphere voxel counts were found among subjects and the three patient groups ($p < 0.001$) (see table 1; figure 2).

Left and right focus. Patients with a left hemisphere focus had an overrepresentation of atypical language compared to right hemisphere focus patients (χ^2, $p < 0.002$). In patients with a left focus, we found a trend toward lower IFG AI for patients with earlier onset epilepsy ($p = 0.07$). The age at seizure onset did not correlate with asymmetry index in MFG or WA or with activated voxel number in any ROI in either hemisphere. All patients with atypical language dominance, however, either had seizure onset before age 6 years (four children), had risk factors (atypical handedness [three children]), or had brain lesions (MTS, dysplasia, vascular malformations [five children]) attributable to an age before 6 years. Duration of epilepsy was not associated with regional AI or voxel counts.

A trend toward differences in language activation between left and right focus patients was found ($p = 0.10$). This difference was largely accounted for by the significantly lower AI in IFG for left hemisphere patients ($p < 0.01$). All other voxel counts and AI values were similar among left and right focus patients. However, differences are revealed when patients are grouped according to seizure focus and language representation.

LF/AL. By definition, patients with LF/AL had lower AI than normal controls and other patient groups for all regions (IFG, $p < 0.01$; MFG, $p < 0.05$; WA, $p < 0.001$). However, due to the small sample size, the underlying, lateralized regional voxel counts that contributed to the AI differences showed trends rather than significant differences. LF/AL patients activated fewer voxels in left hemisphere regions compared to either subjects or other patients. Right hemisphere activation for the atypical group did not differ from the other two patient groups but was greater than the normal group.

LF/LL. LF/LL patients had a lower AI than normal controls for all tested areas ($p < 0.05$). For WA and MFG, LF/LL patients had AI values similar to those of RF/LL patients. For IFG, the AI was lower in LF/LL than RF/LL patients ($p < 0.05$).

RF/LL. RF/LL patients had AI values similar to those of normal controls for IFG, but were similar to left focus patients for MFG and WA. Although IFG AI values of RF/LL patients were similar to those of normal controls, the underlying distribution of voxels accounting for this pattern differed. RF/LL patients activated more left IFG voxels than any other group, normal or patient ($p < 0.05$). This group also activated more right IFG hemisphere voxels than subjects ($p < 0.05$). For MFG, right focus patients showed a trend toward lower AI values than normal controls ($p < 0.07$), remaining more similar to the LF/LL patient group. For WA, right focus patients had lower AI values than normal controls ($p < 0.05$) and laterality values comparable to those of left focus patients.

Lobar focus. Due to insufficient sample numbers, patients were divided into two groups: temporal lobe focus (n = 43) and nontemporal lobe focus (n = 7). MANOVA revealed no significant differences between the groups for voxel count or AIs for any ROI. In addition, subsequent analyses that omitted the five patients with an extratemporal focus did not alter interpretation of results.

Neuropsychological correlations. Table 2 shows IQ measures for patient groups. MANOVA found that the LF/AL patients performed the same as LF/LL in all tests but Performance IQ (PIQ) where their performance was lower than the LF/LL group ($p < 0.05$). There were no differences between LF/LL and RF/LL groups. Table 3 shows fMRI-neuropsychological correlations. For the LF/LL patients, higher Verbal IQ (VIQ) ($p < 0.05$) and higher FSIQ ($p < 0.05$) correlated with lower AI in IFG. Higher naming scores correlated with lower AI in MFG ($p < 0.05$). A trend was found for better verbal fluency to

Table 2 *IQ measures for patient groups*

Group	FSIQ (range)	VIQ (range)	PIQ (range)
Left focus/left language, n = 22	95 (68–138)	99 (64–133)	93 (66–136)
Right focus/left language, n = 12	92 (55–129)	95 (57–1423)	91 (556–111)
Left focus/atypical language, n = 4	84 (60–99)	77 (54–95)	95 (726–106)

FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ.

correlate with lower AI in IFG ($p = 0.09$). For the RF/LL patients, neuropsychological data were significantly positively correlated with activation in temporal and frontal lobe regions. Higher PIQ ($p < 0.01$), higher FSIQ ($p < 0.05$), and greater verbal fluency ($p < 0.01$) correlated with greater AI in WA. Better verbal fluency also correlated with greater AI in IFG ($p < 0.01$).

Discussion. We found both widespread and focal effects of localization-related epilepsy on the regional and hemispheric distribution of language processing. Age at seizure onset and the presence of a remote symptomatic cause influenced the frequency and extent of atypical language representation. As predicted, left hemisphere seizure focus patients had a higher incidence of atypical language dominance (20%) than right hemisphere focus patients (0%) or normal volunteers (3%). Atypical language dominance is reported 4 to 6% in the healthy right-handed population and 22 to 24% of the left-handed population.[1,15,16,34,35] All patients with evidence of atypical hemispheric dominance for language had either seizure onset or a risk factor for neurologic insult before age 6. Insult to the dominant hemisphere at an early age predisposes to atypical language representation.[1] The decrease in language laterality among the LF group in large part reflects the high incidence of atypical language dominance.

Studies in normal adult and child populations, using a variety of paradigms, find highly lateralized language both in degree of AI and percentage of subjects with left dominant activation. These left dominant findings pertain to frontal areas (IFG, MFG) and temporal regions (along the superior temporal sulcus) and are similar to findings from the normal population used in the present study.[5,21] Most previous studies have employed tasks that target, on an individual basis, frontal expressive language with an emphasis on verbal fluency,[11-13,19,36-38] or semantic decision.[11,14] Some investigations have employed reading or listening tasks that stress whole language comprehension using sentences or phrases rather than single words.[5,10,39,40] We selected a paradigm that requires both text comprehension and semantic recall that identifies expressive and receptive language networks in order to examine the effect of epilepsy on regional language processing.[5,9,21]

The proportion of patients with atypical language in the left hemisphere focus group is similar to reports of others using fMRI verbal fluency,[23,24,41] semantic decision,[15] and listening comprehension[24] where 23 to 33% of patients exhibit atypical language. These studies also report low atypical dominance in right hemisphere focus groups. fMRI studies in epilepsy populations find atypical language to be associated with early-onset seizures but did not consider remote symptomatic pathology.[15,22,24]

Patients with a left hemisphere focus, who remained left hemisphere dominant for language, demonstrated a lower AI than healthy volunteers. This observation supports the hypothesis that seizures, or their remote symptomatic cause, may have a deleterious effect on left hemisphere language- processing

Table 3 *Neuropsychological test and fMRI correlations*

Patient Group	Neuropsychological Measure	IFG AI	MFG AI	Wernicke area AI
Left focus/left language	VIQ	−0.471†	−0.276	0.022
	FSIQ	−0.488†	−0.346	−0.027
	BNT	−0.37	−0.494†	−0.224
	Fluency	−0.485‡	−0.377	0.111
	PIQ, story memory	No significant correlations		
Right focus/left language	PIQ	0.177	0.196	0.682*
	FSIQ	0.147	0.110	0.541†
	Fluency	0.886*	−0.057	0.850*
	VIQ, BNT, story memory	No significant correlations		
Left focus/atypical language	VIQ, PIQ, FSIQ	No significant correlations		

* $p < 0.01$; † $p < 0.05$; ‡$p = 0.09$.

IFG = inferior frontal gyrus; AI = asymmetry index; MFG = midfrontal gyrus; VIQ = Verbal IQ; FSIQ = Full Scale IQ; BNT = Boston Naming Test; PIQ = Performance IQ.

networks and cause a partial shift of language processing to homologous regions in the right, typically nondominant, hemisphere. Furthermore, LF/LL patients show that higher scores on IQ, naming, and fluency measures correlate with bilateral frontal activation. For the left hemisphere focus patients, successful recruitment of right frontal homologous regions is an adaptive cognitive strategy that preserves language capacity. Recent fMRI studies support the observation that patients with atypical language perform better on language measures than those with a left focus who remain left hemisphere dominant for language.[24]

Contrary to experimental predictions, however, the RF/LL group demonstrated a pattern similar to that of the LF/LL group rather than that of the healthy controls in MFG and WA. Only for IFG did the data support the study hypothesis: patients with a right-side focus activated significantly more voxels than any other group in the left IFG and AI was comparable to that of normal controls. For MFG, an intermediate pattern was seen, likely reflecting increased demands on working memory and planning.[42] For WA, where AI was reduced, higher scores on IQ and verbal fluency measures correlated with greater left lateralized temporal activation. Some of the RF patients paradoxically recruit right temporal regions for task. A right-sided seizure focus may have a deleterious effect on contralateral receptive language processing or on nonlinguistic aspects of language processing mediated by right temporal regions.[43-45] Increased right WA activation may be an adaptive response to these effects. There is some evidence of language-processing impairment in patients with right temporal lobe epilepsy[46] including paradoxically poor performance on phonologic and semantic tasks.[25] There is also evidence of improved verbal measures following right temporal lobectomy, supporting the notion of a remote deleterious effect of right hemispheric seizures on left hemisphere language functions.[47]

Regardless of side of seizure focus, patients had diminished AI values due to increased activation in homologous right cortical areas. There are several possible explanations for these observations: motion, medication, cognition, and the epilepsy disease process. Movement artifact may account for group differences by increasing the number of activated voxels, thereby decreasing AI values. Yet, movement measurements confirm that patients moved less than normal volunteers. Activation differences may be an effect of antiepileptic drugs (AEDs) in the patient population. AEDs are known to reduce global cerebral metabolic rates for glucose and cerebral blood flow, but neocortical region–specific effects of AEDs are not described.[48,49] It is unknown whether AEDs alter the blood oxygen level–dependent response on which fMRI is based or have region-specific cognitive effects.[50]

Differences in activation laterality and extent may be explained by differences in cognitive abilities, effort, and performance between patient sand control populations. Although the patients fell within the normal spectrum for IQ, the healthy volunteers likely had a higher cognitive profile and narrower IQ band.[7,27,51] The task was designed to be performed accurately by a 10-year-old child, but the paradigm design did not allow for monitoring performance measures such as accuracy or reaction time. Without in-scanner behavioral data, it is not possible to determine whether patients and normal volunteers differed in performance. Between-group differences could account for the increased activation in right homologous regions, as may be seen when the linguistic complexity of a task is greater.[5,52] Similarly, if the experimental task required greater effort, regardless of performance, for patients compared to normal volunteers, the general increase in voxel counts and lower AI may reflect engagement of homologous hemisphere networks recruited to compensate for perceived level of difficulty.[37]

Focal dominant hemisphere injury early in life is associated with reorganization of language processing. fMRI studies show left hemisphere neonatal stroke and left hemisphere congenital lesions result in reorganization of language functions to homologous regions in the right hemisphere.[53-56] Perinatal injury restricted to frontal periventricular areas causes a shift in frontal, but not temporal, processing networks, to right homologous areas.[57] Localization-related epilepsy exerts both regional and remote effects on brain structure and function. Volumetric structural imaging studies in temporal lobe epilepsy demonstrate hippocampal formation and temporal lobe atrophy,[58-61] atrophy in projections from temporal lobe such as thalamus,[62,63] and remote nonspecific global changes in gray and white matter volume.[64-67]

Localization-related epilepsy affects laterality and extent of brain activation in temporal and frontal language-processing areas. As most of our patients had a temporal lobe focus, the effect on frontal expressive language-processing networks in the left seizure focus group suggests a remote functional effect of epileptic activity beyond a local influence on temporal networks. A recent study used separate paradigms to target frontal (verbal fluency) and temporal language (listening to stories) -processing areas in adult patients with right and left mesial temporal lobe epilepsy (TLE).[24] The left TLE focus group had reduced AI for both regions compared to healthy controls and the right TLE group. When divided into patients with and without atypical language, collapsing the left and right focus patient groups, the AIs were reduced for the atypical patient group only. AI differences were less pronounced in the frontal region, which may reflect either 1) differing effects on frontal language processing found in mesial TLE or 2) a task effect because more bilateral activation is typically found in verbal fluency tasks relative to story-listening tasks.[13,37,40] Given the limited patients in our study with a frontal lobe focus, we cannot exclude a specific frontal seizure focus

effect on regional activation patterns, as reported in some intracarotid amobarbital test series.[68,69]

Patients with epilepsy may respond to the cognitive processing constraints of the disease process by using different regions of a widely distributed network here an adaptive regional weighting within the language-processing network. Additional support for this view is provided by a recent functional imaging study showing greater recruitment of frontal lobe areas implicated in single-word semantic and phonologic processing in adult patients with TLE compared to healthy volunteers.[25] Another study of verbal episodic memory, also in adult patients with TLE, found reduced left mesial hippocampal activation but greater left dorsolateral prefrontal activation relative to healthy controls, lending further support to shifting strategies and their underlying neural networks to meet cognitive processing demands.[70]

Atypical language representation is associated with early seizure onset or history of a risk factor for left hemisphere brain injury before age 6 years. Patients are more likely to engage right homologous areas when performing a task regardless of hemisphere focus. The side and location of the seizure focus differentially affects laterality across cortical language regions. The effect of lobar seizure focus on local and remote distributed language networks requires further study with larger populations divided into homogeneous groups based on focus and underlying pathology. Localization-related epilepsy exerts global brain effects on functional reorganization that may be driven by pathologic processes and furthered by adaptive changes.

Acknowledgment

The authors thank Dr. Bahman Jabbari, Walter Reed Army Medical Cente, and Dr. Carl Bazil, New-York Presbyterian Hospital, for referring patients.

References

1. Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann NY Acad Sci 1977; 299:355–369.
2. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989;71:316–326.
3. Binder JR. Neuroanatomy of language processing studied with functional MRI. Clin Neurosci 1997;4:87–94.
4. Gaillard WD. Functional MR imaging of language, memory, and sensorimotor cortex. Neuroimaging Clin N Am 2004;14:471–485.
5. Gaillard WD, Pugliese M, Grandin CB, et al. Cortical localization of reading in normal children: an fMRI language study. Neurology 2001; 57:47–54.
6. Ramsey NF, Sommer I, Rutten GJ, Kahn R. Combined analysis of language tasks in fMRI improves assessment of hemispheric dominance for language functions in individual subjects. Neuroimage 2001;13:719–733.
7. Shaywitz BA, Shaywitz SE, Pugh KR, et al. Disruption of posterior brain systems for reading in children with developmental dyslexia. Biol Psychiatry 2002;52:101–110.
8. Schlosser MJ, Aoyagi N, Fulbright RK, Gore JC, McCarthy G. Functional MRI studies of auditory comprehension. Hum Brain Mapp 1998; 6:1–13.
9. 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.
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. Poldrack RA, Wagner AD, Prull MW, et al. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. Neuroimage 1999;10:15–35.
12. Brown TT, Lugar HM, Coalson RS, et al. Developmental changes in human cerebral functional organization for word generation. Cereb Cortex 2005;15:275–290.
13. Wood AG, Harvey AS, Wellard RM, et al. Language cortex activation in normal children. Neurology 2004;63:1035–1044.
14. Frost JA, Binder JR, Springer JA, et al. Language processing is strongly left lateralized in both sexes: evidence from function MRI. Brain 1999;122:199–208.
15. Springer JA, Binder JR, Hammeke TA, et al. Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. Brain 1999;122:2033–2046.
16. Pujol J, Deus J, Losilla JM, Capdevila A. Cerebral lateralization of language in normal left-handed people studies by functional fMRI. Neurology 1999;52:1038–1043.
17. 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.
18. Gaillard WD, Balsamo L, Xu B, et al. fMRI language task panel improves determination of language dominance. Neurology 2004;63:1403–1408.
19. Benson RR, FitzGerald DB, LeSeuer LL, et al. Language dominance determined by whole brain functional MRI in patients with brain lesions. Neurology 1999;52:798–809.
20. Rutten GJ, Ramsey NF, van Rijen, PC, Alpherts WC, van Veelen, CW. FMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. Neuroimage 2002;17:447–460.
21. Gaillard WD, Balsamo L, Xu B, et al. Language dominance in partial epilepsy patients identified with an fMRI reading task. Neurology 2002; 59:256–265.
22. Woermann FG, Jokeit H, Luerding R, et al. Language lateralization by Wada test and fMRI in 100 patients with epilepsy. Neurology 2003;61: 699–701.
23. Adcock JE, Wise RG, Oxbury JM, Oxbury SM, Matthews PM. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. Neuroimage 2003;18:423–438.
24. Thivard L, Hombrouck J, du Montcel, ST, et al. Productive and perceptive language reorganization in temporal lobe epilepsy. Neuroimage 2005;24:841–851.
25. Billingsley RL, McAndrews MP, Crawley AP, Mikulis DJ. Functional MRI of phonological and semantic processing in temporal lobe epilepsy. Brain 2001;124:1218–1227.
26. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
27. Gaillard WD, Balsamo LM, Ibrahim Z, Sachs BC, Xu B. fMRI identifies regional specialization of neural networks for reading in young children. Neurology 2003;60:94–100.
28. Dunn L. Peabody picture vocabulary test-revised. Circle Pines, MN: American Guidance Center, 1981.
29. Gardner M. Expressive one-word picture vocabulary test-revised. Novato, CA: Academic Therapy Publications, 1990.
30. Gaillard WD, Grandin CB, Xu B. Developmental aspects of pediatric fMRI: considerations for image acquisition, analysis, and interpretation. Neuroimage 2001;13:239–249.
31. Rutten GJ, RN, van Rijen PC, Noordmans HJ, van Veelen, CW. Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. Ann Neurol 2002;51:350–360.
32. Weinberger DR, Mattay V, Callicott J, et al. fMRI applications in schizophrenia research. Neuroimage 1996;4:S118–S126.
33. Mattay VS, Frank JA, Santha AK, et al. Whole-brain functional mapping with isotropic MR imaging. Radiology 1996;201:399–404.
34. Szaflarski JP, Binder JR, Possing ET, et al. Language lateralization in left-handed and ambidextrous people: fMRI data. Neurology 2002;59: 238–244.
35. Knecht S, Deppe M, Drager B, et al. Language lateralization in healthy right-handers. Brain 2000;123:74–81.
36. Gaillard WD, Hertz-Pannier L, Mott SH, et al. Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. Neurology 2000;54:180–185.
37. Gaillard WD, Sachs BC, Whitnah JR, et al. Developmental aspects of language processing: fMRI of verbal fluency in children and adults. Hum Brain Mapp 2003;18:176–185.
38. Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. Annu Rev Neurosci 2002;25:151–188.
39. Schlosser MJ, Luby M, Spencer DD, Awad IA, McCarthy G. Comparative localization of auditory comprehension by using functional magnetic resonance imaging and cortical stimulation. Neurosurgery 1999; 91:626–635.
40. Ahmad Z, Balsamo LM, Sachs BC, Xu B, Gaillard WD. Auditory comprehension of language in young children: Neural networks identified with fMRI. Neurology 2003;60:1598–1605.

41. Woermann FG, Jokeit H, Luerding R, et al. Language lateralization by Wada test and fMRI in 100 patients with epilepsy. Neurology 2003;61: 699–701.
42. Gabrieli JD, Poldrack RA, Desmond JE. The role of left prefrontal cortex in language and memory. Proc Natl Acad Sci USA 1998;95:906–913.
43. Ross ED, Mesulam MM. Dominant language functions of the right hemisphere? Prosody and emotional gesturing. Arch Neurol 1979;36: 144–148.
44. Beeman M, Friedman RB, Grafman J, et al. Summation priming and coarse coding in the right hemisphere. J Cogn Neurosci 1994;6:26–45.
45. Fletcher PC, Happe F, Frith U, et al. Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. Cognition 1995;57:109–128.
46. Helmstaedter C, Kurthen M, Gleissner U, Linke DB, Elger CE. Natural atypical language dominance and language shifts from the right to the left hemisphere in right hemisphere pathology. Naturwissenschaften 1997;84:250–252.
47. Novelly RA, Augustine EA, Mattson RH, et al. Selective memory improvement and impairment in temporal lobectomy for epilepsy. Ann Neurol 1984;15:64–67.
48. Gaillard WD, Zeffiro T, Fazilat S, DeCarli C, Theodore WH. Effect of valproate on cerebral metabolism and blood flow: an 18F-2-deoxyglucose and 15O water positron emission tomography study. Epilepsia 1996;37:515–521.
49. Theodore WH. Antiepileptic drugs and cerebral glucose metabolism. Epilepsia 1988;29(suppl 2):S48–S55.
50. Loring DW, Meador KJ. Cognitive and behavioral effects of epilepsy treatment. Epilepsia 2001;42(suppl 8):24–32.
51. Schlaggar BL, Brown TT, Lugar HM, et al. Functional neuroanatomical differences between adults and school-age children in the processing of single words. Science 2002;296:1476–1479.
52. Just MA, Carpenter PA, Keller TA, Eddy WF, Thulborn KR. Brain activity modulated by sentence comprehension. Science 1996;274:114–116.
53. Booth JR, Macwhinney B, Thulborn KR, et al. Functional organization of activation patterns in children: whole brain fMRI imaging during three different cognitive tasks. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:669–682.
54. Booth JR, MacWhinney B, Thulborn KR, et al. Developmental and lesion effects in brain activation during sentence comprehension and mental rotation. Dev Neuropsychol 2000;18:139–169.
55. Staudt M, Lidzba K, Grodd W, et al. Right-hemispheric organization of language following early left-sided brain lesions: functional MRI topography. Neuroimage 2002;16:954–967.
56. Liegeois F, Connelly A, Cross JH, et al. Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. Brain 2004;127:1229–1236.
57. Staudt M, Grodd W, Niemann G, et al. Early left periventricular brain lesions induce right hemispheric organization of speech. Neurology 2001;57:122–125.
58. Cascino GD, Jack CR Jr, Parisi, JE, et al. Magnetic resonance imaging-based volume studies in temporal lobe epilepsy: pathological correlations. Ann Neurol 1991;30:31–36.
59. Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. Brain 1992;115:1001–1015.
60. Bernasconi N, Bernasconi A, Caramanos Z, et al. Mesial temporal damage in temporal lobe epilepsy: a volumetric MRI study of the hippocampus, amygdala and parahippocampal region. Brain 2003;126:462–469.
61. Cendes F, Andermann F, Gloor P, et al. MRI volumetric measurement of amygdala and hippocampus in temporal lobe epilepsy. Neurology 1993;43:719–725.
62. DeCarli C, Hatta J, Fazilat S, Gaillard WD, Theodore WH. Extratemporal atrophy in patients with complex partial seizures of left temporal origin. Ann Neurol 1998;43:41–45.
63. Natsume J, Bernasconi N, Andermann F, Bernasconi A. MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy. Neurology 2003;60:1296–1300.
64. Liu RS, Lemieux L, Bell GS, et al. Progressive neocortical damage in epilepsy. Ann Neurol 2003;53:312–324.
65. Theodore WH, DeCarli C, Gaillard WD. Total cerebral volume is reduced in patients with localization-related epilepsy and a history of complex febrile seizures. Arch Neurol 2003;60:250–252.
66. Marsh L, Morrell MJ, Shear PK, et al. Cortical and hippocampal volume deficits in temporal lobe epilepsy. Epilepsia 1997;38:576–587.
67. Lawson JA, Vogrin S, Bleasel AF, Cook MJ, Bye AM. Cerebral and cerebellar volume reduction in children with intractable epilepsy. Epilepsia 2000;41:1456–1462.
68. Woods RP, Dodrill CB, Ojemann GA. Brain injury, handedness, and speech lateralization in a series of amobarbital studies. Ann Neurol 1988;23:510–518.
69. Helmstaedter C, Kurthen M, Linke DB, Elger CE. Patterns of language dominance in focal left and right hemisphere epilepsies: relation to MRI findings, EEG, sex, and age at onset of epilepsy. Brain Cogn 1997;33: 135–150.
70. Dupont S, Van de Moortele PF, Samson S, et al. Episodic memory in left temporal lobe epilepsy: a functional MRI study. Brain 2000;123: 1722–1732.