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Memory Performance is Related to Language Dominance as Determined by the intracarotid amobarbital procedure

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Memory performance is related to language dominance as determined by the intracarotid amobarbital procedure


Abstract

Objective

The goal of this study was to explore the relationship between language and memory lateralization in patients with epilepsy undergoing the intracarotid amobarbital procedure.

Methods

In 386 patients, language lateralization and memory lateralization as determined by laterality index (LI) were correlated with each other.

Results

Language lateralization and memory lateralization were positively correlated ($r = 0.34, P < 0.01$). Correlations differed depending on the presence and type of lesion ($\chi^2 = 7.98, P < 0.05$). LIs correlated significantly higher ($z = 2.82, P < 0.05$) in patients with cortical dysplasia ($n = 41, r = 0.61, P < 0.01$) compared with the group without lesions ($n = 90, r = 0.16, P > 0.05$), with patients with hippocampal sclerosis falling between these two groups. Both memory ($P < 0.01$) and language ($P < 0.01$) LIs were higher in right-compared with left-sided lesions.

Conclusion

Correlation of language and memory is more pronounced in patients with structural lesions as compared with patients without lesions on MRI.

1. Introduction

The intracarotid amobarbital procedure (IAP) has traditionally been used to determine language dominance [1] and [2]. Because of the incapacitating memory deficits after temporal lobectomy in patients with contralateral temporal lobe lesions [3], it was later modified to evaluate memory function [4]. Lateralization of memory function is less pronounced than language lateralization, and thus severe memory loss after resection of a temporal lobe remains rare [5] and [6]. Nevertheless, resection of the speech-dominant temporal lobe has been associated with postoperative memory decline [7], [8] and [9]. A link between language and memory is
supported by investigations of neuronal reorganization of the language system in brain-damaged children, suggesting a critical role of early left mesial temporal lesions in determining hemispheric language lateralization [10]. This may also account for language lateralization in patients with epilepsy. One study provides evidence for a relationship between language dominance and memory processing in a group of healthy patients undergoing fMRI. In this study, verbal encoding correlates well with language dominance, whereas face encoding shows the opposite effect [11] and [12]. The relationship between language and memory dominance in patients with intractable epilepsy needs to be characterized.

The aim of our study was to investigate the concordance between language lateralization and memory lateralization as assessed with the IAP in a group of patients with pharmacoresistant epilepsy. Furthermore, we investigated the hypothesis that side, type, and timing of lesions might be a driving factor for interhemispheric reorganization of both language and memory function.

2. Methods

2.1. Patients

A retrospective chart review of 402 consecutive patients with epilepsy with bilateral (left and right) intracarotid injections and complete language and memory evaluation during the IAP at Cleveland Clinic was performed. Patients were excluded from the analysis if they remembered less than 67% of the presented items under baseline conditions. The final sample comprised 386 patients.

2.2. Epilepsy classification

Epilepsy was classified as left, right, or bilateral based on the ictal and interictal findings obtained during inpatient video/EEG evaluation. Epilepsy classification and side of the lesion were concordant in most cases (Table 1), and lesion side was taken for further analysis.
2.3. MRI scans
A blinded observer classified patients’ MRI scans into subgroups on the basis of lesion type (Table 2). Lesions were further divided into “developmental,” “early acquired,” and “late acquired” lesions. “Developmental” lesions consisted of cortical dysplasia, congenital tumors (dysembryoblastic neuroepithelial tumor or ganglioglioma), and arteriovenous malformation. Hippocampal sclerosis was classified as an “early acquired” lesion, whereas major lesion types in “late acquired” lesions were tumors (mostly gliomas) and encephalomalacia after traumatic brain injury depending on the time of insult.

2.4. Wada testing
Angiography was performed using standard catheter insertion techniques. Selective catheterization of the common carotid artery and, then, the internal carotid artery was performed using road mapping techniques with braided 4- to 5-French catheters with a 1-cm multipurpose curve. Amobarbital or methohexital was injected by intracarotid hand push. Prior to drug administration, a carotid angiogram was performed to rule out atypical vascular anatomy.

2.5. Language lateralization
Language lateralization was quantified based on speech arrest times. Laterality was expressed as laterality index (LI), a continuous variable, defined as the difference between speech arrest times after left ($t_L$) and right ($t_R$) injections, divided by the sum of speech arrest times after left and right injections [($t_L - t_R)/(t_L + t_R)$]. Positive values indicate left-sided lateralization, whereas negative values indicate right-sided lateralization. We categorized patients into left and atypical language dominant. Atypical language dominance was further subdivided into right, bilateral dependent, and bilateral independent language dominant according to the criteria of Benbadis [13]. With this protocol three lateralization measures are defined: (1) the absolute duration of the
speech arrest after left and right intracarotid barbiturate injection being greater than 60 seconds on one side and less than 60 seconds on the other; (2) the difference between left and right injection speech arrest times \((t_L - t_R)\) with a cutoff of 30 seconds; and (3) the LI. The LI reflects the difference between speech arrest times after left and right injections, divided by the sum of speech arrest times after left and right injections as outlined above \([ (t_L - t_R)/(t_L + t_R) ]\), with a cutoff of 0.5. According to Benbadis, left or right language dominance is classified if IAP met two of three of these lateralization criteria. Otherwise patients are classified as bilateral language dominant with absolute speech arrest times of \(\geq 60\) seconds after both left and right injections, and bilateral independent with speech arrest time \(< 60\) seconds after either left or right injection.

2.6. Memory lateralization

The IAP for memory evaluation is described in detail elsewhere [14]. Briefly, immediately after the onset of contralateral hemiparesis following anesthetic injection, the first nonverbal response was obtained. Thereafter, hemispheric memory performance was evaluated by presenting a maximum of 16 items consisting of pictures, designs, object words, and abstract words during the phase of hemiparesis. Memory scores following each injection were expressed as ratios of correctly recognized items to items presented during hemiparesis.

2.7. Memory scoring

Memory scores were calculated as the number of correctly recognized items divided by the number of items presented during hemiparesis (phases 1 and 2). Memory lateralization was expressed by a memory laterality index (MLI). Similar to the language laterality index (LLI), this measure was calculated as the difference between right and left memory scores divided by the sum of memory scores after right and left injections \((m_R - m_L)/(m_R + m_L)\). In contrast to item recognition, speech arrest defines a negative symptom; therefore, left and right scores were
switched in the calculation of MLI, so that both a positive MLI and a positive LLI indicated a lateralization to the left hemisphere.

2.8. Statistical analysis

Statistical testing was performed with SPSS 15.0 (Chicago, IL, USA) and included ANOVA, Student’s $t$ test, Pearson’s correlation, $\chi^2$ test, and Fisher’s $z$ transformation. For all statistical comparisons, a significance level of 0.05 was accepted. If not further indicated, data are given as means $\pm$ SEM.

3. Results

3.1. Descriptives

3.1.1. Patient population

Of the 386 patients included in this study, 202 were female. Average age at IAP was $31.2 \pm 13.4$ (mean $\pm$ SD) years. Age at seizure onset was $14.4 \pm 13.1$ (mean $\pm$ SD) years. In 306 patients, the IAP was performed by injection of amobarbital. In 80 patients, methohexital was used because of a shortage of amobarbital.

3.1.2. Imaging findings

Lesions were identified by MRI in 296 (76.7%) patients. Lesions were found to be left in 155 (52.4%), right in 114 (38.5%), and bilateral in 27 (9.1%) patients. Sixty-eight patients (23.8%) had “late acquired” lesions, 138 (48.3%) “early acquired” lesions, and 90 (31.5%) “developmental” lesions. A detailed description of lesion laterality and types of lesions is provided in Table 2.

3.1.3. Language lateralization

Language lateralization was left in 307 (79.5%), right in 23 (6.0%), bilateral dependent in 26 (6.7%), and bilateral independent in 30 (7.8%) patients.
To characterize the relationship between language and memory lateralization we first investigated if lesion characteristics are related to language or memory lateralization. In a second step, the association between language and memory lateralization itself was evaluated.

3.2. Associations

3.2.1. Association between language lateralization and lesion characteristics

In a univariate ANOVA with the between-group factors “lesion side” (left lesion, right lesion, bilateral lesion) and “timing of lesion” (developmental, early acquired, late acquired) and LLI as dependent variable, there was a significant effect of MRI-identifiable “lesion side” only on LLI ($F(2, 287) = 7.74, P < 0.01$). LLI was significantly higher (more strongly left-sided) in patients with right ($n = 114, 0.84 \pm 0.03$) compared with left ($n = 155, 0.57 \pm 0.05$) MRI-identifiable lesions ($t(261) = 4.7, P < 0.01$). Patients with bilateral lesions ($n = 27, 0.64 \pm 0.11$) did not differ significantly from either patients with left or those with right lesions, but there was a trend toward more left-dominant language lateralization in patients with right-sided lesions as compared with patients with bilateral lesions ($t(31) = 1.8, P = 0.08$).

The same significant association was found if the continuous measure of language lateralization was categorized into language dominance: the pattern of language dominance (left, right, bilateral) differed significantly according to “lesion side” ($\chi^2(6, n = 296) = 18.48, P < 0.01$). Patients with left and bilateral lesions displayed a higher degree of atypical language dominance as compared with patients with right hemispheric lesions (left 29.0% and bilateral 28.6% vs right 8.8%).

To investigate the effect of lesion side on lateralization of memory, the aforementioned analysis was conducted using the MLI.

3.2.2. Association between memory lateralization and lesion characteristics
In a univariate ANOVA with the between-group factors “lesion side” (left lesion, right lesion, bilateral lesion) and “timing of lesion” (developmental, early acquired, late acquired) and MLI as dependent variable, there was a significant effect of “lesion side” on MLI ($F(2, 287) = 39.4, P < 0.01$). The MLI was significantly higher in patients with right lesions as compared with patients with bilateral lesions ($n = 27, t(139) = 4.1, P < 0.01$) and with patients with left lesions ($n = 155, t(267) = -9.8, P < 0.01$) on MRI. The mean MLI in patients with bilateral lesions was not different from that of patients with left hemisphere lesions ($P > 0.05$). On average, patients with right-sided lesions on MRI had a positive, left hemisphere-dominant MLI ($0.24 \pm 0.02, t(113) = 11.8, P < 0.01$), whereas MLI was right lateralized in patients with left-sided lesions ($-0.04 \pm 0.02, t(154) = 2.2, P < 0.05$). Patients with bilateral lesions also showed a numerical lateralization of MLI to the left hemisphere ($0.05 \pm 0.04$), although this degree of lateralization was not significantly different from zero ($P > 0.05$).

Additionally, there was a trend of an interaction between side and timing of lesion ($F(4, 287) = 2.1, P = 0.08$). Albeit only marginally significant, this effect was followed in separate ANOVAs within all three subgroups of patients (i.e. left, right, and bilateral lesions). There was a trend for “timing of lesion” effects only in the group with right-sided lesions ($F(2, 111) = 2.7, P = 0.07$), with the most pronounced left lateralized MLI in the group of early acquired lesions (developmental lesions: $0.18 \pm 0.04$, early acquired lesions: $0.29 \pm 0.04$, late acquired lesions: $0.21 \pm 0.05$). In addition to timing of lesions, we examined the different types of lesions. Comparison of major lesion types within the right-sided lesion group revealed that the MLI was significantly higher (more left lateralized) in patients with right hippocampal sclerosis ($n = 54, 0.29 \pm 0.04$) than in patients with right cortical dysplasia ($n = 16, 0.13 \pm 0.06, t(68) = -2.6, P < 0.05$).
3.3. Correlations

3.3.1. Correlation between language lateralization and memory lateralization

Overall, there was a significant correlation between the LIs for memory and language ($r = 0.34$, $P < 0.01$), indicating concordant lateralization of both functions. Analysis of these correlations according to timing of brain lesion revealed that this correlation was numerically more pronounced in patients with developmental lesions than in those with early and late acquired lesions (developmental: $n = 90$, $r = 0.52$, $P < 0.01$ vs early acquired: $n = 138$, $r = 0.35$, $P < 0.01$, and late acquired: $n = 68$, $r = 0.32$, $P < 0.01$). The only significant difference in correlation was seen between the group without lesions and the group with developmental lesions ($z$ value = 2.77, $P < 0.01$). In contrast, patients without an identified lesion on MRI ($n = 90$) did not show a significant correlation between language and memory LIs ($r = 0.16$, $P > 0.05$) (Fig. 1).

To test whether lesion type influenced the correlation of memory and language lateralization indices, subgroup analyses were performed. There were significant correlations between memory and language LIs in both patients with hippocampal sclerosis ($n = 138$, $r = 0.35$, $P < 0.01$) and patients with cortical dysplasia ($n = 41$, $r = 0.61$, $P < 0.01$). Overall analysis revealed that the correlations between subgroups were not equal ($\chi^2(2, n = 296) = 7.98$, $P < 0.05$, using Fisher’s $z$ transformation). Additional statistical analysis showed that the only significant difference was a lower correlation in the group without lesions as compared with the group with cortical dysplasia ($z = 2.82$, $P < 0.01$) (Fig. 1).

4. Discussion

Our results suggest that language lateralization, as defined by duration of speech arrest, and memory lateralization are related to each other in patients with intractable epilepsy. Although memory is less lateralized than language, both memory and language laterality indices are more
lateralized to the left in patients with right- versus left-sided lesions. Concordant with that, atypical language representation (i.e., low language lateralization index) is more common in patients with left-sided lesions. Furthermore, memory lateralization and language lateralization correlate. Although correlations between material-specific memory and language dominance have been found in healthy individuals [11], our results demonstrate that functional memory performance, as measured with the IAP, is concordant with language lateralization in patients with epilepsy. This relationship was not universal; the correlation between language lateralization and memory lateralization was strong in patients with cortical dysplasia (i.e., developmental lesions), whereas it was not significant in patients without MRI-identifiable lesions. Therefore, our data support the hypothesis that language dominance and memory lateralization are influenced by common factors. Although correlations cannot be interpreted causally, it is likely that structural changes influenced functional shifts (and not vice versa).

4.1. Language lateralization and memory lateralization

The distribution of left (79.5%), bilateral (14.5%), and right (6.0%) hemispheric language lateralization in our patient population is similar to that reported by other investigators in patients with epilepsy [15] and [16]. The degree of atypical language dominance has been found to be higher in pathological circumstances, as the control of language partially or completely shifts to the right hemisphere in the presence of long-standing left hemisphere lesions [15], [17] and [18]. In line with these studies, we found language to be less lateralized to the left in patients with epilepsy with left-sided lesions. Timing and mode of acquisition of a lesion have been found to be crucial in determining language laterality pattern. The proportion of right language dominance has been found to be larger with developmental lesions than with early or late acquired lesions [19]. Despite this, we did not find differences in overall LLI between acquired brain pathology...
and developmental pathology. In patients with temporal lobe epilepsy, language lateralization did not differ between patients with presumably acquired lesions and patients with developmental lesions [20]. Lack of differences in LLI between developmental and acquired lesions may be explained by the large proportion of patients with temporal lobe epilepsies in our cohort (Table 2).

Knowledge of the dominance of memory function is limited. In contrast to language function, memory function has been found to be less lateralized in patients with epilepsy, and reports of significant memory deficits following unilateral temporal resection are rare [3] and [5]. Memory function in our study was assessed using a mixed item stimulus. One study reported memory lateralization measured by fMRI using a mixed stimulus that is a verbally and nonverbally scene-encoding task. In this series, healthy controls, who showed left lateralized memory, were compared with patients with left or right hemisphere epilepsy. Patients with right hemisphere epilepsy showed a nonsignificant increase in the degree of left lateralization. In contrast, patients with left hemisphere epilepsy showed right lateralized memory processing [21]. Concordant with that, we found significant differences in memory lateralization between patients with left- and those with right-sided lesions. In patients with right-sided lesions, we found a slight lateralization of memory to the left. However, we did not find evidence of lateralization of memory processing of a mixed stimulus in patients with right-sided structural lesions, which may be in part due to the pronunciation of verbal stimuli in our paradigm, as a recent study suggests that verbalizability of test items used in the IAP may influence IAP memory asymmetry patterns [14]. In addition, the regions of interest in the fMRI study included the parahippocampal gyrus, which frequently receives its blood supply via the posterior cerebral artery. During the IAP, this area is not anesthetized, a fact that might explain the observed differences in results.
Additionally, there is evidence that lesions of the left hippocampus tend to equalize the memory performance of the left hippocampus to that of the right hippocampus during the IAP using a mixed item stimulation paradigm in patients with mesial temporal lobe epilepsy [21] and [22]. In line with our findings, these data point to the left hippocampus as the more powerful structure in the paradigm of mixed item stimulus memory processing.

4.2. Correlation between language lateralization and memory lateralization

Multiple strands of evidence suggest an important role for the hippocampus in memory in animals and humans. Lesions and epileptic activity of the left hippocampus have been shown to be related to atypical language dominance [12] and [23]. Furthermore, it has been shown that interhemispheric shifts in language dominance are usually associated with lesions found in close proximity to classic language-related areas, but with early-onset lesions in the temporal lobe, thus providing an indirect link between memory and language [10]. There is only limited previous evidence supporting the fact that language lateralization and memory lateralization are linked [11] and [24]. Previous studies using fMRI have shown a material-specific lateralization of memory, with lateralization of verbal memory to the dominant hemisphere in healthy subjects [11]. However, no mixed item stimuli have been applied in this study. We found that language and memory behaved in the same way, in that they both were lateralized concordantly depending on side of epilepsy and side of lesion. We found a correlation of memory lateralization with language lateralization applying a mixed stimulus paradigm in patients with lesional epilepsies. This correlation was most pronounced in cortical dysplasia.
4.3. Limitations

Our data are limited because of retrospective study design. Memory test results may have been confounded by our memory testing paradigm. Retrospective analysis unfortunately did not allow separate analysis for visual and verbal items.

Assessment of language lateralization based on speech arrest times is a simplified approach to evaluation of language dominance in clinical practice. More comprehensive language rating protocols have been evaluated [17]. Previous investigators showed that assessment of language laterality based on speech arrest times attains only discordant classification when compared with comprehensive assessment or fMRI studies [25]. This effect was even more pronounced if language was expressed as a discontinuous variable. Finally, because of a shortage in amobarbital, methohexital was used in some patients [26].

5. Conclusion

Language and memory lateralization is influenced and correlation is more pronounced in patients with structural lesions as compared with patients without lesions on MRI. Pathology of the lesion plays a role in the determination of memory and language lateralization. This correlation may help to estimate the risk of memory impairment after epilepsy surgery in patients with different types of lesions and language lateralization.

Conflict of interest statement

The authors report no conflicts of interest.

Acknowledgments

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References


Table 1. Distribution across categories.

<table>
<thead>
<tr>
<th>Side of MRI lesion</th>
<th>Epilepsy classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
</tr>
<tr>
<td>Left</td>
<td>140 (89.7%)</td>
</tr>
<tr>
<td>Right</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>12 (7.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>156 (100.0%)</td>
</tr>
</tbody>
</table>

Table 2. Type and lateralization of lesion.

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>Side of lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>73</td>
</tr>
<tr>
<td>Tumor (early and late lesion)</td>
<td>34</td>
</tr>
<tr>
<td>Cortical dysplasia</td>
<td>20</td>
</tr>
<tr>
<td>Venous malformation</td>
<td>4</td>
</tr>
<tr>
<td>Encephalomalacia</td>
<td>11</td>
</tr>
<tr>
<td>Unspecific volume loss</td>
<td>5</td>
</tr>
<tr>
<td>Gliosis</td>
<td>2</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>155 (52.4%)</td>
</tr>
</tbody>
</table>

*Rare cases, e.g., polymicrogyria, Rasmussen’s encephalitis.*

Fig. 1. Correlation between memory laterality and language laterality as determined with the intracarotid amobarbital procedure. x axis, lesion type; y axis, Pearson’s correlation coefficient between language and memory indices. (A) Comparison of correlation coefficients between patients without lesions and patients with lesions at different times: D, developmental lesions; EA, early acquired lesions; LA, late aquired lesions. (B) Comparison of correlation coefficients between patients without lesions and patients with different types of lesions: HS, hippocampal sclerosis; CD, cortical dysplasia.