

# fMRI language dominance and FDG-PET hypometabolism



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## ABSTRACT

**Background:** Atypical language dominance is common in patients with temporal lobe epilepsy. We examined the association of left temporal hypometabolism with laterality of fMRI activation in a language task in a cross-sectional study.

**Methods:** Thirty patients with temporal lobe epilepsy (mean age  $32.4 \pm 11.0$  years [range 18–55]; epilepsy onset  $15.3 \pm 11.3$  years [range 0.8–40]; 22 left focus, 8 right focus) had  $^{18}$ fluoro-deoxyglucose (FDG)-PET using noninvasive cardiac input function. After MRI-based partial volume correction, regional glucose metabolism (CMRglc) was measured and asymmetry index,  $AI = 2(L - R)/(L + R)$ , calculated. fMRI language dominance was assessed with an auditory definition decision paradigm at 3 T. fMRI data were analyzed in SPM2 using regions of interest from Wake Forest PickAtlas (Wernicke area [WA], inferior frontal gyrus [IFG], middle frontal gyrus [MFG]) and bootstrap laterality index,  $LI = (L - R)/(L + R)$ .

**Results:** Nineteen patients had ipsilateral temporal hypometabolism; 3 of 4 patients with atypical language had abnormal FDG-PET. Increasing left midtemporal hypometabolism correlated with decreased MFG LI ( $r = -0.41, p < 0.05$ ) and showed trends with WA LI ( $r = -0.37, p = 0.055$ ) and IFG LI ( $r = -0.31, p = 0.099$ ); these relationships became more significant after controlling for age at onset. Increasing hypometabolism was associated with fewer activated voxels in WA ipsilateral to the focus and more activated voxels contralaterally, but overall, activation amount in left WA was similar to subjects without left temporal hypometabolism ( $t = -1.39, p > 0.10$ ).

**Conclusions:** We did not find evidence of impaired blood oxygenation level-dependent response in hypometabolic cortex. Regional hypometabolism appears to be a marker for the temporal lobe dysfunction that leads to displacement of language function. *Neurology*® 2011;76:1322–1329

## GLOSSARY

**AI** = asymmetry index; **AL** = atypical language; **BA** = Brodmann area; **BOLD** = blood oxygenation level-dependent; **CMRglc** = regional glucose metabolism; **FDG** =  $^{18}$ fluoro-deoxyglucose; **IFG** = inferior frontal gyrus; **LI** = laterality index; **LL** = left language; **MCD** = malformation of cortical development; **MFG** = middle frontal gyrus; **MTG** = middle temporal gyrus; **MTS** = mesial temporal sclerosis; **TLE** = temporal lobe epilepsy; **STG** = superior temporal gyrus; **WA** = Wernicke area.

Atypical language dominance is common in patients with temporal lobe epilepsy (TLE), and language processing impairments are particularly common in left TLE.<sup>1</sup> One-quarter of patients with left mesial TLE will have altered language representation even though the focus is remote from Wernicke area (WA). One-third of patients with left TLE who have normal MRI and no other known associated risk factors (i.e., left handedness, early onset) will also have atypical language dominance.<sup>1–3</sup> The causes of language reorganization at a distance from the focus, and in the absence of a structural lesion, are unclear. Decreased glucose consumption (rCMRglc) identified by  $^{18}$ fluoro-deoxyglucose (FDG)-PET is common in patients with TLE.<sup>4</sup> The hypometabolism typically involves lateral temporal neocortex and, less frequently,

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frontal regions, even in patients with a clear mesial focus.<sup>4–6</sup> Functional changes in the temporal lobe could lead to impaired language processing. However, it is also possible that the ability of cortex to sustain the blood oxygenation level–dependent (BOLD) response needed for language mapping on fMRI is affected, while underlying cognitive processing is normal.

We aimed to examine the association of perturbations in glucose consumption with fMRI language lateralization as determined by a fMRI task targeted at both temporal and frontal language processing areas. We hypothesized that hypometabolic cortex would sustain BOLD response and that regional decreases in rCMRglc, an indicator of impaired neocortical function and capacity, would affect language dominance.

**METHODS** **Participants.** We performed a cross-sectional retrospective review of patients who were evaluated for epilepsy surgery who had both fMRI and FDG-PET between 2004 and 2009. We studied 30 patients with TLE confirmed by clinical characteristics, MRI, and ictal video-EEG monitoring. Twenty-four had intracranial monitoring or temporal resection. Twenty-two had a left seizure focus and 8 had a right focus. Fourteen women and 16 men participated; mean age at study was  $32.4 \pm 11.0$  years (range 18–55 years); mean seizure onset age was  $15.3 \pm 11.3$  years (range 0.8–40 years); and mean epilepsy duration was  $17.1 \pm 12.9$  years (range 1–47 years). Patients underwent 3 T structural MRI (General Electric, Milwaukee, WI), fMRI with language activation paradigms, and FDG-PET. Nine patients had mesial temporal sclerosis (MTS) (7 left, 2 right), 2 a tumor or malformation of cortical development (MCD) (both left), and 19 had a normal MRI (13 left seizure focus, 6 right seizure focus). fMRI data were acquired from 49 healthy control subjects (24 women, 25 men; mean age  $27.1 \pm 7.9$  years, range 20–53 years) who were free of neurologic and psychiatric disease, had normal neurologic examinations, and were deemed left hemisphere dominant for language (see fMRI below).

**Standard protocol approvals, registrations, and patient consents.** The protocol was approved by the NIH Central Nervous System institutional review board; all patients provided written informed consent.

**fMRI.** fMRI data were acquired at 3.0 T (General Electric Medical Systems, Milwaukee, WI) using EPI BOLD techniques. Acquisition parameters, paradigm presentation, and analysis methods have been described previously.<sup>17</sup> We used an Auditory Description Decision Task with a 5-block design (30-second hemicycle). During the experimental condition, the participant heard a sentence that described, then named, an object (“a large pink bird is a flamingo”); 70% were correct definitions and 30% were foils. The control condition was reverse speech with an appended tone identification for 70% of reverse items. After normalization to the Montreal Neurological Institute anatomic atlas, language dominance was established by analyzing individual

maps and employing the LI toolbox adapted for SPM2 to process by a bootstrap method.<sup>8</sup> The fMRI tasks reliably elicit activation along the left superior temporal sulcus (Brodmann areas [BA] 21, 22, 39) implicated in “receptive” speech processing, the left inferior frontal gyrus implicated in “expressive” speech processing (BA 44, 45) and semantic decision (BA 47), and left middle frontal gyrus (BA 9, 46) implicated in verbal working memory.<sup>7,9</sup> Regions of interest were based on the Wake Forest Pick Atlas, and included WA broadly defined along the superior temporal sulcus (BA 21, 22, 39; superior temporal gyrus [STG], middle temporal gyrus [MTG]), BA (BA 44, 45, 47; inferior frontal gyrus [IFG]), and middle frontal gyrus (MFG). A laterality index (LI) was calculated for each region where  $LI = (L - R)/(L + R)$ . Left language (LL) dominance for each region was defined as  $LI \geq 0.20$ ; atypical language (AL) was defined as regional  $LI < 0.20$ . Patients were classified as having atypical language overall when either WA or IFG was right dominant ( $LI < -0.20$ ), or when both regions were bilateral ( $LI < 0.20$ ).<sup>10</sup> Regional activation voxel counts were recorded at the individual mean LI threshold level used in the bootstrap method for all subjects.

**FDG-PET.** FDG-PET acquisition and analysis have been described previously.<sup>11</sup> Briefly, FDG-PET was performed following 6-hour fasting, in the awake quiet state, in a quiet, dim room with eyes closed and ears unoccluded. EEG was performed and patients observed to assure interictal studies. Five mCi FDG were injected, and the following 20-minute uptake period data were acquired on a GE Advance Tomograph (GE Healthcare; full width at half maximum, 6–7 mm). Absolute cerebral metabolic rates for glucose (CMRglc) were determined using a noninvasive input function based on cardiac radioactivity. Images were coregistered with a structural MRI and then corrected for partial volume effects. Regional CMRglc were then determined in anatomic regions drawn on the coregistered MRI following an anatomic atlas. Regions included, but were not limited to, the middle temporal gyrus and the mesial temporal region (hippocampal structures, including CA fields, dentate gyrus, pre-subiculum, and subiculum). An asymmetry index was calculated:  $AI = 2(L - R/L + R)$ , with regional hypometabolism defined as  $>2$  SD (the PET AI follows a different historical convention than fMRI).

**Data analysis.** Statistical analysis was performed with SPSS: edition 12.0 for Windows. Descriptive statistics were used to characterize demographic, AI, and LI variables. To examine the relationships among these variables, the appropriate parametric and nonparametric analyses (depending on the nature and distribution) were conducted including *t* test and bivariate correlation. Regression analyses were conducted to determine if hypometabolism predicted language laterality after accounting for age at onset.

**RESULTS** **Language laterality and left temporal hypometabolism.** Hypometabolism was predominantly ipsilateral temporal; only a few patients had extra-temporal or contralateral PET abnormalities (table e-1 on the *Neurology*<sup>®</sup> Web site at [www.neurology.org](http://www.neurology.org)). Nineteen patients (63%) had regional hypometabolism in midtemporal or mesial temporal areas ipsilateral to the seizure focus (table 1). Sixteen patients with ipsilateral temporal hypometabolism had a left focus and 3 patients had a right focus. Ten of 11

**Table 1** Frequencies of typical and atypical language dominance in the presence and absence of ipsilateral temporal hypometabolism

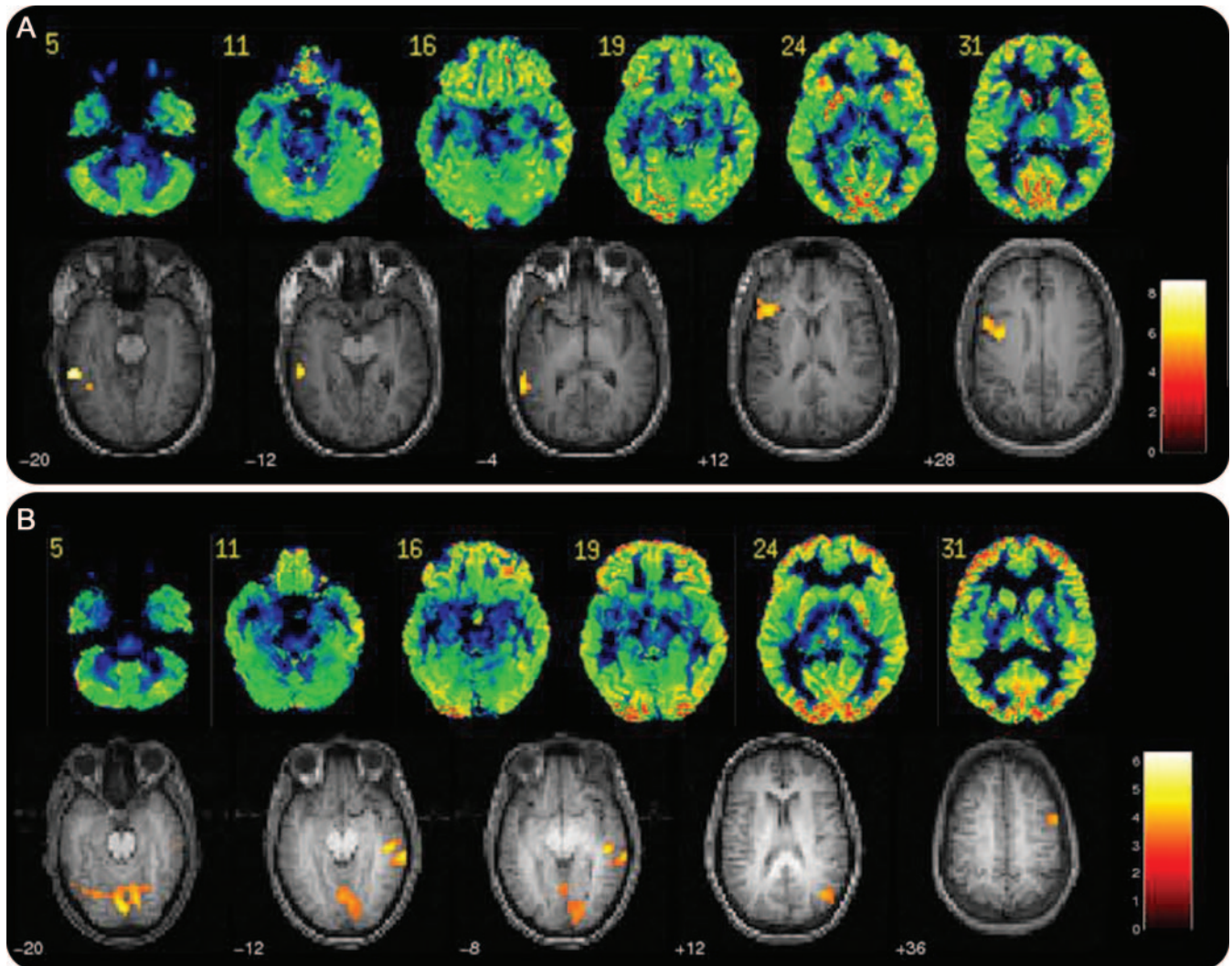
	Left focus		Right focus	
	Ipsilateral temporal hypometabolism	Without ipsilateral temporal hypometabolism	Ipsilateral temporal hypometabolism	Without ipsilateral temporal hypometabolism
Typical language	13	5	3	5
Atypical language	3	1	0	0

(91%) patients without ipsilateral temporal hypometabolism were left language dominant ( $LI > 0.20$ ). Thirteen of 16 (81%) patients with ipsilateral left temporal hypometabolism were left language dominant (table 1). Four patients were classified with atypical language dominance, all of whom had a left seizure focus. Although 3 of 4 patients with atypical language had regional left temporal hypometabo-

lism, most patients with regional hypometabolism remained left hemisphere dominant for language (figure 1).

The few patients with atypical language prohibited statistical comparisons between groups based on language dominance; however, degree of language lateralization (LI) was examined in relation to hypometabolism (AI) in both midtemporal and mesial

**Figure 1** Language dominance



(A) Subject with typical language dominance and left temporal hypometabolism. (B) Subject with atypical language dominance and left temporal hypometabolism. Images are shown in neurologic convention (left is left).

**Table 2** Demographic information, fMRI language LI, and FDG-PET AI for all subjects, for subjects with left temporal hypometabolism, and for subjects without left temporal hypometabolism<sup>a</sup>

	All subjects (n = 30)	Subjects with left temporal hypometabolism (n = 18)	Subjects without left temporal hypometabolism (n = 12)
Age, y	32.4 (11.0)	32.8 (12.0)	31.8 (9.9)
Onset, y	15.3 (11.3)	15.1 (10.5)	15.7 (13.1)
Duration, y	17.1 (12.9)	17.2 (13.2)	17.0 (13.0)
M/F	16/14	8/10	8/4
fMRI WA LI	0.54 (0.43)	0.46 (0.44)	0.65 (0.40)
fMRI IFG LI	0.47 (0.47)	0.29 (0.45)	0.71 (0.41)
fMRI MFG LI	0.34 (0.48)	0.16 (0.44)	0.59 (0.41)
Left WA voxels activated	519 (340)	443 (236)	621 (435)
Right WA voxels activated	193 (129)	215 (129)	162 (127)
FDG-PET mid-temporal AI	0.12 (0.20)	0.23 (0.15)	-0.053 (0.16)
FDG-PET mesial temporal AI	0.047 (0.15)	0.11 (0.15)	-0.051 (0.09)
No. with typical vs atypical language in Wernicke area	24 typical, 6 atypical	14 typical, 4 atypical	10 typical, 2 atypical
No. with typical vs atypical language in Broca area	23 typical, 7 atypical	13 typical, 5 atypical	10 typical, 2 atypical
No. with typical vs atypical overall language dominance	26 typical, 4 atypical	15 typical, 3 atypical	11 typical, 1 atypical

Abbreviations: AI = asymmetry index; FDG = <sup>18</sup>fluoro-deoxyglucose; LI = laterality index; MFG = middle frontal gyrus; WA = Wernicke area.

<sup>a</sup> Values are mean (SD).

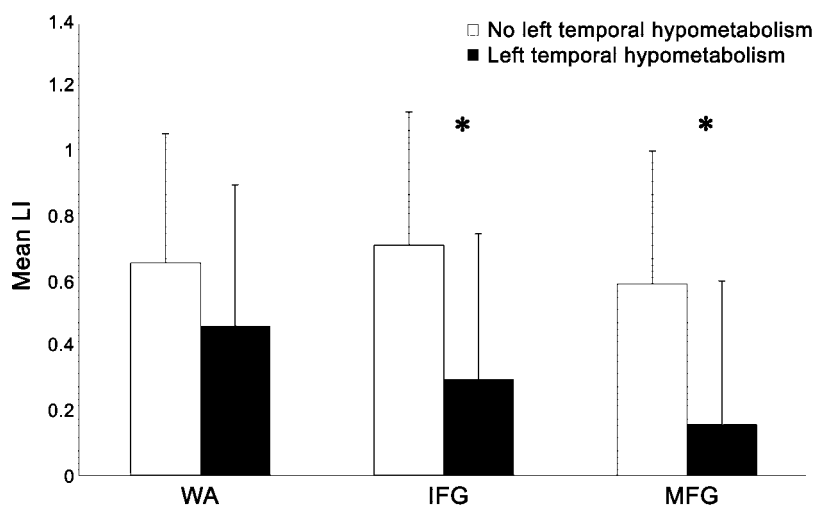
temporal regions. Greater left midtemporal hypometabolism was correlated with decreased MFG LI ( $r = -0.41, p < 0.05$ ) and showed a trend with both WA LI ( $r = -0.37, p = 0.055$ ) and IFG LI ( $r = -0.31, p = 0.099$ ). Additionally, greater left mesial temporal (hippocampal) hypometabolism was correlated with decreased WA LI ( $r = -0.46, p < 0.05$ ), but not MFG LI ( $r = -0.21, p > 0.10$ ) or IFG LI ( $r = -0.15, p > 0.10$ ). Midtemporal and mesial tempo-

ral hypometabolism were tightly linked, but not necessarily predictive of each other ( $r = 0.59, p < 0.001$ ). Using a categorical classification of left temporal hypometabolism (middle or mesial)—defined as AI  $> 2$  SD above normal—subjects with hypometabolism had lower MFG LI ( $t = 2.67, p < 0.05$ ) and IFG LI ( $t = 2.53, p < 0.05$ ), while WA LI was similar for subjects with and without hypometabolism ( $t = 1.21, p > 0.10$ ) (table 2, figure 2).

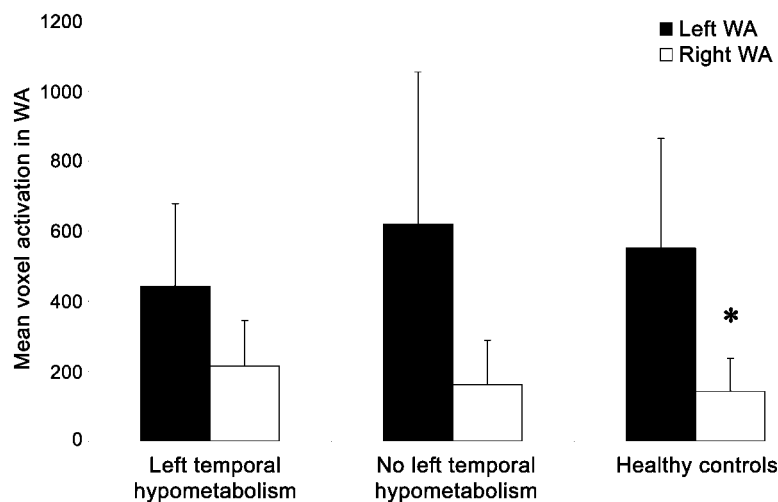
There were no differences in regional LI or degree of left temporal hypometabolism by subject age ( $p > 0.10$ ). Degree of left temporal hypometabolism did not differ by gender (midtemporal AI:  $t = -0.61, p > 0.10$ ; mesial temporal AI:  $t = -0.55, p > 0.10$ ), nor did WA LI ( $t = 1.67, p > 0.10$ ) or MFG LI ( $t = 1.36, p > 0.10$ ), but IFG LI was lower for females than males ( $t = 2.44, p < 0.05$ ).

**fMRI BOLD signal and left temporal hypometabolism.** Increasing temporal hypometabolism was associated with fewer activated voxels ipsilateral to the hypometabolism and more activated voxels contralateral to the hypometabolism. Greater left midtemporal hypometabolism was correlated with fewer activated voxels in left WA ( $r = -0.45, p < 0.05$ ). The amount of right WA voxel activation was not associated with degree of left midtemporal hypometabolism ( $r = 0.28, p > 0.10$ ); however, this correla-

**Figure 2** Mean fMRI laterality index (LI) in Wernicke area (WA), inferior frontal gyrus (IFG), and middle frontal gyrus (MFG) regions for patients with and without left temporal hypometabolism ( $*p < 0.05$ )



**Figure 3** Mean left and right voxel activation in Wernicke area (WA)



Patients with left temporal hypometabolism, patients without left temporal hypometabolism, and healthy controls (\* $p < 0.05$ , amount of activation in right WA differs between controls and patients with left temporal hypometabolism).

tion was in the opposite direction from the ipsilateral correlation such that the tendency was for greater left hypometabolism to be associated with greater right activation. Left mesial temporal hypometabolism was correlated with decreased ipsilateral activation in left WA ( $r = -0.37$ ,  $p = 0.05$ ) and increased contralateral activation in right WA ( $r = 0.40$ ,  $p < 0.05$ ).

When divided into 2 groups by presence vs absence of left temporal hypometabolism above the clinical threshold of 2 standard deviations beyond normal, the amounts of left and right voxel activation in Wernicke area did not differ (left WA voxels:  $t = -1.39$ ,  $p > 0.10$ ; right WA voxels:  $t = 1.09$ ,  $p > 0.10$ ). Additionally, the relationship between fMRI activation and hypometabolism was not a function of overall depressed activation in patients with left temporal hypometabolism because the number of activated voxels in left Wernicke area did not differ from subjects without left temporal hypometabolism ( $t = -1.39$ ,  $p > 0.10$ ) or healthy controls ( $t = -1.27$ ,  $p > 0.10$ ) (figure 3). Patients with left temporal hypometabolism did have more activation in right WA than controls ( $t = 2.44$ ,  $p < 0.05$ ), while patients without hypometabolism did not differ from controls ( $t = 0.60$ ,  $p > 0.10$ ).

**Influence of age at onset on language laterality and hypometabolism.** Age at epilepsy onset was not correlated with degree of midtemporal or mesial temporal hypometabolism ( $p > 0.10$ ), or with IFG LI or MFG LI ( $p > 0.10$ ). However, earlier age at onset was correlated with lower WA LI ( $r = -0.39$ ,  $p = 0.047$ ) and moderated the relationship between left temporal hypometabolism and language laterality.

After controlling for age at onset, greater left mid-temporal hypometabolism was more strongly correlated with lower WA LI ( $r = -0.49$ ,  $p = 0.01$ ) and MFG LI ( $r = -0.43$ ,  $p < 0.05$ ), and became a stronger trend with IFG LI ( $r = -0.37$ ,  $p = 0.06$ ). Also, the strength of the relationship between increasing left mesial temporal hypometabolism and decreasing WA LI became more significant after controlling for age at onset ( $r = -0.54$ ,  $p < 0.01$ ), whereas MFG LI ( $r = -0.23$ ,  $p > 0.10$ ) and IFG LI ( $r = -0.18$ ,  $p > 0.10$ ) remained nonsignificant.

When divided into 2 groups by age at onset (early onset defined as  $\leq 12$  years, the median, for even statistical comparisons between groups), the relationship between WA LI and left temporal hypometabolism can be seen more clearly. Although the group numbers were small, patients with earlier onset ( $n = 13$ ) had decreased WA LI in the presence of left temporal hypometabolism (mean WA LI =  $0.51 \pm 0.49$ ) compared to no hypometabolism (mean WA LI =  $0.80 \pm 0.18$ ). While these mean differences were not significant ( $t = 1.37$ ,  $p = 0.197$ ; Cohen  $d = 0.79$ , effect size  $r = 0.37$ ), the medium effect size suggests that the effect of hypometabolism may become significant with more subjects. Patients with later onset epilepsy did not show these differences in WA LI based on the presence vs absence of left temporal hypometabolism ( $t = 0.04$ ,  $p > 0.10$ , Cohen  $d = 0.02$ , effect size  $r = 0.01$ ).

**DISCUSSION** We found that greater regional temporal hypometabolism correlated with lessened strength of language dominance in the temporal region as assessed by fMRI. Furthermore, we found the relationship was related to younger age at epilepsy onset. These findings are not attributable to a disruption of the BOLD response used to determine language dominance. Our findings indicate that atypical language reflects left temporal functional pathology, which may be more pronounced with an earlier age at epilepsy onset.

These findings may also provide an explanation for the high incidence of atypical language dominance in patients with either normal MRI or MTS alone. Previous studies describe atypical language dominance in one-third of patients with TLE and normal MRI<sup>1</sup> and in one-quarter of patients with MTS.<sup>1-3</sup> The epileptogenic zone may be remote from the temporal neocortex that sustains receptive language processing. FDG-PET studies, however, show that functional metabolic abnormalities extend beyond the epileptogenic zone—often in mesial structures—and may be more pronounced in lateral temporal neocortex than in these mesial structures.<sup>4,5,12</sup> Neocortical foci may be associated with

hypometabolism that extends beyond the margin of the seizure focus.<sup>13</sup> In our study, only one patient with atypical language and normal MRI had normal FDG-PET. There are both structural and PET data to suggest perturbation of a more widespread network involving basal ganglia and frontal cortex.<sup>12,14,15</sup> The mechanism for regional hypometabolism, which is not fully understood, may be explained partially by neuronal loss in the hippocampal formation.<sup>16–19</sup> However, functional disruption is an important factor. The widespread functional disruption identified by FDG-PET, frequently remote from the seizure focus, may provide an explanation for disruption of language processing in patients with neocortical TLE or a mesial seizure focus.

Postictal depression of neuronal function may impair the physiologic basis of BOLD and affect fMRI-based language maps.<sup>20</sup> There are also case reports of language laterality reversing following successful temporal lobectomy.<sup>21</sup> These data raise the possibility that metabolic perturbations by ictal and interictal activity may dampen the BOLD response on which fMRI measurements are based. There are other circumstances when the BOLD response is disrupted,<sup>22,23</sup> including mass lesion effects and vascular steal. Furthermore, the relationship between blood flow and metabolism is altered in TLE neocortex.<sup>6,24</sup> CBF is better preserved than rCMRglc, a divergence that may increase over time.<sup>25</sup> Our data suggest that patients are able to mount a BOLD response in the interictal state, as hypometabolic areas generated a BOLD response comparable to normal volunteers and patients without hypometabolism. The reduced LI is not due solely to reduced left activation, and supports a shift of activity to the right. We do not have measures of CBF in our patients. The degree to which perturbations in perfusion, metabolism, and BOLD response exist may be determined by blood flow studies (arterial spin labeled fMRI or water PET) linked with FDG-PET.

A limitation of our study is that the lateral temporal ROI used for our fMRI and PET analyses overlap but are not entirely congruent across imaging modalities (Wernicke area [BA 21, 22, 39] compared to MTG). They are, however, those used for our standard clinical methods of assessing language dominance and regional hypometabolism, respectively. The relation between hippocampus (mesial temporal region) and neocortical lateral language processing would not be affected by our choice of regions. Although this issue may have a modest effect on lateral neocortical findings, the temporal hypometabolism extends beyond region boundaries.

Although only 8 patients had a right hemisphere seizure focus, they serve as a useful contrast to the

patients with a left hemisphere focus, in showing the absence of an effect of right temporal hypometabolism on language. The degree of left temporal hypometabolism may be more sensitive than a binary categorization of its presence or absence in studying a relationship with fMRI laterality; therefore, including these subjects allows a greater range of glucose consumption with which to explore this relationship.

Ultimately, our findings support the notion that functional disruption in the ipsilateral temporal lobe may displace local cognitive processes.<sup>26–28</sup> The earlier the onset of epilepsy or brain injury, the more likely are these functions to be affected.<sup>1,2,29</sup> Hypometabolism in patients with early seizure onset had a more profound effect on language indices in temporal regions than in those with older onset. Older patients have lower LI values in general.<sup>30</sup> There is some evidence that frequency of interictal discharges correlates with atypical language,<sup>31</sup> but little data link interictal discharges to regional hypometabolism.<sup>32</sup> We did not formally assess spike frequency in our studies. Furthermore, there is evidence that this disruption is not confined to temporal regions. Patients with temporal hypometabolism had lower LI in IFG and MFG. As the MFG is implicated in working memory, this finding may be a nonspecific effect of increased working memory demands as a result of generally compromised brain function, reflect compensation for greater demands on routine language function (in the way tasks perceived to be harder increase verbal working memory demands), or reflect compensation by working memory systems for disturbed hippocampal declarative memory function.<sup>33–35</sup>

The interplay between the seizure focus and widespread regional networks is complex and pervasive. There are functional consequences of focal pathology that may have widespread effects on brain function. In some instances they are associated with a shift of language dominance to the right hemisphere; in others, impaired function results in compensatory mechanisms for drawing upon a widely distributed network to perform essential cognitive functions.

## DISCLOSURE

Dr. Gaillard has served on a scientific advisory board for GE Healthcare and educational material advisory panels for Ovation Pharmaceuticals (now Lundbeck Inc.) and Questcor Pharmaceuticals, Inc.; served as an editor of *Epilepsia*; his department derives income from the clinical evaluation and management of children with epilepsy including performing EEG and vEEG; receives research support from Lundbeck Inc., King Pharmaceuticals, PRA International, Eisai Inc., Marinus Pharmaceuticals, Inc., the NIH (NINDS, NICHD, NIMH), and the CDC; and holds stock in Johnson & Johnson, Eli Lilly and Company, GlaxoSmithKline, and Pfizer Inc. Dr. Berl receives research support from the NIH. E.S. Duke reports no disclosures. Dr. Ritzl's spouse has served on the speakers' bureau for Wyeth. Dr. Miranda, Dr. Liew, A. Finegersh, A. Martinez, and I. Dustin report no disclosures. Dr. Sato receives research support and

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Neurology

Historical Abstract: October 1, 1962

**A HUMAN CEREBRAL DISCONNECTION SYNDROME: A PRELIMINARY REPORT**

*Norman Geschwind, MD and Edith Kaplan, MA*

**Neurology** 1962;12:675-685

We propose in this paper to present a patient whose clinical picture appears to us to be most simply explainable by a partial disconnection of the two cerebral hemispheres. He appears to behave as if there were 2 nearly isolated half-brains, functioning almost independently. In the early years of this century several cases were described which showed some of the phenomena that are present in our patient. Sittig<sup>1</sup> reviews these cases in his monograph on apraxia. The earlier workers generally described these cases as showing apraxia and apractic agraphia of the left side and leftsided astereognosis and attributed these findings to lesions of the corpus callosum.

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**Comment from David S. Knopman, MD, FAAN, Deputy Editor:** Norman Geschwind was a major force in the development of behavioral neurology as a field. This is his first paper on a topic in behavioral neurology, which anticipated a pair of long articles he published on human disconnection syndromes in *Brain* 3 years later. Those latter articles are considered by many to represent the founding moment of behavioral neurology in the US.