

LANGUAGE BRAIN DOMINANCE IN PATIENTS WITH REFRACTORY TEMPORAL LOBE EPILEPSY

A comparative study between functional magnetic resonance imaging and dichotic listening test

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Abstract – Purpose: To identify brain dominance for language functions with DLT and correlate these results with those obtained from fMRI in patients suffering from intractable temporal lobe epilepsy. **Method:** This study reports on 13 patients who underwent pre-surgical epileptic evaluation between April and October 2004 at the Epilepsy Surgery Program, Hospital Sao Lucas, PUCRS. In DLT, dominance was assessed through a consonant-vowel task, whereas in fMRI patients performed a verb generation task. **Results:** Our results identified a correlation between the fMRI lateralization index and the DLT ear predominance index and reply difference index ($r=0.6$, $p=0.02$; Pearson Correlation Coefficient), showing positive correlation between results obtained from fMRI and DLT. **Conclusion:** DLT was found to significantly correlate with fMRI. These findings indicate that DLT (a non-invasive procedure) could be a useful tool to evaluate language brain dominance in pre-surgical epileptic patients as it is cheaper to perform than fMRI.

KEY WORDS: dichotic listening test, functional magnetic resonance imaging, refractory temporal lobe epilepsy, brain dominance, language.

Determinação de dominância cerebral para linguagem em pacientes com epilepsia refratária de lobo temporal: estudo comparativo entre ressonância magnética funcional e teste de escuta dicótica

Resumo – Objetivo: Identificar a dominância cerebral para funções de linguagem através do teste de escuta dicótica (TED) e correlacionar com os resultados de ressonância magnética funcional (RMf) em pacientes com epilepsia refratária de lobo temporal. **Método:** Foram estudados 13 pacientes com epilepsia refratária de lobo temporal, que realizaram avaliações pré-cirúrgicas no período de abril a outubro de 2004 no Programa de Cirurgia de Epilepsia do Hospital São Lucas da PUCRS. Realizada investigação da dominância hemisférica para linguagem através do TED Consoante-Vogal e da RMf pela geração de verbos. **Resultados:** Verificou-se a existência de correlação entre os índices de lateralidade (RMf) e os índices de predomínio de orelha e de diferença de resposta (TED) ($r=0,6$, $p=0,02$). **Conclusão:** Existe correlação entre os resultados obtidos através da RMf (índice de lateralidade) e do TED (índice de predomínio de orelha e índice de diferença de resposta) em pacientes com epilepsia refratária de lobo temporal.

PALAVRAS-CHAVE: teste de escuta dicótica, ressonância magnética funcional, epilepsia temporal refratária, dominância cerebral, linguagem.

Epilepsy is a consequence of altered cerebral functions caused by various pathologic processes. Depending on the localization of the epileptogenic discharges, the disease can assume different forms, which may be asso-

ciated with several distinct neurological impairments¹⁻⁴. Epileptogenic activity in the Rolandic region, for example, may be accompanied by motor symptoms, whereas left frontal or temporal discharges may cause speech

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arrest. Consequently, assessment of cerebral dominance, particularly for language function, is of fundamental importance in the evaluation of candidate patients to refractory epilepsy surgery. In addition, the presence of epileptic discharges since childhood can cause an atypical reorganization of cortical functions, resulting in migration of language to other areas of the same hemisphere or even to the contra-lateral (usually right) hemisphere. According to Portuguese⁵, "what is most important and necessary is mapping the language cortex and identifying memory dominance in the brain hemispheres of patients who will undergo epilepsy surgery, to guide the neurosurgeon and minimize the deficits in the post-surgical period."

Functional magnetic resonance imaging (fMRI) currently is one of the most important and used techniques for brain mapping. It has been employed by many epilepsy centers to replace the sodium amobarbital test (SAT) and electrical cortical stimulations (ECS), and is regarded as a non-invasive procedure with minimal risks for patients⁵⁻⁷. As the SAT procedure is not presently performed in Brazil due to difficulties in obtaining the barbiturate (whose import is forbidden), we employed the dichotic listening test (DLT) to determine cerebral dominance of language functions. This is a non-invasive alternative technique, which consists of verbal stimuli simultaneously delivered to both ears of the patient⁸.

This study aimed at identifying brain dominance of language through the dichotic listening test and correlating the results to those obtained with functional magnetic resonance imaging in order to assess the validity of DLS as a pre surgical planning tool.

METHOD

A transversal study was performed with patients from the Epilepsy Surgery Program of the Hospital São Lucas da PUCRS (PCE-HSL-PUCRS). All individuals were enrolled between April and October 2004. fMRI and DLT were performed in all of them to establish brain dominance of language. The results were then analyzed in terms of left or mixed hemisphere language dominance and the correlation between both tests.

Patients

Male and female adult patients (older than 16) were enrolled. The sample consisted of 13 patients (seven men and six women) between 17 and 48 years old ($\pm 33,4$ years old), all with an established diagnosis of refractory temporal lobe epilepsy.

Patients with previous brain surgery, presenting other neurological and/or psychiatric disorders or loss of audition in the audiometric examination, as well as patients with altered language understanding (worse than a small alteration as assessed through the Token Test), or with IQ values below the inferior average, were excluded from the study.

The patients of this study were included after receive an in-

formed agreement that was previously obtained by HSL-PUCRS and sign by the patients or responsables.

Procedures

Examinations were performed when the patients were clinically stable and able to keep the level of attention required for the neuropsychological and language tests. These included language understanding with the Token Test, Estimated IQ through the WAIS-R (vocabulary and cubes) subtests and a hearing test with an air conduction audiometer, performed in a soundproof cabinet.

After the hearing evaluation, the Dichotic Consonant-Vowel Listening Test was performed in an attention-free situation to analyze the perception asymmetry of language stimulation, which provided results on cerebral dominance for language functions.

The test consisted of a total of 12 pairs of different syllables with the "a" vowel ("ta", "da", "ga", "ca", "ba", "pa"), presented in a synchronized way and with the same intensity (50 dBNA), applied to both ears in an acoustically isolated room to avoid the interference of external noise. In the attention-free test, the patients were instructed to repeat one of the syllables they heard (the one that appeared to be loudest), while the examiner wrote down the verbalized syllable on the answer sheet. The same procedure was then repeated after inversion of the headphones. The number of repeated syllables and the mistakes observed were recorded for posterior analysis. The prevalence of correct answers for one of the ears as compared to the other was called the "ear predominance index" (EPI), and the difference between correct answers derived from the right and the left ears was called the "reply difference index" (RDI)⁷.

During the fMRI exam, patients performed a verb-generation task. They heard concrete words through the scanner headphones and were asked to think of their utility (e.g. pencil >> write), without verbalizing or making any facial or tongue movements, keeping silent and with eyes closed. The patients were previously instructed about the proposed task. We used a blocked paradigm and the control blocks (rest condition) consisted simply of absence of verbal stimuli, when they should keep their eyes closed and think of a white screen. In each run X xx-seconds blocks were interleaved with X rest blocks (TR=4.5s).

Functional T2*-weighted images were realigned, normalized to MNI space, and smoothed with the SPM package (Wellcome Department of Imaging Neuroscience, London, UK).

We took the whole hemisphere bilaterally (excluding cerebellum) as two distinct regions of interest (ROI). The number of activated voxels in each ROI (L and R) was then counted, and a lateralization index (LI) was calculated as follows⁹⁻¹⁶. The number of activated voxels on the right side is subtracted from the number of activated voxels on the left side, and the result is divided by the sum of the two quantities, $LI = (L - R) / (L + R)$. The result is thus within the interval -1 and +1, where the former indicates 100% right dominance and the later, 100% left dominance. Mixed lateralization is indicated by values between -0.25 and +0.25.

Statistical analysis was performed by a Pearson correlation coefficient to establish a correlation between the results from the Dichotic Listening Test and the fMRI.

RESULTS

Language hemisphere dominance: DLT and fMRI

Results relative to language hemisphere dominance will be presented through DLT, according to ear predominance (EPI) and reply difference (RDI) indices and through

Table 1. Correlation between side index (fMRI) and ear predominance and reply difference indices (DLT).

Characteristic	r	p	Test
SI x EPI	0.62	0.02	Pearson Correlation
SI x RDI	0.6	0.02	Pearson Correlation

EPI, Ear predominance indice; RDI: Reply difference indice; SI, Side index.

Table 2. Comparison between lateralization of the temporal epileptogenic focus and language hemisphere dominance tested by fMRI: Kappa's Concordance Coefficient and Fisher Exact Test.

	fMRI		Total
	Left	Right	
Right Temporal Epileptogenic Focus n (%)	7 (100)	0	7 (53.8)
Left Temporal Epileptogenic Focus n (%)	5 (83.3)	1 (16.6)	6 (46.2)
Total	12 (92.3)	1 (7.7)	13

Fisher Exact Test, p=0.26; Kappa=0.17, p=0.13; fMRI, functional magnetic resonance image.

Table 3. Comparison between lateralization of the temporal epileptogenic focus and language hemisphere dominance tested by DLT: Kappa's Concordance Coefficient and Fisher Exact Test.

	DLT		Total
	Left	Right	
Right Temporal Epileptogenic Focus n (%)	7 (100)	0	7 (53.8)
Left Temporal Epileptogenic Focus n (%)	4 (66.6)	2 (33.3)	6 (46.2)
Total	11 (84.6)	2 (15.4)	13

Fisher Exact Test, p=0,19; Kappa=0.68, p=0.005; DLT, dichotic listening test.

fMRI, according to the side index (SI). For EPI, the dominant language hemisphere is the one contralateral to the predominant ear.

The determination of language hemisphere dominance by fMRI and DLT showed that all left-handed patients presented left hemisphere language dominance (DLT and fMRI). Among the right-handed patients, 81.8% showed left hemisphere language and 18.8% mixed language function, as detected by DLT; fMRI results showed that 90.9% of them presented left hemisphere language and 9.1% mixed language function. No cases of right hemisphere language dominance were observed.

The analysis of the values obtained by DLT (ear predominance and reply difference indices) and by fMRI (laterality index) showed a relationship between the laterality indices (fMRI) and the ear predominance and reply difference indices (DLT). Table 1 shows that, in the comparison of LI with EPI and LI with RDI, the Pearson test with r of 0.62 and 0.6 respectively presented a significant result (p=0.02).

Language hemisphere dominance and lateralization of the temporal epileptogenic focus

Tables 2 and 3 present the relationship between the side of the temporal epileptogenic focus and language brain dominance as assessed by fMRI and DLT. Analysis by the Fisher Exact Test did not show correlation between the temporal epileptogenic focus and language lateralization, as tested by fMRI or DLT. Concordance between the temporal epileptogenic focus and language lateralization as analyzed by DLT was however apparent.

Language hemisphere dominance and age of beginning of the epileptogenic crises

Patients were divided in two groups according to the age of beginning of the crises: those in whom the epileptic crises began before five years of age, and those in whom they began later on.

The comparison of age of appearance of the crises and language lateralization, as determined by fMRI (Table 4), showed that patients in whom the crises began after five years old presented left hemisphere language dominance (p=0.15). Evaluation of patients through DLT showed that

Table 4. Comparison between age of beginning of the epileptogenic crises and language hemisphere dominance testes by fMRI: Kappa's Concordance Coefficient and Fisher Exact Test.

		fMRI		Total
		Mix	Left	
Age of beginning of the epileptogenic crises	Before 5 years old n (%)	1 (50)	1 (50)	2 (15.4)
	After 5 years old n (%)	0	11 (100)	11 (84.6)
	Total	1 (7.7)	12 (92.3)	13 (100)

Fisher Exact Test, p=0.15; Kappa=0.63, p=0.007; fMRI, functional magnetic resonance image.

Table 5. Comparison between age of beginning of the epileptogenic crises and language hemisphere dominance testes by DLT: Kappa's Concordance Coefficient and Fisher Exact Test.

		DLT		Total
		Mix	Left	
Age of beginning of the epileptogenic crises	Before 5 years old n (%)	1 (50)	1 (50)	2 (15.4)
	After 5 years old n (%)	1 (9.1)	10 (90.9)	11 (84.6)
	Total	2 (15.4)	11 (84.6)	13 (100)

Fisher Exact Test, $p=0.29$; Kappa=0.41, $p=0.07$; DLT, dichotic listening test.

one of them presented mixed language, whereas the other ten patients presented left hemisphere language dominance (Table 5).

DISCUSSION

Language hemisphere dominance: DLT and fMRI

DLT and fMRI are widely employed for the study of language brain dominance, but no studies were found in which results relative to the ear predominance index obtained with those tests were analyzed for their correlation with the reply difference index (DLT) and with the laterality index (fMRI). On the other hand, most of the researches does the relationship between the fMRI and the DLT has been very scarcely studied.

The present study showed that 92.3% of the patients analyzed by fMRI presented left hemisphere language and 7.7% presented mixed language function, supporting the results reported by Springer et al.¹⁰, who however investigated healthy individuals. In that work, language brain dominance was investigated by fMRI in normal and epileptic individuals, showing that 94% of the normal persons presented left hemisphere dominance for language, whereas 6% presented bilateral language. Among epileptic patients, 78% presented left hemisphere dominance, 16% bilateral, and 6%, right hemisphere dominance. The report by Springer et al.¹⁰ included, contrary to the present work, not only temporal but also extratemporal epilepsies.

It is believed that the frequency of left hemisphere dominance for language is higher among the patients studied in the present work, since all of them presented hippocampal sclerosis, limited to mesial structures of the temporal lobe, as the only lesion.

The analysis of brain dominance through DLT showed that 84% of the patients presented left hemisphere language and 15.4% mixed language function, with no cases presenting right hemisphere language dominance. These results are in accordance with reports by Geffen and Caudrey¹⁷, Zatorre¹⁸, and Hugdahl et al.¹⁹, who compared DLT and the Sodium Amobarbital Test (SAT) and concluded that most of the individuals presented left hemisphere language dominance.

According to Strauss et al.²⁰, however, a predominant ear was not found in the case of patients with right hemisphere language function, but only in patients with left hemisphere dominance for language, with a predominance of the right ear in 100% of them. The results obtained in present work, similarly, do not allow the conclusion that DLT is efficient in the detection of hemisphere dominance in patients with right hemisphere language function, since no patient with this characteristic was present in the sample group.

The analysis of correlation (Pearson's Correlation Coefficient) between the two tests employed in this work (DLT and fMRI), based on the quantitative results of EPI, RDI and LI, showed a positive association. DLT is correlated to fMRI, with a simultaneous increase in the values resulting from both examinations. A number of other studies have already compared DLT with SAT¹⁷⁻²¹, and fMRI with SAT^{9,11,13,15,16,22}, showing a positive relationship and confirming the efficiency of the two tests. The relationship between DLT and fMRI, however has been scarcely studied. We can cite the studies of Fernandes et al.²³ and Bethmann et al.¹⁷.

Fernandes et al.²³, investigating the DLT and the fMRI in 14 children with epilepsy, verified that it does exist concordance between both tests, and the DLT can be used to determine the dominant language hemisphere in pre-surgical patients. The DLT results showed that 6 children had mixed language (both ears response), 8 left hemisphere dominance (right ear dominance), and no one of the patients had right hemisphere language dominance.

Bethmann et al.²⁴ made a comparison between these 2 tests in 30 healthy people. The authors went to a conclusion that there was short difference between the ears, suggesting that the DLT can not be used with the aim of determine a laterality of the language, on the opposite of the fMRI, that efficiently identified the dominant hemisphere of the participants.

Language hemisphere dominance and lateralization of the temporal epileptogenic focus

Bilateral or right hemisphere language representation is uncommon in the populations, since in most people

the left hemisphere is dominant for language functions. In case of neurological lesions with injury on the left hemisphere, there is an increased probability of language transfer to other regions. Loring et al.²⁵ observed that language transfer to the right hemisphere is more related to extensive lesions in areas beyond the temporal lobe. Chugani et al.²⁶, furthermore, pointed out that small neocortical lesions are associated to compensation of ipsilateral brain regions, whereas more extensive lesions induce compensatory modifications on the contralateral hemisphere.

The results observed in the present work support those studies, since no correlation was observed between the brain hemisphere affected by epilepsy and language brain dominance, as tested by DLT or fMRI. The patients analyzed presented lesions limited to mesial (hippocampus) structures, with no evidence of extensive brain lesions. In the three cases in which mixed language dominance was observed after individualized analysis, however, bilateral language localization occurred only in patients with left temporal epilepsy, with a partial brain reorganization in the contralateral hemisphere. Furthermore, concordance between the temporal epileptogenic focus and language lateralization as evaluated by DLT was apparent, since the two patients with mixed language function had left epileptogenic foci.

Knecht²⁷ observed, in a study with fMRI, results similar to the three cases described above. The author concluded that, in cases in which the lesions were located in or near the Broca's area, language brain lateralization to the right hemisphere did not occur; lesion on the left hippocampus, parahippocampus or on the inferior temporal pole, however, resulted in right or bilateral lateralization of language functions.

Language hemisphere dominance and age at epilepsy onset

It is well known that the sooner the brain lesions occur, the higher are the probabilities of recovering the damaged functions, due to the increased brain plasticity in that life period. According to Springer et al.¹⁰ and Janszky et al.²⁸, modifications of the left hemisphere result in an interhemispheric reconstitution of language functions to the right hemisphere. The same authors observed that after five years of age, when language becomes gradually more lateralized, the contralateral reorganization of language after a brain seizure occurs less frequently. For this reason, the sample was separated in two groups in the present work: patients with onset of the epileptic crises before 5 years old, and after patients in whom epilepsy onset occurred later on.

Although the sample is not large, with only two patients presenting epileptogenic crises before 5 years old, the results of fMRI showed that in all patients in whom the crises began after 5 years old language was on the left brain hemisphere, with a concordance among the results.

One of the two patients in whom the crises began before 5 years of age presented mixed language as tested on fMRI; this patient presented left hemisphere temporal epilepsy, began before one year old. These results support the theory of brain reorganization (neuronal plasticity) mentioned by Springer et al.¹⁰ and Janszky et al.²⁸, as well as the theory proposed by Duchowny et al.²⁹, stating that only damages on the first years of life result in consistent contralateral reorganization of language. Risse et al.³⁰ emphasize that the incidence of atypical language is much more frequent in patients with a history of left hemisphere early lesions (from childhood). Springer et al.¹⁰ showed that all the cases of atypical language were associated to onset of epileptic crises in childhood.

In a study with refractory epilepsy patients, Duchowny et al.²⁹ concluded that language transfer to the right hemisphere happens only in cases of lesions occurring before five years of age and in which the language cortex is destroyed, and not in cases of development lesions and epileptogenic discharges.

In relation to the patients investigated through fMRI, all those in whom the crises began after five years of age presented left hemisphere language dominance, without brain reorganization in those patients with left temporal epilepsy, probably due to a late crisis onset when neuronal plasticity is smaller. According to Lent³¹, neuroplasticity is higher during development, decreasing gradually in adult life without however disappearing.

In DLT, two of the patients, both with left temporal epilepsy, showed mixed language representation; however, in one of them the crises began before age 5 while in the other one they began later on. The first case suggests the occurrence of brain reorganization due to neuronal plasticity, but modification exclusively of pathways involved in the central hearing processing can also be suggested since the patient showed left hemisphere language dominance in the fMRI test. According to Ortiz et al.³², the processing of hearing information during childhood may be modified if any predisposition factor is present during development, and neurological alterations represent one of the risk factors for dysfunctions of the hearing processing.

Related to the second case, which crises began after 5 years old, the fact of has been noticed the mixed language in DLT agrees with the neuroplasticity theories, although been smaller, it also occurs in adults as well^{27,28,31}. Regarding to that, we believe even more that the cognitive re-

habilitation, mainly the linguistic one, can be successfully achieved in cases of people with neuronal damage.

In conclusion, considering the observation conditions and the sample selected in the present study, the results indicate a correlation between the results obtained by fMRI and the DLT, allowing its application in the evaluation of language lateralization in patients with refractory temporal lobe epilepsy. Left hemisphere dominance for language is more frequent, as shown by DLT as well as by fMRI, independent on hand dominance. No correlation was observed between the hemisphere affected by the epileptogenic focus and language brain dominance, employing fMRI and DLT. The comparison of age crises onset and language lateralization showed that all the patients in whom the crises began after five years of age present left brain hemisphere language dominance, as studied by fMRI. These results do not represent a suggestion for the replacement of fMRI by DLT, since the two exams, in spite of having the same objectives, represent different procedures. The first one is an image test, more specific and capable to inform about specific regions for language activation in the brain; the second informs about the brain hemisphere which is responsible for language functions. DLT, however, besides being an exam of low cost and easy performance, represents an alternative in centers where SAT and fMRI are not available.

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