Atypical Language Lateralization in Patients with Left Hippocampal Sclerosis: Does the Hippocampus affect language lateralization?

Sol Hipokampal Sklerozlu Hastalarda Atipik Konuşma Lateralizasyonu: Hipokampus konuşma lateralizasyonunu etkiler mi?

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ABSTRACT

AIM: To provide information related to atypical language activations (right or bilateral) in positron emission tomography in patients with left clear-cut hippocampal sclerosis.

MATERIAL and METHODS: Twelve right-handed patients who had been operated on left-sided hippocampal sclerosis and 12 right-handed normal subjects were included and the synonym generation task was used for evaluation of language lateralization.

RESULTS: Atypical language activations were frequently found in the patients compared to the controls. A total of 3 (25%) subjects in the controls showed atypical activations: 2 bilateral with right and 1 bilateral with left-sided activations. There were no clear right-sided Broca activations in the control group but almost 25% of the patients showed clear right-sided Broca activations. In the patients the incidence of atypical language activations was 91.6% (11 patients).

CONCLUSION: From the present study, it is clear that functional reorganization of the language-related neuronal network is modified in patients with left hippocampal sclerosis. Although the lesion is far from the primary language-related areas, atypical language lateralization is common in these patients and this should be considered in preoperative period.

KEYWORDS: Atypical activation, Language, Speech, PET, Plasticity, Cerebral dominance

ÖZ

AMAÇ: Sol hipokampal sklerozlu hastaların pozitron emisyon tomografilerindeki atipik konuşma (sağ veya bilateral) aktivasyonları hakkında bilgi vermek.

YÖNTEM ve GEREÇ: Sol hipokampal skleroz nedeniyle ameliyat edilmiş olan 12 sağlak hasta ile 12 sağlıklı sağlak kişiler çalışmaya dahil edildi ve konuşma aktivasyonlarının değerlendirilmesi için eşanlamlı sözcük bulma testi kullanıldı.

BULGULAR: Kontrol grubu ile karşılaştırıldığında atipik konuşma aktivasyonları hasta grubunda daha fazla oranla bulundu. Kontrol grubunda toplam 3 kişide (%25) atipik konuşma aktivasyonları görüldü: 2 kişide bilateral sağ ve 1 kişide de bilateral sol ağırlıklı aktivasyonlar. Kontrol grubunda sağ taraflı Broka aktivasyonu görülmezken hastalarda %25 oranında görüldü. Hastalarda atipik konuşma aktivasyonu insidansı %91.6 (11 hasta) olarak bulundu.

SONUÇ: Bu çalışma açıkça ortaya koymuştur ki sol hipokampal sklerozlu hastalarda lisan ile ilgili sinir sistemi ağında yeniden yapılanma olmaktadır. Lezyon, primer lisan bölgelerinden uzakta da olsa bu hastalarda atipik lisan aktivasyonları görülmektedir ve bu husus ameliyattan önce dikkate alınmalıdır.

ANAHTAR SÖZCÜKLER: Atipik aktivasyon, Lisan, Konuşma, PET, Plastisite, Serebral dominans

INTRODUCTION

Since the mid-19th century in which the role of the left hemisphere in language production was shown (8,14), there have been a lot of discussions in order to show the exact location of the brain region where speech is produced. Based on the studies including sodium amobarbital (Wada test) tests (3,6, 19,21,36,37,54) and functional neuroimaging such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) (42), it has been accepted that most people have left hemisphere dominance for language. This left-sided (typical) language dominance is commonly seen in right-handed people but most of the left-handers also have left-sided dominance for language (36). On the other hand, a small proportion of people demonstrate atypical (either right or bilateral) language representation. Although the exact rate of atypical language representations (ALR) is not known, recent functional imaging studies have estimated the rate of atypical language as 6% (42).

The ALR rate can be higher in patients with pathological conditions involving the dominant hemisphere, especially if the lesion occurs at an early age (5,36,43). Thus, with the introduction of PET or fMRI during the last two decades, the plasticity-mediated shift of language from the left to the right side has been discussed extensively and results suggest that brain plasticity occurs not only in children but also in the adult population. Atypical language seems to be more common in epileptic patients, ranging from 4 to 30% (19,36,42,43). It has been demonstrated that left hemispheric epilepsy (lesional or non-lesional) and younger age at the time of seizure onset are strongly associated with ALR (19,36,42,43). Furthermore, epileptic activity itself could also influence language representation (21,22). The type of reorganization of language seems to be also associated with the location of pathology and it has been shown that ALR is commonly seen in patients who had a lesion in either the frontal or temporo-parietal regions (48, 49). More importantly a language shift from the left to the right hemisphere has been demonstrated in patients with clear-cut left hippocampal sclerosis (HS) in a few recent studies (6,7,13,22). Patients with left HS only showed high involvement of right frontal region or supplementary ipsilateral recruitment of frontal regions during the language task, especially synonym generation, suggesting that the hippocampus may play a role in either inter- or intra-hemispheric brain plasticity (6,7,13,22).

Demonstration of language shift in cases of clear-cut HS is important because other brain regions including classical language zones are intact. Up to date there have been a few studies evaluating language lateralization in patients with clear-cut HS only since most studies have generally included lesional temporal lobe epilepsy so that further investigations of this issue are required. Therefore our aims in this study were 1) to provide results from the Montreal Neurological Institute (MNI) with a small number of patients who underwent surgery due to clear-cut left HS; 2) to determine whether the patients have high rate of ALR, and 3) to compare the patients with the healthy controls to find out whether there are differences regarding ALR.

MATERIALS and METHODS

Patients

We included 12 right-handed patients who were evaluated and operated for intractable left mesial temporal lobe epilepsy (MTLE) at the MNI in this study. All patients were right-handed and handedness was determined according to patient preference for writing and drawing, which was determined by patient report and by direct observation. A more detailed analysis of hand preference was obtained from routine neuropsychological test preoperatively. The patient group included 4 males and 8 females with a mean age of 28.9 ± 6.6 years. Neurological examination showed no language-related deficits. All patients underwent PET studies as a part of pre-surgical evaluation. The Wada test available in 7 patients showed ALR in 5 (1 bilateral and 4 right) and typical (left) language representation in 2 patients. Histopathological diagnosis in all patients showed gliosis or HS. (Table I) presents the summary of some demographic data of the patients.

Controls

The control group consisted of 12 right-handed sex-matched subjects (8 females and 4 males; average age of 36.7±1.8 years) without known history of neurological or psychiatric illness in this study. Written informed consent was obtained from all patients and controls after a full explanation of the purpose of the study.

Task paradigm

We presented the subjects with a word-repetition

Table I: Clinical summary of the 12 patients with left-sided clear-cut hippocampal sclerosis.

No	Age (yr)	Sex	Onset (yr)	Duration (yr)	Freq/month	VIQ	PIQ	FIQ	Wada	LI (PET)[a]
1	23	Female	12	11	3	108	109	99	-	-0.17
2	25	Male	19	6	4	108	109	99	-	+0.19
3	24	Female	3	21	10	81	81	80	-	+0.10
4	43	Male	4	39	30	99	102	100	-	+0.17
5	24	Female	1.5	22.5	3	96	81	87	Right	-0.63
6	23	Female	12	11	8	108	109	99	Right	-0.17
7	31	Female	9	22	24	85	94	87	Right	-0.20
8	37	Female	7	30	2	95	113	101	Left	-0.18
9	25	Female	24	1	30	87	112	87	Bilateral	-0.07
10	26	Female	2	24	120	86	87	86	Left	+0.47
11	37	Male	2	35	7	85	75	80	Right	-0.55
12	29	Male	25	4	4	82	101	95	-	-0.88
Mean	**28.9 ±6.6**	**-**	**10.0 ± 8.5**	**18.8 ± 12.3**	**20.0 ± 33.2**	**93.1±10.2**	**96.8±13.1**	**92.0±8.3**	**-**	**-0.16±0.3**

Freq: Seizure frequency; **FIQ:** Full intelligence quotient; **LI:** Laterality index; PET: Positron emission tomography; **PIQ:** Performance intelligence quotient; **VIQ:** Verbal intelligence quotient. [a]**LI (PET):** Laterality indices were shown in this table for Broca.

and synonym generation paradigm. We performed synonym generation test, which has been shown to lateralize the language (24,56). Each subject alternated three times between first completing the word repetition baseline task, followed by the semantic generation task, for a total of six separate trials per subject. In each 60-second test, a set of 15 verbal stimuli at a frequency of 0.25 Hz were presented bi-aurally through insert earphones. The subjects were instructed to generate a single-word response. Stimuli were matched for syllable number and difficulty. The set of words presented in each trial were unique in order to prevent habituation to the stimuli (25).

PET scanning

PET scans were obtained using a Scanditronix PC-2048 system which produced 15 image slices at an intrinsic image resolution of 5.0 x 5.0 x 6.0 mm (15). Relative cerebral blood flow (rCBF) after intravenous bolus injection of 5 mCi of H_2150 (35) was measured for each condition. Data were reconstructed using a 20 mm Hanning filter. MRI data were obtained on a 1.5T Philips MR Scanner to provide localization of functional data (T1-FFE: TE 10 ms, TR 18 ms, flip angle 30 degrees). The MR volumes were co-registered with the PET data (15). Te matched MRI-PET data were linearly resampled into a stereotaxic standardized coordinate system (15,44) using a multi-scale, feature-matching algorithm that matches the native image of each brain to a template along the anterior and posterior commissure (AC-PC) lines (12). The functional data were normalized for global CBF value, averaged across subjects for each activation state, and the mean CBF change was obtained (17). We applied a spherical Gaussian filter with 18 mm full width at half maximum kernel size. This resulting volume was converted to t-statistical representation by dividing each voxel by the mean standard deviation in a normalized CBF for all intra-cerebral voxels (57).

Regions of interest

Regions of interest (ROIs) in this study were restricted to the cerebral areas that are known to be essential for language processing. These regions include 1) inferior frontal gyrus (IFG) or classic Broca area [including pars orbitalis (BA 47), triangularis (BA 45), and opercularis (BA 44), 2) supramarginal gyrus (SMG; BA 40), 3) angular gyrus (AG; BA 39), 4) posterior part of the superior temporal gyrus including auditory cortex (STG; BA 42), 5) posterior part of the middle temporal gyrus (MTG; BA 20), and 6) supplementary motor area (SMA). In addition to above mentioned supratentorial ROIs, we also included the cerebellum in the analysis because it is complementary to the left IFG show activations in the right hemisphere (contralateral to the dominant hemisphere) in normal healthy subjects in the language production. Anatomical ROIs (seven in this study) were delineated in standardized-space using an iterative non-linear registration model-based segmentation algorithm and a probabilistic atlas neuroanatomist (11,12).

Functional activation data

We obtained activation images through subtraction analysis on the normalized PET data, in which the average for the three synonym generation scans were subtracted by the average of the three word repetition scans. Activations in several anatomical regions of interest were found significant based on a criterion of t ? 2.5 (57).

Laterality index calculations

To assess the extent of inter-hemispheric differences in functional activation, we computed a lateralization index (LI) for each subject for each ROI. The measure was determined according to the formula: LI = $[(\sum Li - \sum Ri) / (\sum Li + \sum Ri)]$ where Li represents a significantly activated voxel within the ROI in the left hemisphere, Ri represents a significantly activated voxel within the homogolous region in the right hemisphere. Language lateralization was considered "left-sided" if the LI was > + 0.2 and "right-sided" if LI was < – 0.20. A LI between + 0.2 and – 0.20 was taken to reflect bilateral language representation. The minimum and maximum values from above formula ranges from –1 to +1 and –1 indicating *complete right* hemisphere language dominance, +1 showing *complete left* hemisphere dominance. And "0" represents complete bilateral hemisphere dominance.

Statistical analysis

Statistical analyses were performed using SPSS (version 14.0). A combination of non-parametric Mann-Whitney *U*, chi-squire (x^2), and "student's" test analyses was used. Since the distribution of LI in controls and patients was not normal, the Mann-Whitney *U* test was used to evaluate group differences between patients and controls and between those with and without atypical activations. Categorical differences (group differences in prevalence rates) were evaluated with x^2 (or Fisher's Exact Test in situations with cell counts less than 5) test. A non-parametric correlation analysis was used to identify numerical variables associated with LI in each group. A probability value less than 0.05 was considered to be statistically significant.

RESULTS

Activations in controls

The Mean LI analyses for controls revealed that the most extensive and prominent activations in all controls were observed in the left IFG and MTG (Figure 1). Other less prominent clusters of activations were seen in the left SMA. As expected, bilateral STG activations (left>right) was observed. Inferior parietal lobule (IPL) including SMG and AG activations tented to be bilateral but more on the right. As seen in normal healthy individuals, our mean LI showed right-sided activations in the cerebellum (Table II).

When we consider the number of the controls for each individual ROI activation, one of the striking findings was that none of the controls showed complete right-sided IFG activations. Nine (75%) and three (25%) controls showed typical (left) and atypical (right or bilateral) IFG activations. All three controls with atypical IFG activations showed bilateral activations (one with left and two with right side dominance).

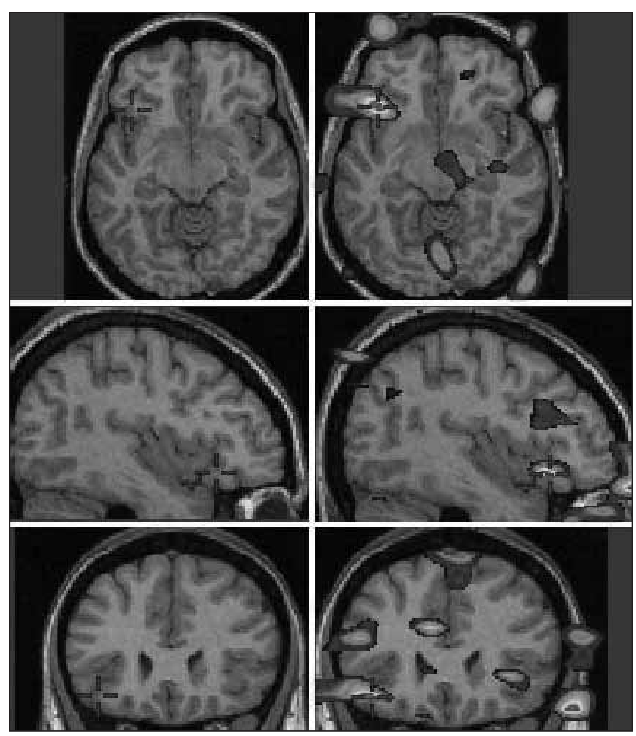

***Figure 1.** Example of speech activation in normal subjects following synonym generation task. Inferior frontal gyrus (Broca) activations are seen in the left hemisphere in the majority of the controls (n = 9; 75%). Maximum activations have been centered in the images. The left side of the patient's brain is on the left and the right side of the brain is on the right.*

Table II: Mean and standard deviations of the laterality indices[a] related to each regions of interest of the patients and controls.

Regions of Interest	Patients (n=12)	Controls (n=12)	*P* value[b]
Frontal lobe			
1. Inferior frontal gyrus	- 0.16 ± 0.38	+ 0.36 ± 0.32	**0.004**
Medial Frontal lobe			
2. Supplementary motor area	- 0.33 ± 0.31	+ 0.21 ± 0.31	**0.001**
Inferior Parietal lobe			
3. Supramarginal gyrus	+ 0.24 ± 0.39	- 0.27 ± 0.32	**0.006**
4. Angular gyrus	- 0.04 ± 0.58	- 0.20 ± 0.36	0.67
Temporal lobe			
5. Superior temporal gyrus	- 0.19 ± 0.41	+ 0.23 ± 0.27	**0.005**
6. Middle temporal gyrus	- 0.24 ± 0.46	+ 0.35 ± 0.32	**0.001**
Cerebellum			
7. Cerebellum[c]	+ 0.26 ± 0.75	- 0.21 ± 0.26	**0.007**

a LI^- indicates atypical lateralization (right or bilateral) and LI^+ indicates typical lateralization (left).
b Non-parametric Mann-Whitney U test.
c Right side in the cerebellum (negative LI) is the typical lateralization.

Atypical SMA activations were observed in a total of 4 (33.3%) controls: two showed bilateral with right dominance and one had *complete* bilateral activations. The forth one had right-sided SMA activations. As expected, in the majority of the controls (n=7; 58.3%), STG showed *complete* bilateral activations and the rest had left-sided activations. Regarding the MTG, we again had expected results. Eight controls (66.6%) showed left-sided activations. *Complete* bilateral activations were seen in 3 (25%) and 2 (16.6%) of the controls regarding the SMG and AG, respectively. In 6 (50%) and 2 (16.6%) controls we observed right and bilateral with right side dominance SMG activations, respectively. In only one control we had bilateral but left side dominance SMG activations. Six (50%) controls again showed right-sided AG activations. Two (16.6%) had bilateral AG activations with left-sided dominance and other two (16.6%) showed left AG activations. These dissociated activations are expected in PET scans under synonym generation minus word repetition in healthy subjects (9). The cerebellar activations showed expected activations (activations contralateral to the left IFG): six (50%) had activations in the right side, 5 bilateral activations with right side dominance. In only one control we observed atypical (left) cerebellar activations.

Activations in patients

Analyses of mean LIs showed inconsistent findings in the patient group. Regarding the frontal lobe, the global maximum of activation was observed in bilateral IFG (Broca) with right-sided dominance (Figure 2) and in the SMA we observed right side activations. Regarding the IPL, we observed dissociation of SMG (left side activations) and AG (bilateral activations with right side dominance) as expected. In the temporal ROIs, patients showed atypical activations: STG showed bilateral activations with right side dominance and MTG had activations in the right side. Complementary to the IFG in the patient group, the cerebellum showed atypical (left) activations. Table II summarizes the mean values of the LIs for each ROIs in both controls and patients.

When considering number of the patients who showed atypical language lateralizations for each ROI, obviously IFG showed atypical activations in most of the patients [11 patients (91.6%)]: five had bilateral right dominance, 3 had bilateral left, and three had right-sided activations. Interestingly, almost all patients showed atypical PET activations regarding the SMA. Of the 12 patients, seven (58.3%) had right-sided activations and 5 showed bilateral activations: in 2 with left and in 3 with right side

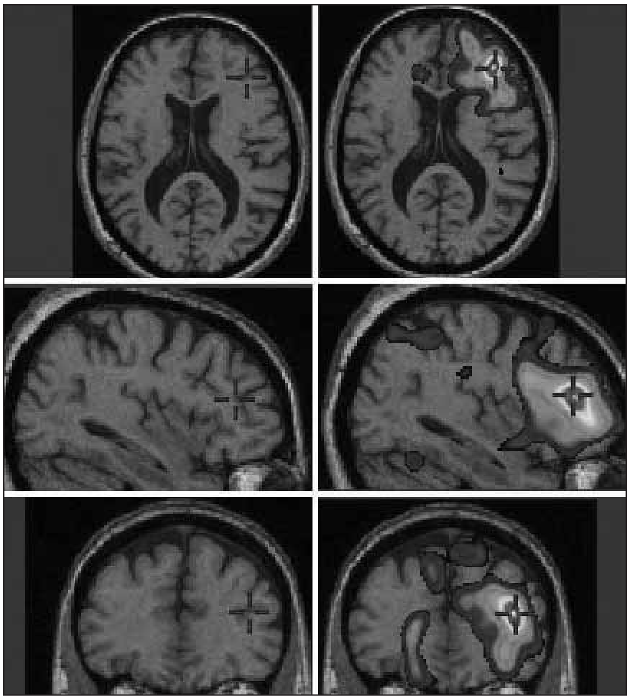

Figure 2. *An example of atypical (in this case right) speech activations. A 37-year-old female who had her first seizure at 2 years of age. She was operated on for left mesial temporal lobe epilepsy, which was diagnosed histopathologically with hippocampal sclerosis. On the PET scan, strong speech activations are seen in the right inferior frontal gyrus (Broca) and atypical (right or bilateral activations) pattern was seen in 91.6% of our patients. Maximum activations have been centered in the images. The left side of the patient's brain is on the left and the right side of the brain is on the right.*

dominance. Five patients (41.6%) showed atypical activations with respect to the SMG: right side activations and bilateral activations with left side dominance were seen in 3 and 2 patients, respectively. Again, the majority of the patients (58.3%) demonstrated atypical PET activations in the right AG. Bilateral activations were expected regarding the STG and MTG but the bilateral activations were mostly right-sided dominance in both STG and MTG in the patient group. Five (41.6%) and 7 (58.3%) patients showed PET activations in the right STG and MTG, respectively. Finally the atypical (left) cerebellar activations were found in 7 (58.3%) patients. Bilateral activations with left side dominance (atypical) were seen in 2 patients.

Comparisons

Although we tried to include sex and age-matched controls, mean age comparisons between the controls and patients unfortunately showed a significant difference (Student's t test; p=0.002). Comparisons of the LIs between the patient and control groups showed interesting findings. All but one (AG) ROIs studied here showed significant differences between the patients and controls with respect to the IFG (Mann-Whitney U test; p=0.004), SMA (Mann-Whitney U test; p=0.001), SMG (Mann-Whitney U test; p=0.006), STG (Mann-Whitney U test; p=0.005), MTG (Mann-Whitney U test; p=0.001), and cerebellum (Mann-Whitney U test; p=0.007) (Figure 3). The difference regarding the AG did not reach a significant level (Mann-Whitney U test; p=0.67). Table II shows the summary of the statistical analysis. The ROIs in the frontal and temporal lobes showed obvious atypical PET activations in the patients. We were able to confirm atypical speech representations in 7 patients following a Wada test (54). The main reason to perform a Wada test in 7 patients was the ambiguous results that were found in either PET or routine neuropsychological testing. Interestingly, the Wada test in the 7 patients showed

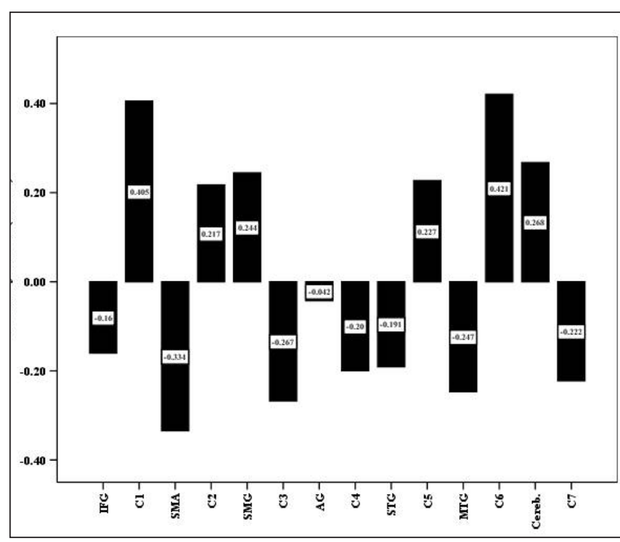

Figure 3. *Bar graphs showing mean laterality indices in patients and controls for every region of interest. The patients demonstrated more atypical language activations (right or bilateral) in positron emission tomography compared to the controls. All but one (angular gyrus) showed significant differences between the two groups.*

<u>Patients:</u> IFG: Inferior frontal gyrus; SMA: Supplementary motor area; SMG: Supramarginal gyrus; AG: Angular gyrus; STG: Superior temporal gyrus; MTG: Middle temporal gyrus; Cereb: Cerebellum.

<u>Controls:</u> C1: Inferior frontal gyrus; C2: Supplementary motor area; C3: Supramarginal gyrus; C4: Angular gyrus; C5: Superior temporal gyrus; C6: Middle temporal gyrus; C7: Cerebellum.

complementary results to the PET: 5 had atypical and 2 had typical speech lateralization (Table I).

When considering the number of the patients and controls who showed atypical speech representations regarding the IFG, the difference was statistically significant that most patients showed atypical activations compared to the controls (11 vs. 3) (x^2 test; p=0.001). We specifically focused on the IFG since its obligatory role in synonym generation test has been demonstrated (25).

Factors associated with Broca lateralization

In this study we analysed several variables including mean age, age at onset, sex, duration of seizure, frequency of seizure, presence of initial precipitating injury (IPI), early onset of seizure, mean age of IPI, VIQ, PIQ, and FIQ, if they were associated with atypical activations. Table III shows summary of the variables between the patients with and without atypical PET activations. Here, we defined "early onset" if the seizure started at age of 5 years or less since it has been accepted that the language lateralization is generally completed until age of 5 (cut-off age) (36,41). IPI includes febrile illness, head trauma or infection (encephalitis or meningitis) etc. In our study 5 patients had the history of IPI: 2 had febrile illness, 1 meningitis, 1 febrile illness and head trauma, and one had history of the maternal infection and forceps delivery which caused head trauma. None of the variables showed significant differences between the patients those who had typical (n=1) and atypical (n=11) PET activations. These results were most likely due the fact that we had only one patient who had atypical speech representation and the number of the patients (n=12) included was low.

Correlations

Non-parametric correlation analysis (Bivariate Spearman's correlation) showed that none of the variables mentioned above correlated with atypical IFG activations. However, frequency of seizure/month tended to be correlated with atypical activations in the IFG group although it did not reach a statistically significant level (Bivariate Spearman's correlation; r=0.50, p=0.09). We observed that some variables were significantly associated with some ROIs. Age at onset of seizure (Bivariate Spearman's correlation; r=-0.69, p=0.012), PIQ (Bivariate Spearman's correlation; r=-0.64, p=0.02) and FIQ (Bivariate Spearman's correlation; r=-0.66, p=0.018) were negatively correlated with LIs of the SMA. Seizure frequency/month was positively correlated with atypical activations in the MTG (Bivariate Spearman's correlation; r=0.58, p=0.04). Interestingly,

Table III: Factors that were supposed to be associated with atypical speech representations regarding the inferior frontal gyrus (Broca) lateralization: typical versus atypical PET activations.

Factors	Typical (n=1)	Atypical (n=11)	*P* value
Left/Right/Bilateral	1/0/0/	0/3/8	**0.001**[a]
Mean Age (years)	26.0 ± 0.0	29.1 ± 6.9	0.88[b]
Sex (Male/Female)	0/1	3/8	0.75[a]
Mean onset (years)	2.0 ± 0.0	10.7 ± 8.5	0.25[b]
Early (Yes/No)	1/0	4/7	0.33[a]
Duration (years)	24.0 ± 0.0	18.4 ± 12.8	0.46[b]
Frequency/month	12	10.9 ± 11.3	0.10[b]
IPI (Yes/No)	1/0	4/7	0.41[a]
Mean age of IPI	1.0 ± 0.0	1.3 ± 1.1	1.0[b]
Verbal IQ	86.0 ± 0.0	94.0 ± 10.6	0.66[b]
Performance IQ	87.0 ± 0.0	98.7 ± 13.8	0.46[b]
Full IQ	86.0 ± 0.0	92.1 ± 8.1	0.30[b]

IPI: Initial precipitating factors such as febrile illness or head trauma; **IQ:** Intelligence quotient; **PET:** Positron emission tomography.
a Chi-square test (Fisher's exact test).
b Non-parametric Mann-Whitney U test.

we observed a significant but negative correlation between VIQ and atypical activations in the STG.

DISCUSSION

The main findings from the limited number of the patients and controls included in the present study are; 1) ALR is infrequent in healthy subjects and none showed *complete* right-sided activations; 2) patients with left HS showed high rate of ALR. Higher incidence of bilateral language representations over right hemisphere dominance has not been observed in addition to complete right-sided dominance; 3) age at onset, age at IPI or IQ were associated with ALR but seizure frequency showed a tendency to be associated with ALR.

The unusually high percentage of ALR in our results depending on the limited number of patients with left HS is consistent with previously published studies using the Wada test for speech lateralization (3,7,19,21,36,37). In one of the largest and commonly cited Wada study, Rasmussen and Milner (36) evaluated the effects of early injury and handedness on language dominance. They showed that patients with left-sided temporal lobe epilepsy were more likely to have ALR and the incidence of ALR was higher in patients with early brain injury. Rausch and Walsh (37) described right hemisphere language dominance in 15% of the 26 right-handed patients with HS. In addition, bilateral hemispheric speech representation was observed in 2 additional patients (8%). Consistent with our results, a higher incidence of bilateral language representations has also been reported in left temporal lobe epilepsy patients by Helmstaedter, et al. (19). Recent Wada studies including temporal lobe epilepsy also showed similar results to our study. Brazdil, et al. (7) demonstrated 13.6% (6 patients) of atypical language in a total of 44 patients with MTLE. Interestingly, all the patients who showed ALR had left MTLE with HS. They found that the age of the patient at the time of seizure onset was the only variable that was significantly correlated with ALR. In contrast to our results in the present study, Brazdil, et al (7) observed a markedly higher incidence of right-sided language representations in their sample instead of higher incidence of bilateral speech representation with right hemisphere dominance. In a voluminous study Janszky, et al. (21) performed the Wada test in 100 MTLE patients (83 left-sided and 17 right-sided MTLE). Interestingly, no patients with right-sided MTLE had atypical speech lateralization and 20 of the 83 left-sided (24%) MTLE patients had ALR. Among the variables such as age at onset, presence of IPI or age at IPI, only frequency of interictal activity showed a significant correlation with atypical speech representation. Similar to Brazdil, et al (7) and Janszky, et al. (21), we found a significant correlation between seizure frequency and atypical activations in the MTG and nearly significant association in the IFG, supporting the notion that even if the epileptic focus is situated far from the primary language area as in patients with clear-cut HS, an epileptic disorder can nevertheless result in a clinically significant disturbance of the functional organization of speech (7,21). Thus the role of spreading epileptiform activity, rather than sole pathological functioning of the epileptic foci for the shift of language dominance from the left hemisphere to the right, is enhanced. In this context, our results support the hypothesis of "the disruptive effect of spreading epileptiform activity on the cortical association areas," which was suggested by Rausch and Walsh (37) and Gloor et al. (18).

PET and fMRI studies related to HS

Despite a large body of current literature with respect to ALR, there have been relatively few clinical studies using functional imaging modalities such as PET and fMRI in patients with only clear-cut HS. The majority of the functional imaging studies included a heterogeneous group of epilepsy patients (frontal plus temporal, etc) with heterogeneous groups of pathology (lesional plus non-lesional). Most of these studies showed a higher incidence of ALR in right handed patients with left-sided lesions (28,48,49). Nevertheless, Wada and functional imaging studies have supported the common notion that brain plasticity could occur not only in children but also in adults.

There has been no PET study evaluating ALR in patients with left-sided HS only and our study is the first to show ALR using PET in a homogenous group of patients (left MTLE) with a homogenous group of pathology (left-sided HS). However, a few clinical studies using fMRI to show language lateralization in patients with only HS have been reported recently (6,13,22). Brazdil, et al. (6) investigated inter- and intra-hemispheric reorganization of the language in 13 right-handed patients with left HS. fMRI results were compared to 13 sex- and age-matched healthy controls. In comparison with the healthy controls, the patients showed maximum activations in the right-sided IFG. A slightly less significant and mainly less extensive cluster of activation was found in the left IFG. In the patient group, atypical activation was also revealed within the left-sided IFG. Laterality indices related to the IFG in the patients showed lower values compared to the controls, suggesting epileptics showed atypical language representation. The lateralization of the language functions in terms of LI in the epileptics significantly decreased in connection with an earlier age of initial insult but there was no significant correlation between the age of seizure onset and ALR, similar to our results. The left-sided accentuation of cerebellar activation patterns observed in this study and our epileptic patients can be viewed as a presumed consequence of the pathological development.

In another interesting clinical study, Janskzy, et al. (22) investigated whether the frequency of left-sided interictal epileptic activity (IED: spikes or sharp waves on the EEG) was associated with ALR in 28 patients with left-sided HS and 11 patients with right-sided HS was used as a control population. The patients with left-sided HS showed smaller mean LI compared to the patients with right-sided HS, suggesting ALR was frequently seen in case of left HS. The majority of the patients with atypical speech activations showed a more bihemispheric language representation than the control group; a finding consistent to the present study. Furthermore, the authors demonstrated that higher IED frequency was correlated with left–right shift of lateralization of speech-fMRI activity. Similar to our results Janskzy, et al. (22) also found that age at epilepsy onset, gender, age, seizure frequency, IQ measures, and IPI did not have an effect on ALR. They found that only the IED frequency had a statistically significant association with the ALR. Nevertheless, depending on the results from the present PET study and above fMRI studies we can speculate that the epileptic activity itself might be a third, independent factor that is capable of inducing speech reorganization beyond the time and structural injury since most variables were not associated with ALR (6, 22). A most recent fMRI study included seven healthy right-handed volunteers and seven preoperative adult patients with MTLE [(6/7 had left HS, 4/6 had ipsilateral HS, 4/7 had early (before age of 6) seizure and 3/7 had late seizure, 4/7 right and 3/7 left handed) (13). The authors hypothesized that at the hemispheric level, the difference between left and right hemisphere activity should be greater in healthy participants than in epileptic patients due to significant involvement of the right hemisphere; at the regional level, and the reorganisation would significantly concern temporo-parietal than frontal regions, as the epileptogenic zone is temporal, and the MTLE associated with HS would induce higher degree of ALR than MTLE without HS. Their results showed that patients with left HS showed more ALR compared to the controls and suggested that right hemisphere is supplementary involved in patients than in controls during language, although the patients keep left hemispheric predominance. They also obtained a significant effect of the age of seizure onset on the left and right infero-medial temporal gyrus (IMTG), and IPL but not on the left IFG. The suggested that early age of seizures onset could induce supplementary activations of the right homologue temporal and parietal regions and in the patients. For the IFG, intra-hemispheric rather than inter-hemispheric reorganization was likely to occur. Interestingly, we also obtained significant correlation between only the right IMTG and the associated left HS, suggesting that patients with associated HS were more likely to involve their homologue IMTG during language. Comparing our results with the results from above study (13) might be difficult because they did not include homogeneous patients with respect to handedness which has been shown to be a factor for language lateralization (19,36,37). However, we agree with the authors (13) that patients have significantly reduced left hemispheric lateralization for language than right-handed healthy participants who are classically strongly left-lateralized and the language reorganization should be explored at regional rather than at hemispheric level, because the reorganisation pattern depends on the region taken into account as suggested also by others (26,38,50). As seen in our study (Table II), while IFG showed bilateral activation with right side dominance with respect to mean LIs, the SMA showed right-sided dominance for example. Whether these dissociations are specifically seen in patients with left HS are not known and cannot be answered from our study. Thus future studies with a larger cohort are required in order to provide more accurate data. In contrast to Cousin, et al. (13) our results showed inter-hemispheric reorganization of IFG activation with respect to the controls. Despite variability in the results, the above mentioned studies together with the present study seem to show that the left HS plays an important role on the cerebral plasticity for language.

Anatomical basis

Depending on previously published Wada and functional imaging studies together with our own results from the present study, one can ask or speculate how a lesion such as HS in this study far from the language zones, especially IFG, could affect language lateralization? The answer to this question could be that seizure activity itself rather than HS in such a chronic disorder could have caused ALR. However, there must be anatomical or pathophysiological evidence for this. Indeed, there is anatomical evidence showing close interconnection between the frontal lobes and mesial temporal structures. Several studies have demonstrated that subhuman primate amygdale and hippocampus efferents project to various regions of the frontal lobe including the anterior cingulate, SMG or orbitofrontal regions (20, 39). Furthermore, it has also been shown that the amygdale efferents give fibers to the medial magnocellular subdivision of the mediodorsal nucleus (MDN) of the thalamus in monkeys (29). The MDN of the thalamus, in turn sends fibers to all areas of the prefrontal cortex as has been demonstrated in either monkeys (55) or humans (2, 51). Hippocampal efferents originate in the subiculum and travel directly, without subcortical relays, to cortical areas in the frontal and temporal lobes and cingulate gyrus, as well as to the amygdale in monkeys (39). Hence, in the monkey, the subiculum is the sole source of direct efferents from the hippocampal formation to the cerebral cortex as well as the source of subcortical fornix efferents which reach beyond the septal area to the diencephalon (39). It has also been observed in monkeys that the posterior parahippocampal areas have strong and widespread projections to many areas of association cortex and virtually all other parts of the limbic lobe. The former terminate in both multimodal and sensory-specific association cortices located in the frontal, parietal, occipital and temporal lobes (52). As pathophysiologic evidence, the interrelationship between mesial temporal and orbitofrontal cortex in humans has been demonstrated using strychnine neuronography (23). Gloor et al. (18) showed that seizures originating in the mesial temporal structure may initially spread to the ipsilateral temporal isocortex, followed by spread to the ipsilateral frontal and to the contralateral frontal lobe before spreading to the contralateral temporal lobe. Language networks including the connections between the IFG and mesial temporal lobe have recently been visualized in normal (10, 30, 31, 34) and diseased (33) conditions using functional imaging techniques. The cerebellar activations contralateral to the dominant IFG (right in healthy subjects and left in left-sided pathologies) are attributed to the anatomical courses of the cortico-pontine and ponto-cerebellar projections (4,40). The cortico-pontine projection is overwhelmingly ipsilateral, so that, for example, the right cerebral hemisphere projects to the right pons (40). Brain stem connections with the cerebellum cross twice: once on the way to, and once when returning from, the cerebellum. The ponto-cerebellar projection is mostly crossed. Thus the right pons is connected more strongly with the left cerebellum. The left cerebellum sends a predominantly crossed projection (through the decussation of the superior cerebellar peduncle, or brachium conjunctivum) to the right thalamus. The ipsilateral thalamo-cortical projection then terminates in the cerebral hemisphere of origin (40).

Taken together, the studies mentioned above provide clear evidence of the neural circuitry for transmitting mesial temporal lobe seizure discharges to the ipsilateral and contralateral frontal and temporal lobes, which could explain how a lesion far from the IFG or other language centers can reorganize the language network in chronic pathological conditions, such as MTLE due to HS.

Interpretation of the present study

MTLE secondary to HS is the most common drug-resistant epilepsy syndrome and surgery has been shown to be the most effective treatment in terms of seizure outcome and quality of life (45-47). Thus, detailed evaluation of surgical candidates such as psychological tests preoperatively provides important information to the surgeon who decides on the type of resection depending on the results of the preoperative tests. Getting information about the language dominance becomes important if the epilepsy syndrome particularly affects or originates in the left or dominant hemisphere. During the last two decades, functional neuroimaging techniques such as PET or fMRI has led the clinicians to evaluate language and other cognitive functions in vitro and they started to replace invasive techniques such as the Wada test (54) although it is still accepted as the "gold standard." When considering our results to be interpreted, the first issue that we can underline that atypical language dominance is frequently observed in patients with left MTLE with HS compared to healthy subjects and reorganization of language or more commonly used term "brain plasticity" could also occur in adults since only 5 patients had early onset of seizure. These results suggest that evaluation of the lateralization of language is mandatory in preoperative period in left-sided HS. Among the variables that have been thought to be associated with ALR tested in our study, seizure frequency seems to correlate with atypical PET activations in the MTG and in the IFG although statistical analysis showed a tendency to have a significant value between atypical activations in the IFG and seizure frequency. Early age of seizure onset is also correlated with atypical activations in the SMA. Surprisingly our study showed neither the age at IPI nor the age at epilepsy onset was correlated with atypical activations in the IFG. These results support various clinical studies that the language reorganization should be explored at regional rather than at hemispheric level (13,26,38,50). Surprisingly we did not observe a significant difference between those with typical and atypical IFG activations regarding early onset (≤ 5 years). The analysis of individual cases supported previous functional imaging studies (6,7,13,22,27, 42,53) in which early age at onset correlated with atypical speech lateralization. We had 5 cases that started to have their epilepsy at an earlier age. Of the 5, four showed atypical activations in the preoperative PET scan. Two patients whose age at seizure onset was very young (1.5 and 2 years) showed strong right lateralization compared to other 3 patients whose age at seizure onset was 2, 3, and 4 years respectively and had bilateral activations with left-sided dominance. Nevertheless, early age at seizure onset in patients with HS seems to have an effect of language reorganization. But our results are not able to provide a reasonable answer to the question "why do all patients who started to have seizures at an early age not present ALR?"

As has been demonstrated by previous fMRI studies (1,32,42), our results showed that IQ levels including VIQ, PIQ, and FIQ do not have an effect on the speech lateralization in patients with left-sided HS, suggesting intra- or inter-hemispheric reorganization has taken place.

Our results also support Rausch and Walsh (37), Brazdil, et al. (7), and Janszky, et al (21) in that even if the epileptic focus is located far from the primary speech area, an epileptic disorder such as left MTLE with HS can result in disturbances in functional organization of language, supporting the hypothesis of "the disruptive effect of spreading epileptiform activity on the cortical association areas rather than the structural injury itself." Therefore, we can speculate that atypical language lateralization does not require the presence of a lesion in the language-associated cortex in left HS patients.

When considering the results either from previous functional imaging studies or the present study including MTLE with HS, important questions can arise: "how can we interpret these non-dominant or atypical activations? or "are the brain regions (right or atypical regions in the left hemisphere) where we observe atypical language activations in PET or fMRI in patients with left MTLE with HS essential or not?" These questions remains to be answered and future studies including patients with left HS should focus on these issues because it is clear that our resective surgical strategy is mostly dependent on the results that are obtained from the preoperative cognitive tests, especially in epilepsy patients.

Limitations

The authors who have contributed to this study want to acknowledge some limitations. First and foremost, the current study was retrospective and included a smaller number of patients with left HS. This could have decreased the power of the statistical analysis and retrospective nature could have caused a bias while gathering the data from the patient's charts. Furthermore, our small sample size did not allow us to provide more accurate data regarding the differences between the patients with and without atypical activations. Depending on the retrospective studies one cannot predict the clear age cut-off in which language lateralization occurs. Thus dividing the age at onset as early/late (≤5 or>5 years, respectively) might result in arbitrary findings.

Finally, including healthy subjects as a control group may have been problematic because they have a higher IQ and other strategies in word generation tasks compared with epileptic patients and it might have caused bias in correlation analysis.

CONCLUSION

From the present study, it is clear that functional reorganization of the language-related neuronal network is modified in patients with MTLE with HS. Although the lesion is far from the primary language-related areas, atypical language lateralization is common in these patients and this should be considered in the preoperative period. Earlier age at seizure onset and frequent seizure episodes seem to be associated with atypical speech representations and reorganization of language-related network does not require a structural lesion in the primary language cortex. Future studies should first include larger sample of patients with left MTLE with HS and secondly evaluate whether or not the regions where atypical language activations take place are essential for language processing in this group of patients. The role of the hippocampus in language reorganization may have escaped our attention.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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