Atypical language in lesional and nonlesional complex partial epilepsy

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ABSTRACT

Objective: We investigated the relationship between partial epilepsy, MRI findings, and atypical language representation.

Methods: A total of 102 patients (4 to 55 years) with left hemisphere epileptogenic zones were evaluated using three fMRI language tasks obtained at 1.5 or 3T with EPI BOLD techniques: verbal fluency, reading comprehension, and auditory comprehension. fMRI maps were visually interpreted at a standard threshold and rated as left or atypical language.

Results: Atypical language dominance occurred in 30 patients (29%) and varied with MRI type ($p < 0.01$). Atypical language representation occurred in 36% (13/36) with normal MRI, 21% (6/29) with mesial temporal sclerosis, 14% (4/28) with focal cortical lesions (dysplasia, tumor, vascular malformation), and all (6/6) with a history of stroke. Multivariate logistic regression analysis found handedness, seizure onset, and MRI type accounted for much of the variance in language activation patterns ($\chi^2 = 24.09$, $p < 0.01$). Atypical language was more prevalent in patients with early seizure onset (43.2%, $p < 0.05$) and atypical handedness (60%, $p < 0.01$). None of the three clinical factors were correlated with each other ($p > 0.40$). Patients with atypical language had lower verbal abilities ($F = 6.96$, $p = 0.01$) and a trend toward lower nonverbal abilities ($F = 3.58$, $p = 0.06$). There were no differences in rates of atypical language across time, age groups, or MRI scanner.

Conclusion: Early seizure onset and atypical handedness, as well as the location and nature of pathologic substrate, are important factors in language reorganization. *Neurology*® 2007;69:1761–1771

GLOSSARY

FOV = field of view; **MTS** = mesial temporal sclerosis; **RRN** = read response naming; **TE** = echo time; **TR** = repetition time; **WAIS** = Wechsler Adult Intelligence Scale; **WISC** = Wechsler Intelligence Scale for Children.

fMRI is an effective and reliable means to lateralize and localize language processing regions in patients with refractory localization related epilepsy, and has been used to plan epilepsy surgery.[1,2] fMRI may also be employed to study the effect of epilepsy on language networks.[3-5] Early seizure onset age and atypical handedness have been associated with atypical language representation.[2,6-8] However, the impact of other factors, particularly underlying pathology, on laterality and location of language networks is uncertain.

In this study we employed a panel of language tasks known to activate expressive frontal language processing networks and receptive temporal processing areas.[9] These tasks are designed to provide regional redundancy—aspects of two tasks target the same region—to assure reproducible findings. Previous studies demonstrated and confirmed the reliability of visual rating, a clinical approach used increasingly for fMRI evaluation, in comparison to ROI quantitative methods and in relation to invasive methods.[1,6,9-12]

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Our results illustrate the effects of pathologic substrates on language processing networks.

METHODS Subjects. We evaluated 102 consecutive successfully scanned patients with complex partial seizures and left hemisphere seizure focus, ranging in age from 4 to 55 years (mean 22.7 years; 56 boys and men; 46 girls and women; 4 additional patients were not included in the study due to excessive movement and poor cooperation). Seven participants were between ages 4 and 9 years; 37 were between ages 10 and 17 years. Patients were evaluated between 1996 and 2005. The study was approved by the institutional review boards 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.

Mean age at seizure onset was 11.5 years (range 6 months to 43 years). Since Edinburgh handedness inventories and comparable scales for children were not available uniformly, we based categorization on clinical evaluation, and checked the procedure against the inventories we had. Using this procedure, we found that 71 patients were right handed, 16 were left handed, and 4 were ambidextrous (able to use either hand for a number of activities, or using different hands for different activities). All participants had left hemisphere seizure focus lateralization based on clinical features, neurologic examination, standard EEG/ictal video-EEG, and high resolution structural 1.5 T MRI (Signa, General Electric Medical Systems, Milwaukee, WI). A clear temporal lobe focus was identified in 70 patients. MRI was normal in 35 patients; 29 had mesial temporal sclerosis (MTS); 28 had a low grade tumor, focal dysplasia, or vascular malformation in temporal (25; 8 mesial) or frontal (4) regions (one had vascular malformations in left frontal and temporal regions); 6 had a history of a vascular event ("stroke"); and 3 had suspected Rasmussen encephalitis. Dual pathology was seen in 2 patients: 1 with periventricular nodular heterotopia, perinatal ischemia (left MCA), and MTS (scored under stroke); 1 left superior temporal gyrus glioma resected at age 2 (scored under lesion). Stroke was congenital/perinatal in 5 (left middle cerebral artery cortical in 4, grade IV intraventricular hemorrhage in 1): the other child had a left basal ganglia infarct at age 5.

Cognitive testing. Cognitive testing was conducted across the five epilepsy centers that referred patients for functional MRI studies. Patients were given the most recent version at the time of testing of the age-appropriate Wechsler measure (Wechsler Intelligence Scale for Children, Third or Fourth Edition [WISC-III (n = 10) or WISC-IV (n = 22)], Wechsler Adult Intelligence Scale, Revised or Third Edition [WAIS-R (n = 2), WAIS-III (n = 34)]). Therefore, data were analyzed using only the verbal (VIQ) and performance (PIQ) composite scores as the full-scale IQs vary significantly depending on the edition (e.g., WISC-III vs WISC-IV). Intellectual test scores were available for 68 of 102 patients.

MRI. MRI methods have been described previously, and are briefly summarized here.[10,13] Our scanners and paradigms have been upgraded and modified over the past several years. The principal changes included moving to higher magnetic fields and decreasing repetition time (TR) (subsequent upgrades allowed moving from 5 mm to 4 mm axial slices), and modifying covert language paradigms to allow for in scanner performance monitoring during experimental and control conditions. Fifty-eight patients were scanned using whole-brain functional MRI on a conventional 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, WI). Echoplanar images were collected using the following parameters: echo time (TE) = 40 msec, field of view (FOV) = 22 × 22 cm, acquisition matrix = 64 × 64. 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). Images were collected parallel to the anterior commissure–posterior commissure plane.

Forty-five patients were scanned using whole-brain functional MRI on a conventional 3 Tesla scanner (General Electric Medical Systems, Milwaukee, WI). Gradient echoplanar images were collected using TE = 30 msec, FOV = 22 × 22 cm, acquisition matrix = 64 × 64, and interscan interval (TR) = 2,000 msec. Brain volumes consisted of 24 × 5-mm-thick axial slices (31 patients) or 28 × 4-mm-thick axial thick slices (15 patients). Anatomic images were collected using a three-dimensional fast SPGR sequence and brain volumes consisting of 24 to 28 axial slices (4 to 5 mm thickness). Images were collected parallel to the anterior commissure–posterior commissure plane.

For covert unmonitored paradigms, performed in 58 patients, 96 sequential echoplanar volumes were collected with an interscan interval (TR) of 4 seconds during functional image data acquisition (total scanning duration = 6 minutes 24 seconds). The functional studies employed a block design with six epoch cycles; each cycle consisted of an experimental condition that alternated with a control condition, each hemicycle lasted 32 seconds. Total time for each paradigm was 6 minutes 24 seconds. Visual stimuli were presented through a MacIntosh computer using Superlab software onto a rear projection screen positioned at the end of the scanner bed. Auditory stimuli were digitized and presented via a PC using E-Prime computer software v1.1 (Psychology Software Tools, Inc., Pittsburgh, PA) through pneumatic earphones. Patients were instructed to remain silent and motionless.

For monitored paradigms, performed in 45 patients, the functional studies employed a block design composed of five epoch cycles; each cycle consisted of an experimental condition that alternated with a control condition, each hemicycle lasted 30 seconds. Total time for each paradigm was 5 minutes. The control and experimental tasks were designed and run using the Windows-based program E-prime. Visual stimuli were presented through a rear projection screen, auditory stimuli were digitized and presented via pneumatic earphones. Patients were instructed to remain silent and motionless. Responses were performed via fiber-optic push button response recorded by PC in E-prime.

Language paradigms. Our early paradigms performed in just over half of our patients were covert and unmonitored. The unmonitored covert auditory paradigms were subsequently modified to incorporate a reverse speech control condition. To achieve in-scanner monitoring the covert generation tasks were transformed to semantic decision tasks.

Verbal fluency (55 patients). The verbal fluency experimental condition required patients to generate words from letters (C, L, F, P, R, W) or categories (animals, food, clothes, furniture, toys, and TV shows) (performed in the

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younger children). The control condition was silent rest. The two verbal fluency paradigms show similar activation patterns and were targeted to identify dominant IFG and MFG.[14-16]

Auditory semantic decision task (43 patients). The verbal fluency task was modified to the auditory semantic decision task to allow for in scanner performance monitoring. During the active condition patients were presented with a category (animal, food), and asked to decide if subsequent words presented every 2 seconds for that hemicycle matched the category. Tasks were designed for 70% correct targets, 30% foils. The control condition consisted of reverse speech, sounds followed by a high pitched beep. Subjects used a button press response for correct targets or tone.[17]

Reading comprehension: Read response naming (44 patients). The read response naming (RRN) experimental condition required the subject to provide a covert one-word response to a brief written question describing an object (e.g., "What is a long yellow fruit?" answer "banana").[10,13,18] There were eight sentences delivered per epoch. Control stimuli consisted of dot patterns matched for sentence length and visual angle subtended. The same experimental paradigm was used for all patients, and was not adjusted for individual ability. Paradigm sentence clues were designed so that 85% of task items could be readily answered by a 10-year-old. The paradigm was targeted to identify dominant mid and superior temporal regions and dominant IFG and MFG.[10,13]

Reading comprehension: Reading stories (88 patients). The reading stories experimental condition consisted of reading stories adapted from *Aesop for Children*.[13,19] Paradigms were selected from two levels to account for patients' reading skills. A paragraph was presented every 10.2 seconds during the experimental condition. Control stimuli consisted of dot patterns matched for sentence length and horizontal degree of visual angle subtended. The paradigm was targeted to identify dominant middle temporal gyrus and superior temporal gyrus in addition to dominant IFG and MFG.[13] The task was modified (subset 42 patients) adjusted for reading ability based on DIBELS for reading levels third grade and below, and GORT IV for fourth grade and above, and to provide for in scanner monitoring by adding a button press for periods following sentences during active condition and button press for open vs filled dots.

Auditory comprehension: Listening to stories (88 patients). The listening to stories experimental condition consisted of listening to stories adapted from *Aesop for Children*.[19,20] The control condition was silent rest for 13 patients, and reverse speech for 42 patients. The reverse speech control, which balanced the length tone and pitch of the experimental condition, was added to account for first and second order auditory processing and to isolate better language processing areas in the dominant temporal lobe.[20] This paradigm was targeted to identify temporal receptive cortex regions along the dominant superior temporal sulcus.[20-22] The paradigm was modified further to provide for in scanner monitoring and adjusted for language ability based on DIBELS for reading levels third grade and below, and GORT IV for fourth grade and above, with an intermixed button push response for inserted beeps in active and control conditions (45 patients).

Auditory comprehension: Auditory response naming (45 patients). The auditory response naming experimental condition required patients to covertly respond to auditory clues similar to the RRN paradigm described above.[10,18] Stimuli were presented every 3 seconds for adults and every 4 seconds for children. The control condition was silent rest for 19 patients, and reverse speech for 26 patients. The reverse speech control was added to account for primary and secondary auditory processing. The paradigm was targeted to identify dominant superior temporal regions and dominant IFG and MFG.[9,18,23]

Auditory description decision task (44 patients). The auditory description decision task is a modification of the auditory response naming task, designed to provide in scanner monitoring of performance by requiring a semantic decision identified by button press response. Thus, for the active condition, "A long yellow fruit is a banana"; 70% of items are correct targets, 30% foils. The control condition is reverse speech with tone identification.

Ninety-seven patients performed a verbal fluency/semantic decision task, 88 a reading comprehension task, 88 an auditory comprehension task, and 93 some version (auditory or visual) of naming to description/semantic decision naming.

Overall, 399 tasks were performed (mean, 3.9 tasks per patient) with the 102 study participants. One patient performed seven tasks (both a monitored set at 3 T and an unmonitored set at 1.5 T; results were the same); 1 performed six tasks; 30, five tasks; 45, four tasks; 16, three tasks; and 9, two tasks. The time in the scanner needed to obtain four tasks, including localizer and three-dimensional SPGR anatomic sequence, was 45 to 50 minutes. Of 399 data sets, 27 were nondiagnostic (7% of all runs) either showing no activation, movement artifact, or were technical failures. Typically the younger and Spanish-speaking patients performed three tasks, and the youngest patients only two. In addition to selecting tasks to identify frontal and temporal language processing areas, tasks were designed so that at least two paradigms targeted similar language processing functions and regions. For example, verbal fluency and response naming were targeted to frontal regions, and reading and listening comprehension targeted to identify temporal receptive language areas.

Individual image processing and interpretation. Unmonitored paradigms performed at 1.5 T were processed using a semiautomated program that generated individual t maps comparing control and experimental conditions on a voxel by voxel basis after images were reconstructed and corrected for motion.[9,13] Voxels that exceeded the statistical threshold were deemed activated. Monitored studies performed at 3 T (45 patients) were analyzed in native space using SPM 2. Paradigms at 1.5 T were viewed and rated at $t = 4.0$,[10] and those at 3 T and analyzed in SPM were rated at $p < 0.001$ uncorrected.[24] Whole brain fMRI images were visually inspected and rated for lateralization.[1,9-12] For a region (Broca or Wernicke) to be deemed lateralized, 60% or more of activated voxels in a paired region had to occur in one hemisphere compared to the homologue; this criterion corresponds to an AI of greater than 0.20 and is commonly used to define language dominance.[10,25,26] Left dominance was defined as typical language as 96% of right-handed individuals are left hemisphere dominant for language[7,8,26]; right or bilateral language representation was considered to be atypical language. For clinical interpretation, studies were clustered to verbal fluency, reading comprehension, auditory comprehension, and rated for frontal and temporal activa-

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Table 1 fMRI atypical language: Clinical and MRI variables

	All language classifications		Left hemisphere language		Atypical language	
	No.	% of whole sample	No.	% of LH language	No.	% of RH language
All patients	102		72	70.6	30	29.4
Clinical factors						
Atypical handedness	20	19.6	8	11.1	12	40
Onset before age 6	37	36.6	21	29.6	16	53.3
MRI type						
Normal MRI	36	35.3	23	31.9	13	43.3
MTS	29	28.4	23	31.9	6	20
Lesion	28	27.5	24	33.3	4	13.3
Stroke	6	5.9	0	0	6	20
Inflammatory	3	2.9	2	2.8	1	3.3
Verbal IQ	Mean = 94.03		Mean = 97.33		Mean = 86.27	
Performance IQ	Mean = 93.03		Mean = 94.98		Mean = 87.77	

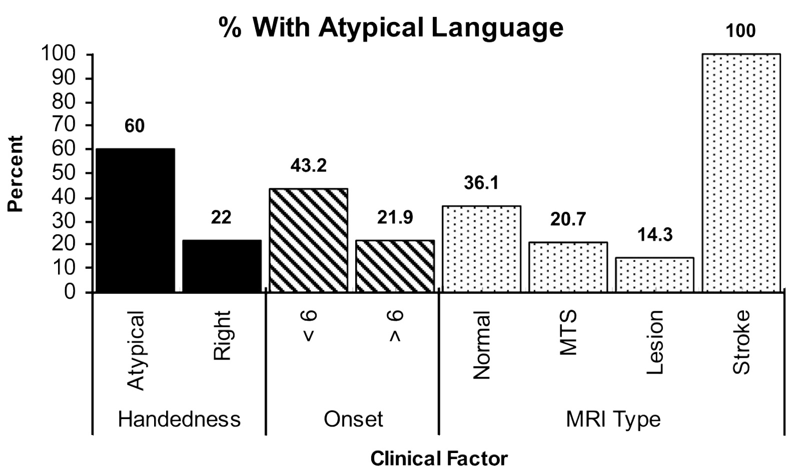
LH = left hemisphere; RH = right hemisphere; MTS = mesial temporal sclerosis.

tion. A patient's language dominance was deemed lateralized (left or right) if one or more paradigm clusters lateralized and no more than one cluster was rated bilateral; a patient's language was deemed bilateral if two clusters were deemed bilateral (and the third cluster lateralized), or if one paradigm cluster was right lateralized with one other left lateralized, or if none lateralized with at least one cluster rated bilateral.[9] Atypical language occurred when activation patterns were right lateralized or bilateral activation. Bilateral activation took several forms: bilateral frontal activation but unilateral temporal activation, bitemporal activation but unilateral frontal activation, diaschisis of activation between frontal and temporal areas, and inconsistent lateralization of activation across different tasks.[2,4]

Six of our patients spoke Spanish as their first language. Their tests were conducted in their first language as the cortical representation of second languages likely varies with proficiency in, and age at acquisition of, the second language.[27,28] Localization of native language functions is the same regardless of the language as demonstrated by fMRI studies conducted in French, German, Dutch, and Chinese.[11,21,28,29]

Following coding of fMRI data, handedness, age at onset, and pathology based on MRI, analyses were conducted in SPSS using parametric and nonparametric comparisons including χ^2, correlation, multivariate analysis of variance, and logistic regression.

Figure 1 Atypical language and subgroups



MTS = mesial temporal sclerosis.

RESULTS

Descriptive analyses. Thirty (29.4%) of the 102 patients had atypical language activation patterns (table 1). Atypical handedness was also common in this population (19.6%). Over a third (36.6%) of the patients had seizure onset before age 6. As described above, patients had normal MRI (35.3%) or were classified according to one of four abnormal MRI types (MTS [28.4%], lesion [27.5%], stroke [5.9%], and inflammatory [2.9%]). There was no difference in sensitivity for identifying atypical language between studies performed at 3 T compared to 1.5 T. The relationships among the three clinical factors (handedness, age at onset, and MRI type) and atypical language representation are presented below (figure 1).

Handedness. Atypical language was found in 22% of right handed patients compared to 60% of atypical handed patients ($\chi^2 = 11.12$, $p = 0.001$) (figure 1). Similarly, a higher proportion of patients with atypical language (40%) had atypical handedness compared to 11.1% of patients who were left-language dominant ($\chi^2 = 5.03$, $p < 0.05$) (table 1).

Seizure onset. Atypical language was found in 43.2% of patients with seizure onset age 6 years or younger compared with 19.7% of those with onset after 6 ($\chi^2 = 5.127$, $p < 0.05$) (figure 1).

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There was a trend toward earlier seizure onset in patients with atypical language (8.8 vs 12.7 years; $p = 0.07$). Moreover, the incidence decreased with age as 23.7% of patients with seizure onset between 7 and 15 years and 13.6% of patients 16 years and older had atypical language. Similarly, a higher proportion of patients with atypical language (53.3%) had early onset compared to 29.6% of patients who were left-language dominant ($\chi^2 = 10.21$, $p < 0.01$) (table 1).

MRI type. MRI structural lesions affected the incidence of atypical language ($\chi^2 = 19.349$; $p = 0.001$) (figure 1). All 6 (100%) patients with a history of stroke had atypical language. Patients with a normal MRI were more likely (36.1%) to have atypical language than patients with lesions (excluding MTS) on MRI (14.3%). The incidence of atypical language in patients with MTS (20.7%) was not significantly different from the lesion or normal MRI groups. The distribution of MRI types did not differ between patients with atypical language and left-language dominance ($\chi^2 = 0.001$, $p = 0.98$). There was a trend toward a higher prevalence of stroke; 20% with atypical language, compared to no left dominant patients ($p = 0.06$) (table 1). Patients with inflammatory MRI were excluded from this analysis as there were only three cases.

Relationships among clinical factors. The relationships among the clinical factors were highly influenced by the six patients with stroke: all had atypical language, atypical handedness, and seizure onset before age 6. Within the entire sample, atypical handedness (Spearman rho = −0.33, $p < 0.01$) and early age at seizure onset (Spearman rho = −0.23, $p < 0.05$) were both correlated with atypical language. Moreover, none of the three clinical factors (handedness, seizure onset, and MRI type) were correlated ($p > 0.40$). Excluding the patients with stroke, MRI type (Spearman rho = −0.21, $p < 0.05$) was correlated with atypical language and there was a trend for atypical handedness (Spearman rho = −0.18, $p = 0.09$) and early age at seizure onset (Spearman rho = −0.17, $p = 0.10$) to be correlated with atypical language. Without the patients with stroke, there was a trend for MRI type and handedness (Spearman rho = 0.18, $p = 0.09$) to be correlated. A multivariate logistic regression analysis revealed that the three clinical factors accounted for much of the variance in atypical language ($\chi^2 = 24.09$, $p < 0.01$) with early seizure onset being the strongest factor, followed by handedness. Discriminant analysis revealed that onset ($F = 9.7$, $p < 0.01$) and handedness ($F = 12.33$, $p < 0.01$) correctly classified language dominance in 74.5% of the patients, with greater classification accuracy in patients with left-language dominance (88.4%). MRI type was not a significant predictor.

Table 2 Distribution of clinical factors for subset of sample who underwent cognitive testing

	No.	% of whole sample
Total sample with cognitive data	68	
Clinical factors		
Atypical language representation	23	33.8
Atypical handedness	15	22.1
Onset before age 6	28	41.2
MRI type		
Normal MRI	27	39.7
MTS	22	32.4
Lesion	13	19.1
Stroke	5	7.4
Inflammatory	1	1.5

MTS = mesial temporal sclerosis.

Cognitive abilities. Cognitive results were available for a representative subset of the study population, which did not differ significantly in terms of distribution across clinical factors (atypical language representation, handedness, MRI type; table 2). Verbal (mean VIQ = 94.03) and nonverbal (mean PIQ = 93.03) fell in the average range (table 1). Patients with atypical language had lower verbal abilities ($F = 6.96$, $p = 0.01$) and a trend toward lower nonverbal abilities ($F = 3.58$, $p = 0.06$). Specifically, patients with atypical language showed low average abilities (mean VIQ = 86.27) compared to solidly average verbal abilities in left-language dominant patients (mean VIQ = 97.33) with an 11-point IQ advantage. Similarly, patients with atypical language showed low average nonverbal abilities (mean PIQ = 87.77) compared to solidly average nonverbal abilities (mean PIQ = 94.98) with a seven-point IQ advantage.

There were some differences in cognitive abilities according to the three clinical factors (figure 2). Patients with atypical handedness had lower nonverbal abilities ($F = 7.93$, $p < 0.01$) and a trend toward lower verbal abilities ($F = 3.24$, $p = 0.08$). There were no significant differences in verbal or nonverbal abilities based on early age at onset ($F = 1.36$, $p = 0.26$). Patients with different MRI types were overall not different on cognitive testing ($F = 1.58$, $p = 0.16$); however, there was a trend for patients with stroke ($p = 0.10$) to have low average abilities (mean VIQ = 81.00; mean

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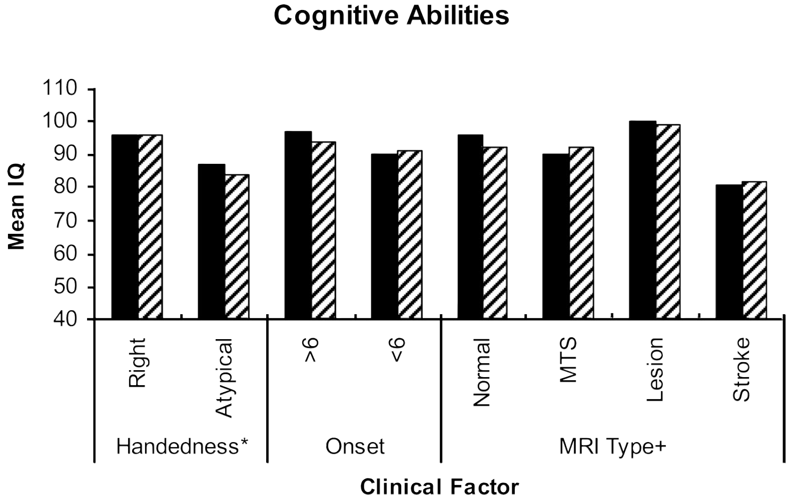
Figure 2 IQ measures and subgroups



Solid bars = verbal IQ; striped bars = performance IQ. *$p < 0.05$; +$p = 0.10$.

PIQ = 82.40) compared to solidly average abilities for all other MRI types.

DISCUSSION Our study suggests that atypical handedness, specific structural lesions, and age at onset are the most important factors leading to atypical language representation in patients with left hemisphere epileptic foci. Handedness and age at seizure onset did not appear to be related, and may be separate indicators of atypical language laterality. Previous fMRI studies have suggested an association of atypical language networks with epilepsy onset before age 5 or 6, but generally have not examined the contribution of the underlying remote cause.[2,6,7,30] The relationship between lesion type and atypical language may have important implications for understanding the factors leading to functional reorganization, and have clinical implications for patients with epilepsy.

We found atypical language representation, presumably due to reorganization of cognitive functions, to be associated with lower verbal and nonverbal abilities. Although patients with atypical language exhibited abilities within the low average range, there was a two-thirds SD (11 IQ points) difference compared to left-language patients for verbal abilities. Moreover, stroke and atypical handedness are indicators of early insult that negatively impact cognitive development, reflected by lower cognitive abilities in these subgroups. The patients with a history of stroke were the lowest functioning group, with abilities falling at the very lowest end of the average range (mean VIQ = 81, mean PIQ = 82). These findings support previous research suggesting that early neurologic insult to the dominant hemisphere for language puts children at risk for cognitive difficulties despite compensation.[31-37]

Atypical handedness is known to be associated with atypical language representation.[8] Several studies in adults, all using verbal fluency or semantic decision tasks that primarily target anterior language networks, show atypical language in 22 to 24% of left handed normal volunteers compared to 4 to 6% of right handed volunteers.[7,26,38] Left handedness is found in 8 to 15% of the general population.[39] In our study atypical language occurred in one quarter of right handed patients and over 50% of atypically handed patients (table 3). However, we did not gather data to determine history of left handedness in our patients. Only three patients, or 3%, akin to normal adult studies, had atypical language that was not associated with early seizure onset, atypical handedness, or pathologic lesion attributable to early life MTS, focal cortical dysplasia, stroke, and tumor. For most of our patients it is likely that atypical handedness and atypical language are partly independent results of early brain insults leading to both altered speech representation and handedness.[2]

Age at brain insult is important for establishing language dominance. Several studies involving verbal fluency, reading comprehension, and auditory comprehension demonstrate that language dominance and the regions that sustain language processing are fundamentally established by 5 to 7 years.[15-17,20,40,41] There is some evidence for continued maturation and subtle changes in language processing maps—especially in frontal regions known to undergo continued myelination—through mid childhood.[15,40,42] It is not possible to determine from cross-sectional studies whether atypical language identified in our study represents reorganization, compensation, or developmental persistence of an immature pattern of activation during language tasks.

Not surprisingly, patients with vascular events, all involving cortical regions implicated in

Table 3 Right-handed patients and atypical language

MRI	Number	Atypical	% Atypical
All	81	18	22
Normal	27	8	30
MTS	27	6	22
Stroke	—	—	—
Lesion	25	3	12

MTS = mesial temporal sclerosis.

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language, or their connecting fibers, had evidence for varying degrees of language reorganization. If patients with dominant hemisphere language region stroke are to speak, reorganization must occur. Reorganization always was related to regions directly affected by the area of injury, and sometimes also involved the accompanying language processing areas in their ipsilateral projections (i.e., either frontal or temporal areas). Among our patients, five had congenital or vascular events, and one experienced a stroke at age 5. Children with stroke before 2 years show excellent behavioral recovery when tested after age 5.[43] Evidence from the small number of fMRI studies in children or adults with childhood stroke shows activation in homologous brain regions for comprehension as well as expressive language.[44-47] A study of adults with perinatal frontal periventricular ischemia demonstrated reorganization to frontal regions in direct proportion to periventricular white matter destruction, while typical laterality for receptive language was preserved.[48] These findings suggest that both cortical injury and injury to connecting white matter tracts exert similar effects on language processing networks.

Unexpectedly, atypical language dominance was common in patients with nonlesional epilepsy. This group had a high incidence of atypical handedness, yet atypical language occurred in one quarter of right handed patients. The less predictable reliable ascertainment of typical language dominance in the extratemporal neocortical population has been observed in a large series employing a covert verbal fluency task.[6] Intracarotid amobarbital test and fMRI verbal fluency paradigm data suggest that interictal spike frequency may be related to atypical language dominance in patients with mesial temporal lobe epilepsy.[49,50] We did not assess interictal spike or seizure frequency, which were not obviously different between typical and atypical language fMRI groups in one study.[6] It is important to remember as well that nonlesional epilepsy tends to become lesional as increasingly sophisticated imaging techniques and field strengths detect discreet focal dysplasia or more widespread microscopic abnormalities.[51]

Nearly one quarter of patients with left MTS had evidence for reorganization of language functions. Reports of atypical language in left MTS are similar across a number of fMRI series.[3,4,52-54] Most patients with MTS have some history of febrile seizures or other insult such as meningitis or encephalitis, prior to age 5.[55] These patients often demonstrate reorganization of language functions in frontal regions in addition to temporal areas suggesting regional and remote effect of epilepsy on the higher ordered cognitive domains of language[3-5,30,50,54] and memory.[56] Unlike other lesions that are heterogeneous in location and networks disrupted, MTS is a reasonably homogeneous systems disease affecting both local networks and its projections. Atypical language in this population may be a consequence of injury to hippocampal-based verbal working memory systems.[30,57]

In our study, small focal lesions—tumor, dysplasia, and vascular malformations—were not as commonly associated with atypical language as MTS or nonlesional epilepsy. One study that used covert verbal fluency in 10 children with various brain lesions (dysplasia, infarct, tumor, cysts, MTS, encephalomalacia) found only one in five children with a frontal lesion had language reorganized to the right hemisphere. The one patient with right language had dysplasia occupying the entire extent of the left IFG and insula.[47] In another limited series children with focal cortical dysplasia and low grade tumors, also using a verbal fluency paradigm, approximately 15%, similar to findings observed here, had atypical language.[58] Another study reporting group mean regional asymmetry indices in adults with epilepsy and developmental lesions—tumor, focal cortical dysplasia, and vascular malformations—in left frontal and left lateral cortex did not find differences with a control group.[30] In contrast, a fourth study using verbal fluency and listening comprehension tasks, in 14 children with cortical dysplasia, found nearly all children had reorganization to the contralateral hemisphere, and only one had evidence of intrahemispheric reorganization.[59] In this study, only patients who had dysplasia that occupied substantial portions or all of either Wernicke or Broca areas were included. The microscopic severity of the dysplasia was not related to atypical language dominance. Other investigations using fMRI and cortical stimulation demonstrate that dysplasia can sustain language function.[60-62] Thus, the limited evidence suggests that location and extent of developmental lesions are more important than microscopic pathology.

Only one of three children with suspected Rasmussen encephalitis (all with onset in mid to later childhood) had atypical language. This child had evidence of bilateral frontal language processing shortly after onset of seizures, with no change in activation laterality on two additional fMRI studies conducted over the ensuing 10 months, before complete resection of his dominant hemisphere. The other two patients had onset after age 6,

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when language compensation is less likely to occur.[63] Additional insight regarding language plasticity is provided by children with Rasmussen encephalitis whose seizures began after age 5 or 6. A child with Rasmussen encephalitis who underwent dominant hemispherectomy at age 7 had preoperative left frontal language on verbal fluency fMRI[64]; follow-up fMRI at age 10, several years following surgery, suggested activation in right frontal regions. Behavioral recovery was incomplete with VIQ in the 60s. Behavioral studies in other children with Rasmussen encephalitis reveal evidence of unexpected—but never complete—recovery of language following resection of the dominant hemisphere in mid to late childhood; these series do not report on those who do not recover language capacity.[65-69] It is possible that that transfer of language functions to nondominant hemisphere with active seizures onset following age 5 or 6, if it is to occur, will only happen following hemispherectomy. An intact corpus callosum may allow the dominant hemisphere to suppress assumption of language functions in the traditionally nondominant hemisphere.[67,70,71]

Only two patients had dual pathology, and this is lower than in other reported series, particularly in children with focal cortical dysplasia or other developmental lesions. However, many of these studies are based on surgical pathology findings rather than MRI. Moreover, most of our patients were in an older age range, which may explain the low incidence of dual pathology we found.

Little is known regarding the extent to which pathologic substrates may affect the BOLD response, and if language task-related activation might be underestimated ipsilateral to a lesion. That language networks are identified in atrophic epileptogenic cortex in Rasmussen children suggests a minimal effect. Furthermore, cortical dysplasia is known to sustain BOLD effect for motor and language tasks.[59,61,62] However postictal states, and vascular malformations leading to a vascular steal, may diminish the BOLD response.[72,73]

Language reorganization typically occurs in nondominant hemisphere homologous regions. Only in rare instances is there evidence for recruitment of ipsilateral or contralateral cortical areas beyond normal language processing regions.[2,74] The results of fMRI studies suggest that pathologic substrate, and age at epilepsy onset, in addition to epileptiform activity itself, contribute to language reorganization. The location and extent of lesion, in addition to timing, are important. The ubiquitous atypical language found in patients with an early destructive lesion, such as a stroke, emphasizes the importance of timing and location of underlying pathologic processes on developmental expression of language representation. In contrast, the high incidence of atypical language in patients with normal MRI argues for epilepsy as the primary developmental factor in altered language expression. In other circumstances, however, it is difficult to separate the effect of isolated focal lesions from seizures as all patients in this study had epilepsy. Future studies may be able to elucidate the contribution of these factors by examining patients with focal cortical dysplasia and developmental tumors without epilepsy, or to use EEG activity and epilepsy severity as factor in image data analysis.

In addition to age-related differences, the study represents cumulative experience across several years and reflects advances in paradigm design, MRI technology, and analysis methods. This variability is inevitable in a rapidly changing field; however, we did not find significant changes in the rates of atypical language across time, or age groups. Moreover, our study was clinically based, and its central focus was the relationship of MRI lesions found on 1.5 T to atypical language. Thus, differences in paradigms and scanners are unlikely to have affected the results.

The capacity to transfer language and attain behavioral recovery is age-dependent. However, it is unclear why language is less likely to be affected in subtle lesions such as focal cortical dysplasia than in nonlesional neocortical epilepsy, unless there is a difference in the character of the interictal and ictal effects and propagation.[2,60] The remote effects of TLE on frontal systems, as well as the improvement in language measures following right temporal resection, suggest the strong influence of seizure activity on functional reorganization.[30,47,75] The widespread and remote BOLD effects, in addition to focal activation, found on fMRI of interictal spikes[76] may provide a clue to the basis for disrupted brain function in epilepsy.

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