2009

Atypical Language Lateralization in Epilepsy Patients

Gabriel Möddel

Tara T. Lineweaver
Butler University, tlinewea@butler.edu

Stephan U. Schuele

Julia Reinholz

T. Loddenkemper

Recommended Citation

Moddel, G., Lineweaver, T. T. , Schuele, S. U., Reinholz, J. & Loddenkemper, T. (2009). Atypical Language Lateralization in Epilepsy Patients. *Epilepsia*, 50, 1505-1516. doi:10.1111/j.1528-1167.2008.02000.x
Available from: digitalcommons.butler.edu/facsch_papers/433/

Atypical Language Lateralization in Epilepsy Patients

Gabriel Möddel, Tara Lineweaver, Stephan U. Schuele, Julia Reinholz, Tobias Loddenkemper

Summary

Purpose: To investigate whether atypical language dominance in epilepsy patients is related to localization and type of lesions.

Methods: Four hundred and forty-five epilepsy patients received bilateral Wada testing. Language was classified as left (L), right (R), bilateral-dependent (BD, speech arrest after left and right injections), or bilateral-independent (BI, no speech arrest after either injection). Groups were compared regarding handedness and magnetic resonance imaging (MRI) lesions. Lesions were classified as "early" (congenital), "late" neocortical (acquired after birth), and hippocampal sclerosis (HS).

Results: Of all patients, 78% were L, 6% R, 7% BD, and 9% BI. Right-handers with left lesions did not differ from those without lesions. Left-handers with normal MRI did not differ from right-handers. Left-handers with early left lesions were most likely R (46%). Left-handers with late neocortical left lesions were most likely BD (37%); those with left HS were most likely BD (33%) or L (33%). In both latter groups, R language was rare (13% and 11%, respectively).

Discussion: The data support the notion that R dominance may indicate development of functional language areas in the right hemisphere following an early insult. BD language may signal defective maintenance of right hemispheric language caused by a late left hemispheric insult at a time when left dominance has already started to develop. In contrast, BI language may represent a variant with functional language representation in both hemispheres.

The Wada test (intracarotid amobarbital test, IAT) was first described by Juhn Wada in 1949 (Wada, 1949; Wada & Rasmussen, 1960). Since its application at the Montreal Neurological Institute in 1955, it has become the gold standard for presurgical language lateralization assessment in patients undergoing evaluation for epilepsy surgery. Wada test results have also been the basis for scientific work on hemispheric language lateralization. The landmark study by Rasmussen and Milner (1977) found language functions lateralized to the left hemisphere in 70.7% of patients, with 19.7% classified as right dominant. For bilateral language representation, which was observed in 9.6%, the authors postulated a correlation with left-handedness and early brain insult (Rasmussen & Milner, 1977). Later studies in the 1980s, all with smaller sample sizes, found a similar proportion of bilateral language representation (Mateer & Dodrill, 1983;

Strauss & Wada, 1983; Rey et al., 1988). However, all these studies are lacking detailed documentation of brain lesions, as MRI technology was not widely available at that time.

The phenomenon of bilateral language representation has been controversially discussed in previous publications. Wyllie et al. (1990) found that a significant proportion of epilepsy patients, classified as right language dominant according to Wada testing, had language areas mapped to the left hemisphere by extraoperative cortical stimulation. However, cortical stimulation did not reveal any language areas in the right hemispheres of patients classified as left dominant according to the Wada test. The authors concluded that a large proportion of patients with atypical language representation tend to have at least some bilateral hemispheric contribution to language processing. Other investigators have shown that atypical language representation is associated with anomalous lateralization of other cognitive functions, and may lead to neuropsychological impairment (Mateer & Dodrill, 1983; Loring et al., 1999). Benbadis et al. (1995) proposed two distinct groups of patients with bilateral language representation based on speech arrest times after right and left intracarotid amobarbital injections. One group, termed "bilateral-dependent," showed prolonged speech arrest after both injections, indicating that bilateral hemispheric function was needed for adequate language processing. The other group, termed "bilateral-independent" (or bilateral-autonomous), showed only brief speech arrest after either injection, indicating that each hemisphere alone was sufficient for language generation. Hence, two distinct types of bilateral language representation may exist, with different underlying physiologic or pathophysiologic mechanisms. One goal of our study was to evaluate this concept by comparing bilateral-dependent, bilateral-independent, as well as right and left dominant epilepsy patients with regard to handedness, localization, and type of magnetic resonance imaging (MRI)–detectable brain lesions. Our study is the largest series on hemispheric

language lateralization based on Wada testing so far, and is the first with presurgical MRI scans done on all included subjects.

Methods

Patients

We performed a retrospective chart review of 588 consecutive epilepsy patients undergoing Wada tests for presurgical evaluation of language and memory lateralization at the Cleveland Clinic between 1997 and 2003. Only patients with bilateral (left and right) intracarotid barbiturate injection and valid language assessment were included (n = 445 patients). In 15 patients, the procedure had to be repeated because of invalid results or complications during the first test. Reasons included obtundation or encephalopathy of the patient, leading to inability to cooperate with language testing (n = 10), lack of hemiparesis despite adequate amobarbital dose (n = 4), or bleeding at the catheter insertion site (n = 1). In these cases, we included only the results of the second procedure with valid language assessment. Other complications, which did not lead to exclusion, included seizures following amobarbital injection (n = 5); transient facial paralysis, probably due to transient ischemic attack (n = 1); stroke due to occlusion of the left opercular artery (n = 1), severe groin pain and fever on the day following the procedure (n = 1), and severe agitation (n = 1). In one patient, a previously unknown left medial cerebral artery (MCA) aneurysm was incidentally detected.

Handedness

Handedness was assessed by the Edinburgh handedness inventory. Patients were considered right-handed if their score was ≥ 50.

Wada testing

Angiography was performed using standard catheter insertion techniques. Selective catheterization of the common carotid artery and then internal carotid arteries was performed using road mapping techniques with braided 5 F or 4 F catheters with a 1-cm multipurpose curve. The catheter was placed in the center of the cervical internal carotid artery. Amobarbital (75–175 mg; median 125 mg) was applied by intracarotid hand-push injection. The duration of speech arrest after each injection was assessed by continuous language testing including naming, repetition, comprehension, and reading. Speech arrest time was defined as full recovery of these parameters. Electroencephalography (EEG) was continuously recorded throughout the procedure. Language assessment was considered valid if there was no obtundation that would interfere with cooperation of the patient during testing.

Language lateralization

Assessment of language lateralization was based on speech arrest times, using the protocol proposed by Benbadis et al. (1995). Three lateralization measures were calculated: (1) the absolute duration of the speech arrest after left and right intracarotid barbiturate injection, with the criteria being greater than 60 s on one side and less than 60 s on the other; (2) the difference between speech arrest times after left and right injections ($t_L - t_R$), using a cutoff of 30 s; and (3) the laterality index, defined as the difference between speech arrest times after left and right injections, divided by the sum of speech arrest times after left and right injection $[(t_L - t_R)/(t_L + t_R)]$, using a cutoff of 0.5 (Table 1). Subjects were classified as left or right dominant for language if they met two of three lateralization criteria. All other patients were assumed to have bilateral language representation. Bilateral patients were further subdivided into bilateral-dependent (BD), if absolute speech arrests times were ≥60 s after both left and right

injections, and bilateral-independent (BI), if speech arrest time was <60 s after either the left or right injection.

MRI scans

MRI scans (1.5 T) were performed on all patients prior to Wada testing. The localization of brain lesions on MRI was classified according to hemispheric laterality, lobar site, involvement of the neocortex, and signs of hippocampal sclerosis (HS). Lesions were assessed by a blinded observer and were further subdivided into (1) those that were judged to be most likely congenital or perinatally acquired ("early lesions"), such as malformations of cortical development, vascular malformations, pre- or perinatal encephalomalacia, dysembryoplastic neuroepithelial tumors (DNETs), and gangliogliomas; (2) those that were most likely acquired after the perinatal period and involved the neocortex ("late neocortical lesions"), such as astrocytoma, later stroke, or Rasmussen's encephalitis; and (3) HS.

Comparisons

The incidence of L, R, BD, and BI language representation was calculated for all patients, as well as for the following subgroups (in each case for right-handed and left-handed subjects, respectively): (1) all patients; (2) patients with normal MRI; (3) patients with left-hemispheric lesions including HS; (4) patients with left neocortical lesions (excluding HS); (5) patients with left HS; (6) patients with early left-hemispheric lesions; and (7) patients with "late" neocortical left lesions.

Statistical analysis

Statistical testing was performed with SPSS 10.0 (Chicago, IL, U.S.A.). Frequencies (counts) were compared using the chi-square test. Ordinal variables were tested for normal distribution using Kolmogorov-Smirnov test (K-S). Because K-S was significant in all cases, indicating that

the data were not normally distributed, a nonparametric test (Kruskal-Wallis) was used to compare ordinal variables. For the same reason, medians are given instead of means and 95% confidence intervals (CIs). The usual significance level of 0.05 was corrected for multiple comparisons using the Bonferroni-Holm method.

Results

Patient population and demographics

Details describing patient demographics are outlined in Table 2. There were no significant differences between language lateralization groups concerning sex, age at time of testing, and the number of years of formal education. The incidence of contrast medium crossover to the contralateral side via the circle of Willis was not significantly different after left and right injections, or between the language lateralization groups. Of all 445 subjects, 348 (78%) were classified as left dominant (L), 28 (6%) as right dominant (R), 29 (7%) as BD, and 40 (9%) as BI (Table 3).

Handedness and language lateralization

Fifty-four patients (12%) were left-handed or ambidextrous. The proportion of left-handers was significantly higher in right-dominant (43%), BD (21%), and BI subjects (25%) compared with the left-dominant group (7%, see Table 2).

Age of seizure onset and language lateralization

We compared the median age of seizure onset in the four language lateralization groups. There was a trend toward an earlier age of seizure onset in right-dominant (2 years), compared to left-dominant subjects (8 years). However, this difference was not significant (Table 2).

MRI findings

Tables 4–6 provide an overview of the localization and types of brain lesions detected by MRI in the four lateralization groups. MRI-detected lesions, regardless of location, were equally frequent in the four lateralization groups (Table 4). Left-hemispheric lesions (including HS) were significantly more common in right-dominant (61%) and BD (79%), than in left-dominant patients (39%). When comparing only early left-hemispheric lesions, there were significant differences for right-dominant (32%) and BD (28%), as compared to left-dominant patients (11%). For late left-hemispheric neocortical lesions, as well as for patients with left HS, there were no significant differences between the lateralization groups, although there was a trend toward increased likelihood of both types of lesions in BD patients (Table 4). Right-hemispheric lesions appeared to be less frequent in right-dominant (14%) and BD (10%) patients, compared to left-dominant subjects (35%, $p < 0.01$), but this difference did not withstand correction for multiple comparisons (Table 5). For bilateral lesions, there were no significant differences between the lateralization groups (Table 6).

Cross-relationship between handedness, MRI lesions, and language lateralization

Presence or absence and site of brain lesions had an effect on language lateralization (Table 3). Of 97 nonlesional patients, 80% were left dominant, 4% were right dominant, 4% were BD, and 12% were BI. Among all right-handed patients, 82% showed left dominance, 4% were right dominant, 6% were BD, and 8% were BI. Among all left-handed and ambidextrous patients ($n = 54$), left language dominance was significantly less frequent (48%), whereas the proportion of right language dominance (22%) and BI subjects (19%) was significantly higher. There were no significant differences for BD patients (11%; see Table 3). The differences between right- and left-handed patients were dependent on the presence or absence of brain lesions. Among nonlesional patients, there were no significant differences between right-handers and left-handers

(Table 3). In contrast, for patients with left-hemispheric lesions, differences between right-handers and left-handers were striking. Of 164 right-handed patients with left-hemispheric (including HS) lesions, 77% had left-hemispheric language dominance, 7% were right-dominant, 9% were BD, and 7% were BI. There were no differences among right-handers with regard to presence and type of lesion. Among left-handed patients with left-hemispheric lesions including HS (n = 28), left-hemispheric language dominance was found in only 21%, whereas the majority were right dominant (29%), BD (25%), or BI (25%, Table 3). Left-handers with left neocortical lesions were most likely right dominant (37%), L language dominance was significantly less likely (16%) than in all nonlesional patients. In left-handers with left HS, BD language (33%) appeared to be more frequent than in nonlesional patients, whereas left (L) language appeared to be less common (33%), with no obvious change in the frequency of right (R) language (1%). The difference ($p = 0.02$), however, did not withstand correction for multiple comparisons. Among left-handers with "early" left-hemispheric lesions, only one of 11 (9%) was found to have L language dominance, patients were most likely R dominant (46%). Only 2 of 8 left-handers with "late neocortical" left-hemispheric lesions (25%) were found to have left-sided language dominance; the proportion for BD (37%) language was significantly increased, whereas right language dominance (13%) and BI language (25%) were not significantly more frequent (Table 3).

Discussion

Summary

Among right-handed epilepsy patients, the proportion of L, R, BD, and BI language dominance is not dependent on whether a left-hemispheric lesion is present, or whether a left-hemispheric lesion is congenital or acquired after the perinatal period. Furthermore, left-handed and right-

handed patients with normal MRI do not significantly differ from each other, although there seems to be a nonsignificant trend toward a higher likelihood of BI language representation in nonlesional left-handers. Among left-handed patients with left-hemispheric neocortical lesions, the majority was found to be right dominant (37%) or bilateral (47%; BD 21%, BI 26%), whereas only 16% were found to be left dominant. Among left-handers with left HS, there appears to be an increased likelihood of BD (33%), as well as decreased likelihood of L dominant language (33%), but no difference for R dominance (11%), which just failed to be statistically significant because of the adjustment for multiple comparisons. Left-handers with congenital or perinatally acquired left-hemispheric lesions were most likely right dominant (46%). In contrast, among left-handed patients with left neocortical lesions that were acquired after the perinatal period, exclusive right-dominant language was relatively rare (13%), whereas the majority presented with bilateral language representation (62%; BD 37%; BI 25%).

Comparison with previous studies on language lateralization

Several studies report on hemispheric language dominance in epilepsy patients as analyzed by Wada testing (see Table 7). Rasmussen and Milner (1977), who published the largest series so far, found 71% left-language dominant patients, with 20% right-dominant, and 9% bilateral. Hence, the proportion of right-dominant subjects seemed to be a ratio of 2:1 higher than that of individuals with bilateral language representation. In our series, we found a similar proportion of left-dominant individuals (78% of all patients, regardless of handedness and brain pathology). However, we found an inverse ratio of right (6%) versus bilateral (16%) language representation. This might be due in part to differences in the selected patient population. Other groups have found greater proportions of bilateral language representation than Rasmussen and Milner (1977), ranging from 6–21% (Table 7). In selected subpopulations with unilateral temporal lobe

epilepsy, Zatorre (1989) classified 22 of 61 patients (36%) as bilateral, only 4 (7%) were considered right-dominant. Using functional transcranial Doppler sonography (fTCD) for assessment of hemispheric perfusion differences during a word generation task, Knecht et al. (2001) found right and bilateral language in 9.5% each. Differences between our series and that of Rasmussen and Milner (1977) may arise from our use of speech arrest times as the major criterion for language lateralization, as opposed to the more comprehensive language assessment protocol used at the Montréal Neurological Institute. Patients with very brief speech arrest times after both left and right injections, classified as BI according to our protocol, may have been classified as right-dominant based on very subtle dysphasic errors that may have been underdiagnosed in our protocol. On the other hand, the discrepancy may suggest that a significant proportion of patients classified as right dominant by Rasmussen and Milner (1977) may indeed have had bilateral language representation with some asymmetry in favor of the right hemisphere. This view is supported by the results of Knecht et al. (2000), who investigated language lateralization in healthy volunteers using fTCD. The investigators describe language lateralization as a continuous variable that correlates with the degree of handedness. Most subjects that were not exclusively left dominant for language showed at least some degree of bilaterality. In this context, classification as either right or bilateral dominant critically depends on the cutoff criteria used. Therefore, different criteria for classification as unilateral language dominance used by different investigators may account for the wide range of right versus bilateral language reported in previous studies.

Language lateralization is a spectrum

Dichotomizing a continuous variable into categories produces results that rely on definitions, technique, and cutoff values. Loring et al. (1990) tried to resolve this dilemma in an elegant way

using a comprehensive language rating protocol based on four linguistic tasks. The authors first assessed the presence or absence of linguistic errors following amobarbital injection into each internal carotid artery independently. Patients were classified as "unilateral dominant," that is, exclusive language representation, if errors occurred only after a single injection. According to this protocol, they found 77% left dominant, 2% right dominant, and 21% bilateral. Although our study was based on speech arrest times alone rather than on a comprehensive language assessment protocol, these numbers are surprisingly similar to ours. In a second evaluation paradigm, Loring et al. (1990) defined a "forced relative dominance," with subjects classified as either left or right, if language errors were more severe after one-sided injection or the other. According to this stricter protocol, 89% were classified as left-dominant, 6% as right-dominant, and 5% as bilateral. This demonstrates that left, right, and bilateral language representation are categories that are highly dependent on criteria and definitions. Most individuals with bilateral language representation seem to have more or less asymmetric preference for one or the other hemisphere, with exclusive right-sided language representation being relatively rare. Comparisons between Wada test findings and extraoperative cortical language mapping yielded similar results (Wyllie et al., 1990): In 66 patients classified as left dominant according to the Wada test, no language function was found during cortical stimulation of the right hemisphere. However, in a significant number of patients presurgically classified as right-language dominant (n = 9) by the Wada protocol, cortical mapping revealed language disturbance during left hemisphere stimulation, suggesting that these subjects indeed had bilateral language representation with some preference for the right hemisphere (Wyllie et al., 1990).

Relationship to brain lesion

Previous studies have emphasized that language lateralization is related to handedness and to presence and localization of brain lesions. Rasmussen and Milner (1977) report that 96% of right-handed subjects without evidence for early damage to the left hemisphere were left dominant, with all remaining patients being right dominant. Presence or absence of lesions in their series was based on clinical examination. We found similar results in right-handed individuals with no MRI-detectable brain lesion: 81% left-dominant, 4% right-dominant, and 16% bilateral (5% BD; 11% BI). The majority of our left-handed or ambidextrous patients without MRI-detected lesions (n = 13) were still found to be left-hemispheric language dominant (69%), with most of the remaining individuals showing BI language (23%), and only one of 13 having exclusively right-sided language (8%). This is in concordance with the results of Rasmussen and Milner (1977), who found that 70% of left-handed or mixed-handed individuals without early damage to the left hemisphere were left-dominant, with 15% each showing bilateral and right language representation. Knecht et al. (2000, 2001) demonstrated that language lateralization appears to be a continuous spectrum. Using a combined approach with transcranial Doppler sonography for language lateralization and repetitive transcranial magnetic stimulation (rTMS) for simulating "reversible lesions," they have demonstrated that the degree of language lateralization determines susceptibility to lesions (Knecht et al., 2002). The type and localization of the lesion may influence interhemispheric language development. Very early large or destructive lesions of the left hemisphere that occur before language development may lead to maintenance of inherent language functions in the right hemisphere, and, with increasing hemispheric specialization, may result in right-hemispheric language dominance (Rasmussen & Milner, 1977). Later insults may induce either partial shift of language functions from the dominant to the nondominant hemisphere, if hemispheric specialization is still incomplete, or

ipsilateral shift of language localization if the insult occurs even later, as shown for slow growing neoplasms by DeVos et al. (1995).

Hippocampal lesions have been suspected to play a role in language acquisition and lateralization (Knecht, 2004). In addition, other subcortical centers may also play a role (Banai et al., 2005; Wible et al., 2005). Our results further delineate this hypothesis by suggesting that BD language, but not right or BI language may be increased in patients with left HS. The hippocampus and its projections to the frontal, temporal, and parietal cortical areas have been recognized as important anatomic structures in the acquisition of language and grammar (Gabrieli et al., 1988; Opitz & Friederici, 2003). Liegeois et al. (2004) found that in children with lesions involving the mesial temporal areas, intrahemispheric language relocalization was seen only if the ipsilateral hippocampus was intact. In addition, functional MRI (fMRI) and functional transcranial Doppler ultrasound studies suggest that temporal lobe epilepsy and frequent mesial temporal interictal epileptiform activity may be related to atypical language representation (Briellmann et al., 2006; Janszky et al., 2006; Knake et al., 2006). An intact hippocampus may, therefore, be crucial for intrahemispheric language shift. We did not include hippocampal sclerosis as an "early" lesion based on the fact that the actual MRI-detectable "sclerosis" is not present at birth but develops during childhood, adolescence, or even later. However, we are aware that hippocampal sclerosis may be a secondary phenomenon caused by recurrent epileptiform activity and excitotoxicity on the basis of a congenital underlying alteration of neuronal circuitry such as subtle mesial-temporal microdysplasias (e.g., dispersion or dysmorphy of hippocampal pyramidal cells). Hence, one may ask whether there are parallels in language development between patients with HS and those with congenital ("early") lesions. Our data did not confirm this hypothesis, because left HS in left-handers, just like in "late" left

lesions, showed a trend toward increased likelihood of BD, but not right-language dominance, whereas left-handers with early left-hemispheric lesions were most likely right, but not BD dominant. There were no differences between patients with HS and those with other "late" lesions.

Type and degree of bilateral language lateralization

Lesions that did not lead to a handedness shift were not likely to induce a shift toward atypical language representation in the majority of individuals. As compared with nonlesional right-handed individuals, right-handers with left-hemispheric insults did not differ in terms of likelihood of right or bilateral language in our series, regardless of whether an insult had occurred in the pre- or perinatal period, or later. However, striking differences were seen for left-handed or ambidextrous patients: The majority of left-handed subjects with left-hemispheric neocortical lesions had either right (37%) or bilateral (47%; BD 21%, BI 26%) language representation, whereas only a minority were considered left dominant (16%). Hence, a left-hemispheric lesion that leads to atypical handedness is associated with atypical language lateralization in the majority of patients.

Interestingly, the prevalence of BI language was not significantly increased in association with either early or late left-hemispheric neocortical lesions. Conversely, most left-handed individuals with normal MRIs who were not left-language dominant had BI language (23%) rather than right (8%) or BI (0%) language representation. Knecht et al. (2000), using a comprehensive handedness assessment questionnaire and fTCD to lateralize language, have described a correlation between the degree of left-handedness and the degree of language right-shift. Whereas the majority of right-handers lateralized language exclusively to the left, a significant proportion of left-handed subjects appeared to have more or less bilateral language

representation (Knecht et al., 2000). Based on these results, we hypothesize that bilateral-independent language may represent atypical language representation within the normal range of the continuous lateralization variable, that is, a functional form of language bilaterality resulting from either genetic disposition or maintenance of inherent right-hemispheric language functions during the development of hemispheric specialization. BD language, in contrast, may more likely represent an incomplete language shift due to an insult in the dominant hemisphere at a time when hemispheric specialization has already partly developed.

Timing of the lesion and language lateralization

Prior to the age of approximately one year, development of right-hemispheric specialization for language after left-hemispheric brain injury is more likely than later in life (Strauss & Wada, 1983). Presence of language functions in the right hemisphere is commonly seen in association with left-hemispheric lesions acquired before the age of 6 years (Satz et al., 1988). Our findings support and expand these implications. Early left-hemispheric lesions seem to be associated with right-language dominance. Lesions acquired later during development, in contrast, are more likely associated with BD language. A language shift to the opposite hemisphere may, therefore, be more or less complete with early left-hemispheric insults, but is more likely incomplete after the perinatal period, resulting in BD language representation. These findings correspond with our current understanding of neuronal circuitry formation during language acquisition. Infants initially create a map of language input sounds, and then analyze this input in order to identify combinations of sounds and units that are frequently heard in their native environment. Subsequently, infants focus and "warp in" on previously learned sounds to improve processing by analyzing language (Kuhl et al., 1992; Kuhl, 2000). This is supported by studies of language lateralization in infants using mismatch negativity, an event-related potential elicited by a change

in a repetitive sound pattern (Näätänen et al., 1997). Before 6 months of age, mismatch negativity is observed in response to changes in both native and non-native language contrasts. However, at 12 months of age, mismatch negativity was shown only for native language contrasts (Cheour-Luhtanen et al., 1995). Initially learned maps and processing of sounds may, therefore, be related to early commitment of neuronal networks to this sound perception and analysis (Kuhl, 2003). Our data suggest that the localization of these neuronal networks may be different if a lesion is present or occurs during the language acquisition process. The critical period may be a relatively wide time interval, as evidenced by studies in proficient bilinguals with a second language learned later in life, showing that both first and second languages share overlapping cortical areas (Friederici et al., 2002). Further evidence for variability in this critical period comes from patients with Rasmussen's encephalitis. Under certain circumstances, hemispherectomy of the language-dominant hemisphere after the age of 9 years in these patients does not necessarily subject adolescents to lasting aphasia, even if the Wada test initially demonstrated left-hemispheric language dominance (Boatman et al., 1999; Hertz-Pannier et al., 2002; Loddenkemper et al., 2003). Even in adults with hippocampal sclerosis, more symmetrical language activations, along with reduced left-hemispheric and increased right-hemispheric structural connections have been reported (Powell et al., 2007).

Limitations

Our data are limited because of the retrospective study design and selection bias including only patients with epilepsy. However, this particular patient population offers a unique window into plasticity and atypical language development. There may also be some bias due to the Wada test paradigm and the language lateralization protocol utilized to classify patients. We are clearly aware of the problems and caveats arising from the use of speech arrest as the main determining

variable for language lateralization, as compared to a comprehensive clinical language assessment protocol (Benbadis et al., 1998). In particular, subtle dysphasic errors such as phonematic paraphasias that occur only after unilateral injection despite bilaterally symmetric duration of speech arrest may lead to the diagnosis of bilateral language representation in patients who have indeed asymmetric representation with preference for one hemisphere. Furthermore, our protocol was not sensitive for differentiating between errors of naming and errors in verbal serial functions such as counting or saying the days of the week. Therefore, our data were not sufficient to reconfirm the finding of Rasmussen and Milner (1977), who describe functionally asymmetric contribution of both hemispheres (i.e., dominance of one hemisphere for naming, dominance of the other hemisphere for verbal sequences) in almost half of their patients with bilateral language representation. On the other hand, our data show that our "simple" protocol yields results on language lateralization that are in line with the most important previous findings. This protocol has been successfully used at the Cleveland Clinic for many years, with a rate of complications of resective surgery not exceeding that of other centers. Finally, our group has previously shown that language lateralization with this method is highly reproducible (Loddenkemper et al., 2007).

A further subdivision of "late lesions" into those present before the age of language acquisition (i.e. within the first two to three years of life) versus those acquired after completion of language development may have been desirable. Such an analysis would convey important information about the pathophysiology of language development and on neuronal plasticity in general. Unfortunately, the data available for our retrospective analysis did not allow us to make such a distinction on a valid basis, as very few follow-up MRI scans from early childhood were available for most of our patients. Determination of the age-of-onset of "late lesions" would have

had to rely on the patient's history and could, therefore, not be specified objectively. Future studies may wish to evaluate the relationship between the age-of-onset of lesions and their impact on language lateralization, handedness, and neuropsychological abilities.

Conclusions

We hypothesize that both right and BD language reflect reorganization of language areas in response to an insult to the left hemisphere. Right-hemisphere language dominance may indicate atypical hemispheric specialization due to a left-hemispheric lesion that occurs prior to or during early language development. BD language may be the result of later insults that lead to partial shift of language functions from the dominant to the nondominant hemisphere. Finally, BI language may represent a physiologic variant, with language representation in both hemispheres. Distinguishing the degree and type of language lateralization may help predict deficits and recovery potential after neurosurgical resection or cerebral insults.

Acknowledgments

Author GM was supported by Innovative Medizinische Forschung (IMF), University of Münster, Germany (FoeKz. MO 620202).

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure: None of the authors has any conflict of interest to disclose.

References

Banai K, Nicol T, Zecker SG, Kraus N. (2005) Brainstem timing: implications for cortical processing and literacy. J.Neurosci 25:9850–9857.

Benbadis SR, Dinner DS, Chelune GJ, Piedmonte M, Luders HO. (1995) Objective criteria for reporting language dominance by intracarotid amobarbital procedure. J Clin Exp Neuropsychol 17:682–690.

Benbadis SR, Binder JR, Swanson SJ, Fischer M, Hammeke TA, Morris GL, Frost JA, Springer JA. (1998) Is speech arrest during Wada testing a valid method for determining hemispheric representation of language? Brain Lang 65:441–446.

Boatman D, Freeman J, Vining E, Pulsifer M, Miglioretti D, Minahan R, Carson B, Brandt J, McKhann G. (1999) Language recovery after left hemispherectomy in children with late-onset seizures. Ann Neurol 46:579–586.

Briellmann RS, Labate A, Harvey AS, Saling MM, Sveller C, Lillywhite L, Abbott DF, Jackson GD. (2006) Is language lateralization in temporal lobe epilepsy patients related to the nature of the epileptogenic lesion? Epilepsia 47:916–920.

Cheour-Luhtanen M, Alho K, Kujala T, Sainio K, Reinikainen K, Renlund M, Aaltonen O, Eerola O, Näätänen R. (1995) Mismatch negativity indicates vowel discrimination in newborns. Hear Res 82:53–58.

DeVos KJ, Wyllie E, Geckler C, Kotagal P, Comair Y. (1995) Language dominance in patients with early childhood tumors near left hemisphere language areas. Neurology 45:349–356.

Friederici AD, Steinhauer K, Pfeifer E. (2002) Brain signatures of artificial language processing: evidence challenging the critical period hypothesis. Proc Natl Acad Sci U S A 99:529–534.

Gabrieli JD, Cohen NJ, Corkin S. (1988) The impaired learning of semantic knowledge following bilateral medial temporal-lobe resection. Brain Cogn 7:157–177.

Hertz-Pannier L, Chiron C, Jambaque I, Renaux-Kieffer V, Van de Moortele PF, Delalande O, Fohlen M, Brunelle F, Bihan D. (2002) Late plasticity for language in a child's non-dominant hemisphere: a pre- and post-surgery fMRI study. Brain 125:361–372.

Janszky J, Mertens M, Janszky I, Ebner A, Woermann FG. (2006) Left-sided interictal epileptic activity induces shift of language lateralization in temporal lobe epilepsy: an fMRI study. Epilepsia 47:921–927.

Knake S, Haag A, Pilgramm G, Dittmer C, Reis J, Assmann H, Oertel WH, Rosenow F, Hamer HM. (2006) Language dominance in mesial temporal lobe epilepsy: a functional transcranial Doppler sonography study of brain plasticity. Epilepsy Behav 9:345–348.

Knecht S. (2004) Does language lateralization depend on the hippocampus? Brain 127:1217–1218.

Knecht S, Deppe M, Dräger B, Bobe L, Lohmann H, Ringelstein E, Henningsen H. (2000) Language lateralization in healthy right-handers. Brain 123:74–81.

Knecht S, Dräger B, Flöel A, Lohmann H, Breitenstein C, Deppe M, Henningsen H, Ringelstein EB. (2001) Behavioural relevance of atypical language lateralization in healthy subjects. Brain 124:1657–1665.

Knecht S, Flöel A, Dräger B, Breitenstein C, Sommer J, Henningsen H, Ringelstein EB, Pascual-Leone A. (2002) Degree of language lateralization determines susceptibility to unilateral brain lesions. Nat Neurosci 5:695–699.

Kuhl PK, Williams KA, Lacerda F, Stevens KN, Lindblom B. (1992) Linguistic experience alters phonetic perception in infants by 6 months of age. Science 255:606–608.

Kuhl PK. (2000) A new view of language acquisition. Proc Natl Acad Sci U S A 97:11850–11857.

Kuhl PK. (2003) Human speech and birdsong: communication and the social brain. Proc Natl Acad Sci U S A 100:9645–9646.

Liegeois F, Connelly A, Cross JH, Boyd SG, Gadian DG, Vargha-Khadem F, Baldeweg T. (2004) Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. Brain 127:1229–1236.

Loddenkemper T, Wyllie E, Lardizabal D, Stanford LD, Bingaman W. (2003) Late language transfer in patients with Rasmussen encephalitis. Epilepsia 44:870–871.

Loddenkemper T, Morris HH, Lineweaver TT, Kellinghaus C. (2007) Repeated intracarotid amobarbital tests. Epilepsia 48:553–558.

Loring DW, Meador KJ, Lee GP, Murro AM, Smith JR, Flanigin HF, Gallagher BB, King DW. (1990) Cerebral language lateralization: evidence from intracarotid amobarbital testing. Neuropsychologia 28:831–838.

Loring DW, Strauss E, Hermann BP, Perrine K, Trenerry MR, Barr WB, Westerveld M, Chelune GJ, Lee GP, Meador KJ. (1999) Effects of anomalous language representation on neuropsychological performance in temporal lobe epilepsy. Neurology 53:260–264.

Mateer CA, Dodrill CB. (1983) Neuropsychological and linguistic correlates of atypical language lateralization: evidence from sodium amytal studies. Hum Neurobiol 2:135–142.

Näätänen R, Lehtokoski A, Lennes M, Cheour M, Houtilainen M, Iivonen A, Vainio M, Alku P, Ilmoniemi RJ, Luuk A, Allik J, Sinkkonen J, Alho K. (1997) Language-specific phoneme representations revealed by electric and magnetic brain responses. Nature 385:432–434.

Opitz B, Friederici AD. (2003) Interactions of the hippocampal system and the prefrontal cortex in learning language-like rules. Neuroimage 19:1730–1737.

Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Koepp MJ, Duncan JS. (2007) Abnormalities of language networks in temporal lobe epilepsy. Neuroimage 36:209–221.

Rasmussen T, Milner B. (1977) The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann N Y Acad Sci 299:355–369.

Rausch R, Walsh GO. (1984) Right-hemisphere language dominance in right-handed epileptic patients. Arch Neurol 41:1077–1080.

Rey M, Dellatolas G, Bancaud J, Talairach J. (1988) Hemispheric lateralization of motor and speech functions after early brain lesion: study of 73 epileptic patients with intracarotid amytal test. Neuropsychologia 26:167–172.

Satz P, Strauss E, Wada J, Orsini DL. (1988) Some correlates of intra- and interhemispheric speech organization after left focal brain injury. Neuropsychologia 26:345–350.

Strauss E, Wada J. (1983) Lateral preferences and cerebral speech dominance. Cortex 19:165–177.

Wada J. (1949) A new method for the determination of the side of cerebral speech dominance: a preliminary report on the intracarotid injection of Amytal in man. Igaku Seibutsugaku 14:221–222.

Wada J, Rasmussen T. (1960) Intracarotid injection of sodium Amytal for the lateralization of cerebral speech dominance: experimental and clinical observations. J Neurosurg 17:266–282.

Wible B, Nicol T, Kraus N. (2005) Correlation between brainstem and cortical auditory processes in normal and language-impaired children. Brain 128:417–423.

Wyllie E, Luders H, Murphy D, Morris H 3rd, Dinner D, Lesser R, Godoy J, Kotagal P, Kanner A. (1990) Intracarotid amobarbital (Wada) test for language dominance: correlation with results of cortical stimulation. Epilepsia 31:156–161.

Zatorre RJ. (1989) Perceptual asymmetry on the dichotic fused words test and cerebral speech lateralization determined by the carotid sodium amytal test. Neuropsychologia 27:1207–1219.

Table 1. Criteria for unilateral language dominance based on speech arrest times after intracarotid amobarbital injection

Absolute duration of speech arrest	
$t_L \geq 60$ s and $t_R < 60$ s	Left dominance (L)
$t_L < 60$ s and $t_R \geq 60$ s	Right dominance (R)
Difference between speech arrest times after left and right injection (L − R)	
$t_L - t_R \geq 30$ s	Left dominance (L)
$t_L - t_R \leq -30$ s	Right dominance (R)
Laterality index (LI) = $(t_L - t_R)/(t_L + t_R)$	
$LI \geq 0.5$	Left dominance (L)
$LI \leq -0.5$	Right dominance (R)

t_L, speech arrest time after left-sided injection; t_R, speech arrest time after right-sided injection; LI, laterality index.

Table 2. Demographic characteristics of 445 patients who underwent bilateral injections during the Wada test

	Total (n = 445)	**L dominant (n = 348)**	**R dominant (n = 28)**	**Bilateral-dependent (n = 29)**	**Bilateral-independent (n = 40)**	**Statistics**
Sex (M/F)	M: 220/445 (49%) F: 225/445 (51%)	M: 166/348 (47%) F: 182/348 (53%)	M: 12/28 (43%) F: 16/28 (57%)	M: 18/29 (62%) F: 11/29 (38%)	M: 24/40 (60%) F: 16/40 (40%)	χ^2 p = 0.21
Age in years at time of testing: median [range]	30.5 [5–65]	30.5 [8–66]	33.5 [5–49]	32.0 [9–57]	25.0 [8–64]	Kruskal-Wallis p = 0.25
Years of formal education: median [range]	12 [2–20]	12 [8–20]	12 [2–18]	12 [9–18]	12 [10–17]	Kruskal-Wallis p = 0.99
Crossover of contrast after left (L) vs. right (R) injection	L: 61/177 (34%) R: 54/177 (31%)	L: 25/80 (31%) R: 22/80 (28%)	L: 10/28 (36%) R: 7/28 (25%)	L: 12/29 (41%) R: 8/29 (28%)	L: 14/40 (35%) R: 17/40 (43%)	χ^2 L: p = 0.80 R: p = 0.31
Proportion of left-handed or ambidextrous subjects	54/445 (12%)	26/348 (7%)	**12/28* (43%)**	**6/29** (21%)**	**10/40*** (25%)**	χ^2 **p < 0.01** χ^{2*}) ***p < 0.01** ****p = 0.01** *****p < 0.01**
Age of seizure onset in years: median [range]	8 [0–58]	8 [3–35]	2 [1–24]	7 [0–53]	8 [0–58]	Kruskal–Wallis p = 0.57

L, left; R, right; M, male; F, female. Statistical comparisons using chi-square test. A global test (two-by-four cross table) was used to detect differences in any of the lateralization groups; if the global test was significant, a confirmatory test [*)] was performed comparing the right (*), bilateral-dependent (**), and bilateral-independent (***) groups with the left lateralization group. Kolmogorov-Smirnov test showed that the ordinal variables (age at time of Wada testing [p = 0.01]; years of formal education [p < 0.01]; and age of seizure onset [p < 0.01]) were not normally distributed. Therefore, a nonparametric test (Kruskal-Wallis) was used for statistical comparison. Significance levels were corrected for multiple comparisons using Bonferroni-Holm method. Significant differences withstanding Bonferroni-Holm correction are highlighted in bold font.

Table 3. Cross-relationship between handedness, MRI lesions, and language lateralization

	Total	L dominant	R dominant	Bilateral-dependent	Bilateral-independent	Statistics
All	445	348 (78)	28 (6)	29 (7)	40 (9)	
All right-handed	391	321 (82)	15 (4)	23 (6)	32 (8)	
All left-handed	54	**26* (48)**	**12** (22)**	6*** (11)	**10**** (19)**	Compared to all right-handed pt: **p < 0.01** ***p < 0.01*** ****p = 0.01*** *****p = 0.11*** ******p < 0.01***
Normal MRI	97	77 (80)	4 (4)	4 (4)	12 (12)	
Right-handed with normal MRI	84	68 (81)	3 (4)	4 (5)	9 (11)	Compared to all pt with normal MRI p = 0.98
Left-handed with normal MRI	13	9 (69)	1 (8)	0	3 (23)	Compared to all pt with normal MRI p = 0.58
Right-handed with left lesion (including HS)	164	127 (77)	11 (7)	14 (9)	12 (7)	Compared to all pt with normal MRI p = 0.25
Left-handed with left lesion (including HS)	28	**6* (21)**	**8** (29)**	**7*** (25)**	7**** (25)	Compared to all pt with normal MRI **p < 0.01** ***p < 0.01*** ****p < 0.01*** ******p < 0.01*** *******p = 0.10*
Right-handed with left-neocortical lesion	95	72 (76)	7 (7)	9 (10)	7 (7)	Compared to all pt with normal MRI p = 0.24
Left-handed with left-neocortical lesion	19	**3* (16)**	**7** (37)**	**4*** (21)**	5**** (26)	Compared to all pt with normal MRI **p < 0.01** ***p < 0.01*** ****p < 0.01*** ******p < 0.01*** *******p = 0.12*
Right-handed with left HS	69	55 (80)	4 (6)	5 (7)	5 (7)	Compared to all pt with normal MRI p = 0.67
Left-handed with left HS	9	***3** (33)**	1** (11)	***3**** (33)**	2**** (22)	Compared to all pt with normal MRI ***p = 0.02*** ****p < 0.01*** *****p = 0.34* ******p < 0.01*** *******p = 0.40*
Right-handed with early left-hemispheric lesions	51	36 (71)	4 (8)	6 (12)	5 (10)	Compared to all pt with normal MRI p = 0.23
Left-handed with early left-hemispheric lesion	11	**1* (9)**	**5** (46)**	2*** (18)	3**** (27)	Compared to all pt with normal MRI **p < 0.01** ***p < 0.01*** ****p < 0.01*** *****p = 0.06* *******p = 0.18*
Right-handed with late left-hemispheric lesions	44	36 (82)	3 (7)	3 (7)	2 (4)	Compared to all pt with normal MRI p = 0.43
Left-handed with late left-hemispheric lesion	8	**2* (25)**	1** (13)	**3*** (37)**	2**** (25)	Compared to all pt with normal MRI **p < 0.01** ***p < 0.01*** *****p = 0.29* ******p < 0.01*** *******p = 0.31*

Values within parenthesis are expressed in percentage. L, left, R, right. Statistical comparisons using chi-square test. A global test (two-by-four cross table) was used to detect differences in any of the lateralization groups; if the global test was significant, a confirmatory test was performed comparing the right(*), bilateral-dependent (**), and bilateral-independent (***) groups with the left lateralization group. Significance levels were corrected for multiple comparisons using Bonferroni-Holm method. Significant differences withstanding Bonferroni-Holm correction are highlighted in bold font. Differences with $p < 0.05$ but not withstanding correction for multiple comparison are shown in italics.

Table 4. MRI findings: Left-hemispheric lesions

	Total (n = 445)	**L dominant (n = 348)**	**R dominant (n = 28)**	**Bilateral-dependent (n = 29)**	**Bilateral-independent (n = 40)**	**Statistics**
All MRI-detected lesions	349 (78)	271 (78)	24 (86)	26 (90)	28 (70)	p = 0.19
Left neocortical lesion	114 (26)	Frontal 12 Temporal 37 Par.-occ. 22 Multilobar 4	Frontal 4 Temporal 6 Multilobar 3	Frontal 4 Temporal 5 Par.-occ. 3 Multilobar 2	Frontal 2 Temporal 6 Par.-occ. 4	**p < 0.01** ***p < 0.01** ****p < 0.01** *****p = 0.23**
	∑	75 (22)	**13* (46)**	**14** (48)**	12*** (30)	
Left HS	78 (18)	59 (17)	4 (14)	9 (31)	6 (15)	p = 0.25
∑	192	134 (39)	**17* (61)**	**23** (79)**	18*** (45)	**p < 0.01** ***p = 0.02** ****p < 0.01** *****p = 0.43**
left-hemispheric lesions	(43)					
"Early" left hemispheric lesion	62 (14)	FRONTAL 9 CD 7, DNET/GG 1, EM 1 TEMPORAL 19 CD 9, DNET/GG 4, EM 1, VM 3, Ham 1, Liss 1 PAR.-OCC. 9 CD 6, DNET/GG 1, EM 1, VM 1	FRONTAL 2 CD 2 TEMPORAL 4 CD 3, DNET/GG 1 MULTILOBAR 3 CD 2, EM 1	TEMPORAL 3 DNET/GG 1, VM 1, EM 1 PAR.-OCC. 3 EM 3 MULTILOBAR 2 CD 1, EM 1	TEMPORAL 4 CD 2, DNET/GG 1, VM 1 PAR.-OCC. 4 EM 3, CD 1	**p < 0.01** ***p < 0.01** ****p < 0.01** *****p = 0.08**
	∑	37 (11)	**9* (32)**	**8** (28)**	8*** (20)	
"Late" left hemispheric lesion	52 (12)	FRONTAL 3 Gl 3 TEMPORAL 18 Gl 15, Stroke 3 PAR.-OCC. 13 Gl 7, Stroke 5, Rasmuss 1 MULTILOBAR 4 Gl 4	FRONTAL 2 Stroke 2 TEMPORAL 2 Gl 2	FRONTAL 4 Gl 2, Stroke 2 TEMPORAL 2 Gl 2	FRONTAL 2 Gl 2 TEMPORAL 2 Gl 2	p = 0.43

L, left; R, right; M, male; F, female. Statistical comparisons using chi-square test. A global test (two-by-four cross table) was used to detect differences in any of the lateralization groups; if the global test was significant, a confirmatory test [*)] was performed comparing the right (*), bilateral-dependent (**), and bilateral-independent (***) groups with the left lateralization group. Kolmogorov-Smirnov test showed that the ordinal variables (age at time of Wada testing [p = 0.01]; years of formal education [p < 0.01]; and age of seizure onset [p < 0.01]) were not normally distributed. Therefore, a nonparametric test

(Kruskal-Wallis) was used for statistical comparison. Significance levels were corrected for multiple comparisons using Bonferroni-Holm method. Significant differences withstanding Bonferroni-Holm correction are highlighted in bold font.

Table 5. MRI findings: Right-hemispheric lesions

	Total (n = 445)	**L dominant (n = 348)**	**R dominant (n = 28)**	**Bilateral-dependent (n = 29)**	**Bilateral-independen (n = 40)**	**Statistics**
Right neocortical lesion	74 (17)	Frontal 14 Temporal 36 Par.-occ. 12 Multilobar 3	Frontal 1 Par.-occ. 1	Frontal 1	Frontal 3 Temporal 3	p = 0.09
Σ		65 (19)	2 (7)	1 (3)	6 (15)	
Right HS	62 (14)	56 (16)	2 (7)	2 (7)	2 (5)	p = 0.09
∑ Right-hemispheric lesions	136 (31)	121 (35)	***4* (14)***	***3** (10)***	*8*** (20)*	***p < 0.01*** ****p = 0.03*** *****p < 0.01*** ****p = 0.06*
"Early" right hemispheric lesion		FRONTAL 6 CD 3, EM 3 TEMPORAL 22 CD 9, EM 2, DNET/GG 3, VM 7, Ham.1 PAR.-OCC. 9 CD 2, EM 2, VM 5 MULTILOBAR 3 CD 1, EM 1, Polymicr 1	FRONTAL 1 CD 1	–	FRONTAL 2 EM 1, VM 1 TEMPORAL 1 CD 1	p = 0.13
∑	44 (10)	40 (13)	1 (4)	0	3 (8)	
"Late" right hemispheric lesion		FRONTAL 8 Gl 5, Stroke 3 TEMPORAL 14 Gl 10, Stroke 4 PAR.-OCC. 3 Gl 3	PAR.-OCC. 1 Stroke 1	FRONTAL 1 Stroke 1	FRONTAL 1 Gl 1 TEMPORAL 2 Gl 2	p = 0.78
∑	30 (7)	25 (7)	1 (4)	1 (3)	3 (8)	

Values within parenthesis are expressed in percentage.

Table 6. MRI findings: Bilateral lesions

	Total (n = 445)	L dominant (n = 348)	R dominant (n = 28)	Bilateral-dependent (n = 29)	Bilateral-independent (n = 40)	Statistics p-value
Bilateral neocortical lesion	6 (1)	Frontal 2 Multilobar 2	Multilobar 1	–	Multilobar 1	0.59
∑		4 (1)	1 (4)	0	1 (3)	
Bilateral HS	15 (3)	12 (3)	2 (7)	0	1 (3)	0.50
∑ bilateral lesions	21 (5)	16 (5)	3 (11)	0	2 (5)	0.30
"Early" bilateral lesion	4 (1)	FRONTAL 1 - CD 1 MULTILOBAR 1 Ham. 1	MULTILOBAR 1 Ham 1	–	MULTILOBAR 1 EM 1	0.25
Σ		2 (1)	1 (4)	0	1 (3)	
"Late" bilateral lesion	2 (0.4)	FRONTAL 1 Stroke 1 MULTILOBAR 1 Stroke 1	–	–	–	0.91
∑		2 (1)	0	0	0	

Values within parenthesis are expressed in percentage.

Table 7. Summary of previous language lateralization studies

	N	Left, %	Right, %	Bilateral, %
Rasmussen and Milner (1977)	396	71	20	9
Loring et al. (1990): "exclusive language representation"	103	77	2	21
Loring et al. (1990): "forced relative dominance"	103	89	5	6
Rey et al. (1988)	73	62	23	15
Mateer and Dodrill (1983)	90	83	10	7
Strauss and Wada (1983)	78	81	13	6
Rausch and Walsh (1984)	62	86	6	8
This series	445	78	6	16