Differential Patterns of Language and Motor Reorganization Following Early Left Hemisphere Lesion

A PET Study

Ralph-Axel Müller, PhD; Robert D. Rothermel, PhD; Michael E. Behen, MA; Otto Muzik, PhD; Thomas J. Mangner, PhD; Harry T. Chugani, MD

Objective: There is extensive evidence for post-lesional plasticity in the language and motor domains. We examined possible domain-specific differences in re-organizational patterns, hypothesizing that interhemispheric reorganization would be predominantly homotopic for language, but predominantly nonhomotopic for motor control.

Design: Using oxygen 15–water positron emission tomography, regional cerebral blood flow was studied during rest, listening to sentences, repetition of sentences, and finger tapping of the right hand. Task-specific primary, secondary, and tertiary regions of interest were defined according to the degree of regional involvement in language/motor functions as documented in previous studies. Regional activations were compared within and across functional domains.

Patients: Nine patients (aged 4-20 years) with unilateral left hemisphere lesion involving both the primary motor and perisylvian language cortices were studied. Two samples of healthy adults were included for additional comparisons.

Main Outcome Measure: Hemispheric asymmetry of blood flow changes within regions of interest.

Results: As predicted, rightward asymmetry of activations in primary and secondary regions was stronger for language than for movement, but the expected inverse difference for tertiary regions (greater rightward asymmetry of motor activations) was not found. Within-domain comparisons showed that for listening to sentences, rightward asymmetry was strongest in primary and weakest in tertiary regions, whereas the inverse differences were found for movement.

Conclusion: The findings suggest a greater potential for homotopic interhemispheric reorganization in the language than in the motor domain. Interhemispheric motor reorganization was generally limited.

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A GREAT number of studies using various empirical paradigms have found evidence for lesion-induced reorganizational plasticity in the language and motor domains, following lesions occurring during maturation or in adulthood. However, it is not established whether the patterns of reorganization are the same across domains.

In adults recovering from aphasia after left hemisphere stroke, electrophysiologic and transcranial Doppler studies have shown right hemisphere shifts of language processing. Positron emission tomography (PET) research has further demonstrated that right hemisphere activation predominantly occurs in regions homotopic with the classic language areas of Broca and Wernicke. On the other hand, functional imaging of motor reorganization in patients with stroke and tumor has yielded partly differing results. While some studies indicate a certain degree of homotopic interhemispheric reorganization involving the primary motor cortex in the nonlesional hemisphere, a common finding is pronounced activation in secondary motor areas (both in the lesional and contralesional hemisphere) and in areas normally not directly involved in motor control, such as prefrontal, anterior cingulate, and inferior parietal cortices. Transcranial magnetic stimulation studies in patients who have undergone hemispherectomy support the notion of nonhomotopic motor reorganization.

In previous studies examining the effects of unilateral brain lesion using oxygen 15 (15O)–water PET in pediatric patients with early first risk, we found analogous indications of a potential for homotopic interhemispheric reorganization in the language domain compared with predominantly nonhomotopic
SUBJECTS AND METHODS

PATIENTS

Nine patients, aged 4 to 20 years, were studied (Table 1). All patients had extensive unilateral anatomical and/or functional lesion in the left hemisphere involving both the primary motor cortex and the perisylvian language cortex, as determined by magnetic resonance imaging (MRI) and 2-deoxy-2-[18F]fluoro-D-glucose (FDG) PET (for methods, see Shamot and Chugani29). Functional mapping of language by means of 15O-water PET was performed in preparation for possible resective brain surgery for the treatment of intractable epilepsy. Age at first risk was 10 years or less in all patients (determined by the earliest event indicating possible brain abnormality).21 Further clinical details for each patient are listed in Table 1. Two samples of healthy adult subjects without history of neurologic or psychiatric disorder, which have been described in more detail in previous publications,22,28 were also included for additional comparisons. For the language tasks, these were 9 right-handed native speakers of English (5 men, 4 women; aged 23-44 years; mean, 29.4 years), while for the motor task, 6 men and 2 women (aged 26-40 years; mean, 35 years) were studied. The demographic differences between the control samples were deemed unproblematic since there is (to our knowledge) no evidence for sex-specific differences in the brain organization for finger movement, and age differences were not significant and therefore unlikely to have differential effects on regional blood flow measures.

PET STUDY

Positron emission tomography scans were performed on a scanner (Siemens Exact HR, Knoxville, Tenn) with an axial field-of-view of 15 cm. The reconstructed image resolution obtained in the study was 5.5 mm ± 0.35 mm in plane (mean ± SD), and 6.0 mm ± 0.49 mm in axial direction (mean ± SD) (full-width at half maximum; reconstruction parameters, Shepp filter with 0.3 cycles/pixel cutoff frequency). A scout scan was performed to determine the delay between injection in the antecubital vein and tracer arrival in the brain, followed by an external gallium 68–line source transmission scan for attenuation correction. For each activations scan, the radioisotope dose was 0.36 mCi/kg,29 with a maximum dose of 25 mCi. The 15O-water dose diluted in 6 mL of isotonic sodium chloride solution was administered as a slow bolus over 20 seconds, using a volumetric pump via a peripheral intravenous line. A static 60-second scan acquisition was initiated after the delay that was determined in the scout scan. The stimulation was started 20 seconds before each scan for a total duration of 50 seconds. Interscan intervals were 10 minutes or more for decay of 15O (physical half-life, 123 seconds).

One control condition (rest without stimulation) and 3 stimulation/task conditions were scanned. These included (1) listening to 10 short sentences (such as “He received an important message” or “I like these flowers a lot”; (2) listening to and immediately repeating 8 sentences of the same type as used for condition 1, with slightly longer interstimulus intervals to allow time for repetition; and (3) sequential finger-thumb tapping in the right hand (self-paced, initiated, and terminated by short verbal commands).

Patients had their eyes covered by a black eye-mask, and were instructed to keep their eyes closed under the mask. All verbal stimuli were read by a female native speaker of American English, recorded and reproduced through high-fidelity analog stereo equipment and earphones.

All 4 conditions were scanned twice in each patient (in counterbalanced order), except for patient 1 (only 1 scan each) and patient 5 (only 1 scan in the listening condition). All patients except patient 4 were able to repeat all sentences in condition 2. Patient 4 did not cooperate on the repetition task and instead was engaged in conversation with his mother, during which speech output (yes/no answers and word repetition) could be elicited. On condition 3, mirror movement was observed in patient 5 (moderate) and patients 6 and 7 (slight). Mean tap frequency was higher in the healthy adults than in the patients (1.90 vs 1.44 Hz; P = .10).

DATA ANALYSIS

Forty-seven cross-sectional image planes were reconstructed for each scan. The reconstructed images contained 128 × 128 pixels, each measuring 1.73 × 1.73 mm, with a plane separation of 3.12 mm. The automated PET activation package by Minoshima et al30,31 was used for motion correction, pixel normalization, realignment to automatically detected anterior-posterior commissure line, linear stretching to Talairach space,32 and pixel-by-pixel subtraction of image sets (stimulation minus control). Eight ROIs were identified on axial planes of volumetric MRI or averaged resting blood flow images, coregistered using semiautomated software.33 Regions of interest were identified in each patient separately to correct for lesion-induced structural variation. Regions of interest were defined with regard to task comparisons. Primary, secondary, and tertiary ROIs were distinguished according to the degree of functional involvement (activation) of particular brain regions in the respective task. The anatomical identification of each ROI is specified in Table 2. Classification as primary, secondary, or tertiary was based on the existing literature on language14-18 and motor activations37-39 from other centers, as well as data from our own studies on healthy adults, applying identical task paradigms.22,28 While in our study patients served as their own controls in comparisons of different types of regional activations (within and across domains), these healthy adult samples were included for additional control data. Age-matched normative 15O-water PET data were not available for ethical reasons. In this context, unmatched comparison data were considered the best approach to distinguishing between lesion-induced and healthy domain-specific activational differences.

Mean changes across all pixels were computed for each ROI and patient. Rightward asymmetry (RA) scores were calculated for each subject as the mean blood flow change in a given right hemisphere ROI minus the change in the homotopic left hemisphere ROI. Rightward asymmetry scores served as a gross measure of atypical right dominance for tasks predominantly activating the left hemisphere in healthy adults, and were thus considered to reflect lesion-induced interhemispheric reorganization. Since all regional values were based on normalized data, RA scores were not further normalized.
reorganization in the motor domain. However, none of these studies directly and systematically compared domain-specific patterns of interhemispheric reorganization. In the present study, we addressed the issue by directly comparing language and motor reorganization in patients with unilateral left hemisphere lesions involving both the rolandic and the perisylvian regions. Examining regions of interest (ROIs) known for their primary, secondary, or tertiary involvement in language and motor functions we hypothesized the following domain-specific differences of interhemispheric reorganization: (1) rightward shifts of language activations will be strongest in primary, weaker in secondary, and weakest in tertiary language regions; (2) the inverse will be seen for activations during right-hand movement, ie, rightward shifts of activation will be stronger in tertiary, weaker in secondary, and weakest in primary regions; (3) rightward asymmetry will be stronger for language activations in primary language regions than for right-hand motor activations in primary motor regions, reflecting greater homotopic reorganization for language; and (4) the inverse effect will be found for tertiary regions, ie, rightward asymmetry of activations for respective tasks will be greater in tertiary motor than in tertiary language regions, reflecting greater nonhomotopic reorganization in the motor domain.

## RESULTS

### WITHIN-DOMAIN COMPARISONS

For listening to sentences, the expected differences in RA scores (L1–L2–L3) for the patient group were seen (Table 3). When tested using planned comparisons (linear contrasts, 1-way analysis of variance), this differ-

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**Table 1. Clinical Data**

<table>
<thead>
<tr>
<th>Patient No./</th>
<th>Sex/</th>
<th>Age, y</th>
<th>Handedness</th>
<th>Hemiparesis</th>
<th>Lesion Localization Identified on†</th>
<th>Age at First Risk, y, mo</th>
<th>Cause/ Risk Factor</th>
<th>Antiepileptic Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/4</td>
<td>Right</td>
<td>No</td>
<td>Diffuse</td>
<td>Frontal</td>
<td>CG</td>
<td>Cortical dysgenesis Epilepsy</td>
<td>Carbamazepine, gabapentin, valproate sodium</td>
<td></td>
</tr>
<tr>
<td>2/M/8</td>
<td>Right</td>
<td>No</td>
<td>Diffuse</td>
<td>Parieto-occipital</td>
<td>0; 3</td>
<td>Epilepsy</td>
<td>Phenytoin or phenytoin sodium</td>
<td></td>
</tr>
<tr>
<td>3/M/11</td>
<td>Left</td>
<td>Yes</td>
<td>Diffuse</td>
<td>Mild hemiatrophy</td>
<td>CG</td>
<td>Sturge-Weber syndrome</td>
<td>Clonazepam (Klonopin, Hoffmann-La Roche, Nutley, NJ), gabapentin, valproate</td>
<td></td>
</tr>
<tr>
<td>4/M/14</td>
<td>Left</td>
<td>Yes</td>
<td>Diffuse</td>
<td>Hemiatrophy</td>
<td>CG</td>
<td>Sturge-Weber syndrome</td>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>5/F/15</td>
<td>Left</td>
<td>Yes</td>
<td>Diffuse</td>
<td>Temporal (resection), hemiatrophy</td>
<td>1; 6</td>
<td>Epilepsy</td>
<td>Carbamazepine, gabapentin</td>
<td></td>
</tr>
<tr>
<td>6/F/15</td>
<td>Left</td>
<td>Yes</td>
<td>Diffuse</td>
<td>Hemiatrophy</td>
<td>CG</td>
<td>AVM, stroke</td>
<td>Phenytoin, gabapentin, phenobarbital</td>
<td></td>
</tr>
<tr>
<td>7/F/15</td>
<td>Right</td>
<td>No</td>
<td>Diffuse</td>
<td>Temporal (resection), mild hemiatrophy</td>
<td>10; 0</td>
<td>Epilepsy</td>
<td>Carbamazepine, phenobarbital</td>
<td></td>
</tr>
<tr>
<td>8/M/19</td>
<td>Right</td>
<td>No</td>
<td>No</td>
<td>Frontotemporal Normal</td>
<td>PN</td>
<td>Premature birth (7-8 wk)</td>
<td>Gabapentin, valproate</td>
<td></td>
</tr>
<tr>
<td>9/M/20</td>
<td>Left</td>
<td>No</td>
<td>Diffuse</td>
<td>Normal</td>
<td>6; 0</td>
<td>Trauma, epilepsy</td>
<td>Carbamazepine</td>
<td></td>
</tr>
</tbody>
</table>

*FDG indicates 2-deoxy-2-18F fluoro-D-glucose; PET, positron emission tomography; MRI, magnetic resonance imaging; CG, congenital; AVM, arteriovenous malformation; and PN, perinatal.
†All lesions are lateralized to the left hemisphere.
‡Diffuse indicates widespread functional lesion affecting all 4 lobes of the left hemisphere.

**Table 2. Anatomical Definition of ROIs for Each Condition**

<table>
<thead>
<tr>
<th>ROI Type</th>
<th>Condition</th>
<th>Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>L1</td>
<td>R1</td>
</tr>
<tr>
<td>Secondary</td>
<td>L2</td>
<td>R2</td>
</tr>
<tr>
<td>Tertiary</td>
<td>L3</td>
<td>R3</td>
</tr>
</tbody>
</table>

*ROI indicates regions of interest.
†Numbers indicate Brodmann areas.
A planned comparison by means of linear contrasts (1-way analysis of variance) was significant ($P = .03$). As predicted, differences in RA scores were thus exactly opposite to the trend observed for listening to sentences. Rightward asymmetry scores were greater (in this case less negative) in the patients than in the healthy adults for all 3 regions. However, these differences were not significant ($P > .20$) and, except for the tertiary motor ROI in the patients, RA scores were negative throughout, both in patients and healthy adults, reflecting predominant activation in the hemisphere contralateral to the movement. Remarkable, though, was the much greater SD of motor RA scores in the patients compared with healthy adults ($M_{1}$, 8.7 vs 2.7; $M_{2}$, 7.1 vs 1.8; $M_{3}$, 3.3 vs 0.9), with scores being equally distributed across a wider range in the patient sample.

In the healthy adults, a 1-way analysis of variance comparing RA scores in primary, secondary, and tertiary regions was not significant for listening ($P = .47$) and repetition ($P = .67$), but highly significant for right-hand movement ($P = .001$), indicating that left dominance was strongest in primary and weakest in tertiary regions. Post hoc analysis showed significant differences between $M_{1}$ and $M_{2}$ and between $M_{1}$ and $M_{3}$ ($P < .05$; Fisher least significant difference). Activation in $M_{1}$ was positively correlated with tap rate across the whole sample (both patients and healthy adults), but this correlation was only marginally significant (left hemispheric ROI: $r = 0.47$; $P = .08$; right hemispheric ROI: $r = 0.50$; $P = .06$). No correlation was found for secondary or tertiary motor regions.

**CROSS-DOMAIN COMPARISONS**

The expected difference of RA scores for primary ROIs between the language and the motor domain was found (Table 3). The differences were highly significant for both the comparison with the listening ($L_{1} > M_{1}$, $P = .002$; $L_{2} > M_{2}$, $P = .002$; $L_{3} > M_{3}$, $P = .002$) and the comparison with the repetition ($R_{1} > M_{1}$, $P = .002$; $R_{2} > M_{2}$, $P = .002$; $R_{3} > M_{3}$, $P = .002$). For the secondary ROIs, the difference was significant for the comparison with the listening ($L_{2} > M_{2}$, $P = .002$; $L_{3} > M_{3}$, $P = .002$) but not for the comparison with the repetition ($R_{2} > M_{2}$, $P = .10$; $R_{3} > M_{3}$, $P = .15$).

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<table>
<thead>
<tr>
<th>Type of ROI</th>
<th>Left</th>
<th>Right</th>
<th>RA Scores</th>
<th>Left</th>
<th>Right</th>
<th>RA Scores</th>
<th>Left</th>
<th>Right</th>
<th>RA Scores</th>
<th>Listening vs Movement</th>
<th>Repetition vs Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ($L_{1}$/$R_{1}$/$M_{1}$)</td>
<td>Patients</td>
<td>+0.4</td>
<td>+5.7</td>
<td>+5.2</td>
<td>+0.2</td>
<td>+2.7</td>
<td>+2.5</td>
<td>+5.8</td>
<td>−1.2</td>
<td>−6.9</td>
<td>$L_{1} &gt; M_{1}$†</td>
</tr>
<tr>
<td></td>
<td>Healthy adults</td>
<td>+6.4</td>
<td>+3.3</td>
<td>−3.1</td>
<td>+3.9</td>
<td>+3.0</td>
<td>−0.9</td>
<td>+9.7</td>
<td>+1.1</td>
<td>−8.6</td>
<td>$L_{1} &gt; M_{1}$†</td>
</tr>
<tr>
<td>Secondary ($L_{2}$/$R_{2}$/$M_{2}$)</td>
<td>Patients</td>
<td>+0.7</td>
<td>+5.4</td>
<td>+4.7</td>
<td>+0.1</td>
<td>+3.0</td>
<td>+3.0</td>
<td>+1.2</td>
<td>−0.6</td>
<td>−1.9</td>
<td>$L_{2} &gt; M_{2}$‡</td>
</tr>
<tr>
<td></td>
<td>Healthy adults</td>
<td>+3.7</td>
<td>+2.4</td>
<td>−1.3</td>
<td>+3.1</td>
<td>+0.8</td>
<td>−2.3</td>
<td>+2.4</td>
<td>+0.4</td>
<td>−2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Tertiary ($L_{3}$/$R_{3}$/$M_{3}$)</td>
<td>Patients</td>
<td>+0.3</td>
<td>+1.3</td>
<td>+1.0</td>
<td>+0.6</td>
<td>+1.6</td>
<td>+0.7</td>
<td>+1.1</td>
<td>+0.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Healthy adults</td>
<td>+1.2</td>
<td>+0.2</td>
<td>−1.0</td>
<td>+0.2</td>
<td>−0.1</td>
<td>−0.3</td>
<td>+1.4</td>
<td>+0.7</td>
<td>−0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

RA indicates rightward asymmetry; ROI, regions of interest; NS, $P > .14$.
†$P < .001$.
‡$P < .05$.
§$P < .08$.

Within-domain comparisons of RA scores

Table 3. Regional Blood Flow Changes and RA Scores in Patients and Healthy Adults*
For the most part, direct comparisons across domains also supported our hypotheses. Rightward asymmetry scores for primary regions showed expected and highly significant differences for comparison of motor activations with activations both for listening to sentences (L1>M1) and for repetition (R1>M1) (Table 3). Analogous differences, which were also significant but somewhat less robust, were found for secondary regions. Contrary to our hypothesis, RA scores for tertiary regions were also stronger for the language than for the motor domain, but this trend was not significant (P = .70).

Our data thus support the hypothesis of a greater potential for homotopic interhemispheric reorganization in the language than in the motor domain. The concept of homotopic language reorganization should, however, not be interpreted in the sense of the right perisylvian cortex being a dormant language area waiting to be activated in case of left hemisphere lesion. There is evidence that the right perisylvian cortex normally plays a significant part in paralinguistic functions, such as prosody.41 In addition, “right hemisphere shifts” of language dominance following early left hemisphere lesion are often detrimental to typical right hemisphere (eg, visuospatial) functions.42,43 Such crowding effects underline the independent functional specializations of the right hemisphere in the healthy brain.

Our findings did not clearly underscore the hypothesis of pronounced nonhomotopic interhemispheric reorganization for movement. As already mentioned, our patient sample showed instead a generally limited potential for interhemispheric reorganization in the motor domain. In fact, primary and secondary motor ROIs in both hemispheres showed reduced activation in patients compared with healthy adults. This surprising finding could be due in part to the higher tap rate in the healthy adults than in the patients. Performance rate has been shown to correlate positively with the magnitude in motor cortical activation.44,45 In our sample, primary motor activations were indeed positively correlated in the marginally significant range with tap rate, both in the hemisphere contralateral and ipsilateral to the movement.

As expected, RA scores for all ROIs and subtractions were greater in the patients than in healthy adult samples previously presented.22,28 Overall, this finding supports the notion of left dominance in healthy adults and lesion-induced interhemispheric reorganization in our patients. However, the differences between patients and healthy adults were much more robust and significant for most regional comparisons in the language domain, whereas they were weak and nonsignificant for movement, again reflecting a limited potential for interhemispheric motor reorganization. It should be noted, though, that the variance of RA scores was much greater in the motor domain (for all 3 types of regions) within the patient sample compared with the healthy adult group, a difference that was not seen in the language domain. This variance indicates that some patients indeed showed robust interhemispheric reorganization, while others showed unexpectedly strong deactivation in the right hemisphere.

When considering primary regions in healthy adults, significantly smaller RA scores (ie, more pronounced left
dominance) were found for the motor than for the language tasks. This may appear analogous to the finding for our patient sample and might therefore suggest that our results reflect normal rather than lesion-related differences. Two considerations speak against this interpretation: first, the greater RA scores of patients compared with healthy adults found for primary regions reflect interhemispheric reorganization (strong for language, weak for movement), indicating that activation patterns in the patients were affected by lesions and thus not normal. Second, while differences in RA scores for healthy adults reflect less robust left dominance for primary language compared with primary motor activations, differences in RA scores found in the patients reflect reversed asymmetry (right dominance) for language, but retained (albeit somewhat reduced) left dominance for right-hand movement. This qualitative difference suggests that the activational differences between primary motor and language regions reveal domain-specific patterns of interhemispheric reorganization. Such an interpretation is supported by our convergent findings in the patients for secondary regions (RA scores significantly greater for the language than for the motor domain), for which no analogous differences were found in healthy adults.

Our domain-specific findings could reflect differences in critical periods. Whereas language is phylogenetically recent and has an extended ontogenetic critical period with enhanced reorganizational plasticity, possibly until the onset of puberty, cerebral motor control has a much longer phylogenetic history and a much earlier ontogenetic onset. This is reflected in a early ontogenetic rise of glucose metabolism in motor regions (compared with frontotemporal language regions), demonstrated in PET studies. Our findings might thus partly reflect that some of our patients had lesions that occurred after a period of maturational plasticity for the motor domain but well within the critical period for language acquisition. However, even congenital or neonatal lesions may persistently impair motor functions (as in hemiplegic cerebral palsy). This may suggest that the motor domain is generally characterized by limited postnatal interhemispheric plasticity, while the potential for homotopic interhemispheric reorganization is pronounced in the language domain. Indeed, when only the 5 patients in our sample with first risk before age 1 year were considered, RA scores for finger movement were not higher than for the whole patient sample.

While all patients had left hemisphere lesions as defined in functional terms (hypometabolism on FDG PET), a few had less extensive (or even unidentified) structural lesions on MRI scans. FDG PET is often more sensitive than MRI in identifying lesions in patients with early-onset epilepsy, as in our sample. Nonetheless, it cannot be excluded that our finding of limited interhemispheric reorganization in the motor domain was related to less extensive structural rather than functional lesions. When considering the subgroup of patients with moderate-to-severe hemiatrophy on MRI (patients 4, 5, and 6), RA scores were indeed somewhat greater (ie, less negative) in the primary and secondary motor ROIs (M1, −4.2; M2, −0.5) than for the rest of the sample with predominantly functional lesions. However, the qualitative differences between the language domain (reversed asymmetry) and motor domain (retained asymmetry) were the same for both subgroups. Similarly, there was little difference in the findings for patient subgroups with and without hemiparesis, or for right-handed patients vs those presenting with (most likely lesion-induced) left-handedness (Table 1).

It should be noted that all patients described herein had epilepsy and received antiepileptic medication. It is likely that long-standing seizures and medication have some effect on the nonlesional hemisphere. However, reported effects of antiepileptic medication are generally global (rather than region-specific) and would thus not affect the comparison of normalized 15O-water PET images, as in our study. In addition, since patients served as their own controls in statistical comparisons, it is unlikely that the findings are due to seizure or medication effects.

While these caveats, as well as limitations in sample size and heterogeneity within the patient group, need to be acknowledged, our study all in all supports the concept of differential reorganizational patterns in the motor and the language domains, following early left hemisphere lesion. Additional studies will be necessary to examine whether similar domain-specific differences apply to reorganization following lesions in adulthood.

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Reprints: Harry T. Chugani, MD, PET Center, Children’s Hospital of Michigan, Wayne State University, 3901 Beaubien Blvd, Detroit, MI 48210-2196.

REFERENCES


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