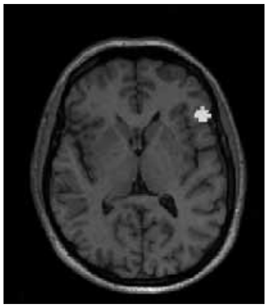

VOLUME AND HIPPOCAMPAL FUNCTION IN MEDIAL TEMPORAL LOBE EPILEPSY

VOLUMEN Y FUNCIÓN HIPOCAMPAL EN EPILEPSIA DEL LÓBULO TEMPORAL MEDIAL

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PALABRAS CLAVE (DeCS)
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SUMMARY

The functional Magnetic Resonance (fMRI) is important in the evaluation of language and memory of patients with temporal lobe epilepsy. The fMRI has also enabled to observe how the structures in the medial temporal cortex have functional laterality according to the dominance of language, with a hemisphere which is specialized in the expressive and receptive aspects of language and the encoding of verbal material. To relate the left hippocampus integrity with the degree of asymmetry of the language dominance seen by fMRI. Images with T1 volumetric information and EPI with T2 information are obtained using a 1.5T magnetic resonator, during the execution of complex scenes encoding paradigms, as well as during the generation of words and a semantic decision in a set of 12 control subjects and different patients who are potential candidates for epilepsy surgery. The automatized volumetric properties of the control group hippocampus do not show significant asymmetry. Indifferent patients with hippocampal sclerosis, numerical indexes are obtained, which are in accordance with the implication of the integrity of the left hippocampus with the asymmetry indexes in the language paradigms. Among the results of the implementation of the memory and language protocol, using fMRI for patients with temporal lobe epilepsy, one can emphasize the evidences obtained using fMRI regarding the implications of the left hippocampus in the language network and the effects of its dysfunction in the migration patterns of language towards the contralateral hemisphere.

RESUMEN

La resonancia magnética funcional (fMRI) es fundamental en la evaluación de lenguaje y memoria en pacientes con epilepsia del lóbulo temporal. También ha permitido observar cómo las estructuras de la corteza medial temporal tienen lateralidad funcional de acuerdo con la dominancia del lenguaje, con un hemisferio especializado tanto en los aspectos expresivos y receptivos del lenguaje como en la memorización de material verbal. Relacionar la integridad del hipocampo izquierdo con el grado de asimetría de la dominancia del lenguaje vista por fMRI. Mediante resonador de 1,5 T se obtienen imágenes con información en T1 volumétricas y EPI con información en T2 durante la ejecución de paradigmas de codificación de escenas complejas, generación de palabras y decisión semántica en un conjunto de 12 individuos sanos y en diferentes pacientes candidatos a cirugía de epilepsia. La volumetría automatizada de los hipocampos del grupo control no muestra asimetría significativa. En los diferentes pacientes con esclerosis hipocampal se obtienen índices numéricos que corroboran la implicación de la integridad del hipocampo izquierdo con los índices de asimetría en las pruebas de lenguaje.

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En los resultados de la implementación del protocolo de memoria y lenguaje por fMRI para pacientes con epilepsia del lóbulo temporal se destacan las evidencias obtenidas acerca de la implicación del hipocampo en la red del lenguaje y el efecto que tiene la afectación del hipocampo izquierdo en los patrones de migración del lenguaje hacia el hemisferio contralateral.

Introduction

Brain plasticity mechanisms play a major role in an assortment of neurobiological disorders. The existing relationship between plasticity and epilepsy is backed by evidence suggesting the following (1):

- Areas specialized in learning and memory are the most susceptible to generate discharges.
- The immature brain has a greater potential of developing epilepsy than an adult brain.
- Cellular elements providing support to plasticity processes are targeted by many antiepileptic drugs.

fMRI is essential in assessing language and memory functions of patients with temporal lobe epilepsy (TLE), given the great degree of refinement reached by current functional brain mapping methods (2-4).

fMRI has also made possible to observe how medial temporal cortex structures have functional laterality, corresponding to language dominance, with an hemisphere specialized in expressive and receptive aspects of language and the memorization of verbal content (5). In this manner, dominance in language may be altered by brain plasticity mechanisms arising from hippocampal affectation in the TLE; therefore, fMRI detection has great prognostic value (6-8).

The present study presents data from the resonance protocol used in candidates to TLE surgery in the INDEC, discussing four such cases to illustrate the relationship between language, the hippocampus, and epilepsy.

Methods

A 1.5T resonator (Siemens, Erlangen) was employed to acquire volumetric T1 MP-RAGE images (TR = 11 ms, TE = 5,2 ms, FA = 15, slab thickness = 1 mm, data matrix = 224 x 256, 176 partitions) and BOLD images during the execution of paradigm-coding complex scenes (EPI T2, TR = 2000 ms, TE = 50 ms, FA = 90, section thickness = 5 mm, data matrix = 64 x 64, 15 partitions), generation of words and semantic decisions (EPI T2, TR = 3000 ms, TE = 50 ms, FA = 90, section thickness = 3 mm, data matrix = 64 x 64, 26 partitions), in a group of 12 healthy individuals and in a series of INDEC patients who were candidates to epilepsy surgery. All individuals are right-handed.

Paradigms (Table 1) were chosen based on reports from previous studies (3,4) and where optimized to obtain greater contrast between task blocks and control blocks (9). All paradigms start from a rest condition. The functional sequences analysis involved the definition of areas of interest that included medial temporal cortex regions for paradigm-coding complex scenes, and Wernicke and Broca areas for language-related paradigms. All results have a corrected threshold (FWE = 0,05).

Paradigm	Active condition block	Base condition block	Block duration (seconds)	Number of active / passive blocks
Complex scenes coding	Memorizing images containing indoor and outdoor scenes.	Discriminating odd and even numbers.	40	8/8
Semantic decision	Discriminating true and false sentences.	Discriminating high-pitched tones in sequences with a random distribution of high and low-pitched tones.	30	6/6
Word generation	Thinking the antonym of the presented word.	Pressing a button to acknowledge the on-screen appearance of a "+" sign.	30	5/5

The index of asymmetry (IA) of functional resonance and volumetry results is calculated as (voxel_l - voxel_r)/(voxel_l + voxel_r), where "voxel_l" corresponds to the total number of active voxels in the left hemisphere and "voxel_r" to the total number of active voxels in the right hemisphere. A positive IA indicates a larger quantity of active voxels per volume in the left hemisphere. This formula is employed in language studies as an index (10), and is usually multiplied by a constant in order to avoid very small decimal values in volumetric studies (11).

We propose a volume-corrected asymmetry index, which is calculated dividing the amount of active voxels in the hippocampus by a given volume of it, which allows for coding tasks to be evaluated without the bias associated to a decrease in size typically found in sclerosis.

Results

Table 2 displays the volumes in cubic millimeters of hippocampus belonging to the control group. Volumes are adjusted according to total intracranial volume, allowing for comparison between measures performed on subjects. There is no significant difference in the size of left and right hippocampus of control subjects. These values have been quantified in order to have a reference value to evaluate epileptic patients. All volumetric analysis was done semiautomatically using the Freesurfer brain imaging software package (12-14).

Individual	Total intracranial volume	Right hippocampus		Left hippocampus		Asymmetry index (L - R)/(L +)
		Volume	Adjustment	Volume	Adjustment	
1	1519522,3	4187,0	$2,76 \times 10^{-3}$	4118,0	$2,71 \times 10^{-3}$	$-8,31 \times 10^{-3}$
2	1693625,9	4657,0	$2,75 \times 10^{-3}$	4772,0	$2,82 \times 10^{-3}$	0,01
3	1443123,3	4123,0	$2,86 \times 10^{-3}$	4406,0	$3,05 \times 10^{-3}$	0,03
4	1564327,4	4594,0	$2,94 \times 10^{-3}$	4705,0	$3,01 \times 10^{-3}$	0,01
5	1570035,6	4035,0	$2,57 \times 10^{-3}$	3806,0	$2,42 \times 10^{-3}$	-0,03
6	1330246,0	4235,0	$3,18 \times 10^{-3}$	3821,0	$2,87 \times 10^{-3}$	-0,05
7	1531930,6	4321,0	$2,82 \times 10^{-3}$	4417,0	$2,88 \times 10^{-3}$	0,01
8	1546486,2	3763,0	$2,43 \times 10^{-3}$	4170,0	$2,7 \times 10^{-3}$	0,05
9	1573594,1	4395,0	$2,79 \times 10^{-3}$	4390,0	$2,79 \times 10^{-3}$	$-5,69 \times 10^{-4}$
10	1819516,0	4504,0	$2,47 \times 10^{-3}$	4452,0	$2,45 \times 10^{-3}$	$-5,81 \times 10^{-3}$
11	1529235,4	4467,0	$2,92 \times 10^{-3}$	4452,0	$2,91 \times 10^{-3}$	$-1,68 \times 10^{-3}$
12	1911510,8	4430,0	$2,32 \times 10^{-3}$	4563,0	$2,39 \times 10^{-3}$	0,01

Results for the memory coding task, semantic decision and word generation for the control group are presented in Figures 1 to 3. Table 3 summarizes functional tests' asymmetry results in. Figure 1 shows bilateral activation of temporal mesial structures, while a symmetrical activation of language representation areas appears in Figures 2 and 3. All statistical analyses were performed using the SPM software package and a corrected p value (FWE = 0,05 (15,16).

Paradigm	Right hemisphere activation	Left hemisphere activation	Asymmetry index (L - R)/(L +)
Complex scenes coding	622	611	$-8,92 \times 10^{-3}$
Semantic decision	0	412	1
Words generation	49	251	0,7

Presentation of cases

Case 1: 21-year-old patient with partial symptomatic refractory epilepsy. Diagnostic imaging pointed out a right hippocampal sclerosis. Volume difference between the hippocampus was 1173 mm3 (IA: 0,1715). Bilateral representation of memory was observed (IA: 0,0722) and left-hemisphere language dominance (IA: 0,7). Memory testing adjustment provided an IAC: 0,1005, similar to the uncorrected value. Figure 4 displays the results of the activation of temporal medial areas for complex scene coding tasks. Results for semantic decision tasks are shown in Figure 5.

Case 2: 48-year-old patient with chronic epilepsy. EEG video monitoring revealed the right medial temporal region as the source of ictal activity. There are no signs of hippocampal sclerosis in the resonance images. Volume difference between hippocampus was 39 mm3 (IA: 0). The Wada test revealed a bilateral memory representation and a left-hemisphere language dominance. Resonance tests where in accordance with Wada's memory (IA: -0,1839) and language (IA: 1) criteria. The memory test's IAC was -0,1791, similar to the uncorrected value. Figure 6 displays the results of medial temporal areas' activation for complex scene coding tasks. Your seven shows the results for word generation tasks.

Case 3: 30-year-old patient with left hippocampal sclerosis. The Wada test revealed left-hemisphere language dominance and right-hemisphere dominance for memory. Volume difference between hippocampus was 1702 mm3 (IA: -0,2185). Resonance studies revealed an asymmetric representation for memory with right-hemisphere dominance (IA: -0,2812) and bilateral representation of language with left-hemisphere dominance, with an asymmetry index lower than that of the control group (IA: 0,2792). The resulting adjustment of the memory test is also in accordance with the Wada test (IA: -0,07). Figure 8 displays the results of temporal medial areas activation for complex scenes coding tasks. Figure 9 displays the results for semantic decision tasks, evidencing a more symmetrical activation.

Case 4: the 36-year-old patient with epilepsy from age 11. Diagnostic images reveal left hippocampal sclerosis. Volume difference between hippocampus was 1737 mm3 (IA: -0,2332). The Wada test reported a left hemisphere dominance for language and memory, with a bilateral but predominantly right hippocampal dysfunction. fMRI showed a bilateral representation of memory with right hemisphere dominance (IA: -0,2201) and left hemisphere language dominance (IA: 1). The resulting adjustment of the memory test provided an IA: 0,0138, which is in accordance with the Wada test. Figure 10 displays the results of temporal medial areas activation for complex scenes coding tasks. Figure 11 displays the results for semantic decision tasks. Despite activation in complex scenes coding tasks is asymmetric, with right-hemisphere dominance, the activation level adjustment in relation with hippocampal volume provides a result that is consistent with the Wada test.

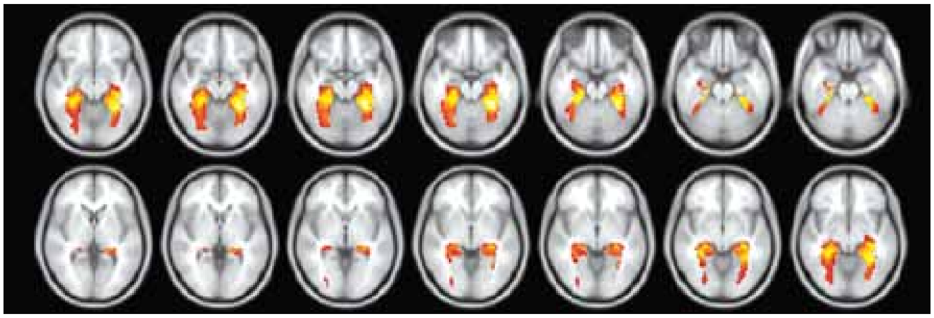

Figure 1. Activation under the complex scenes coding paradigm in control group subjects.

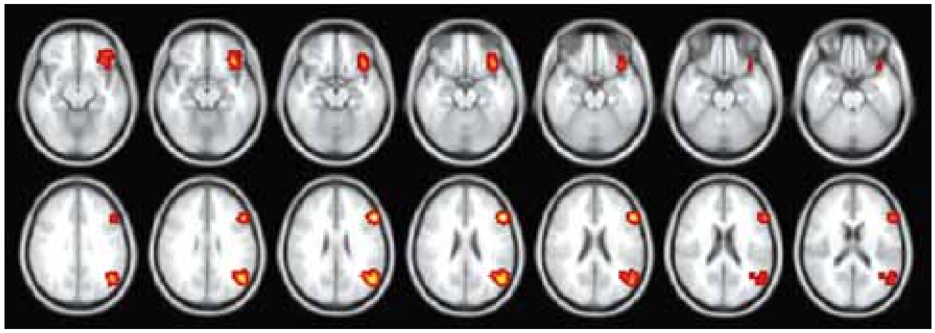

Figure 2. Activation under the semantic decision paradigm in control group subjects.

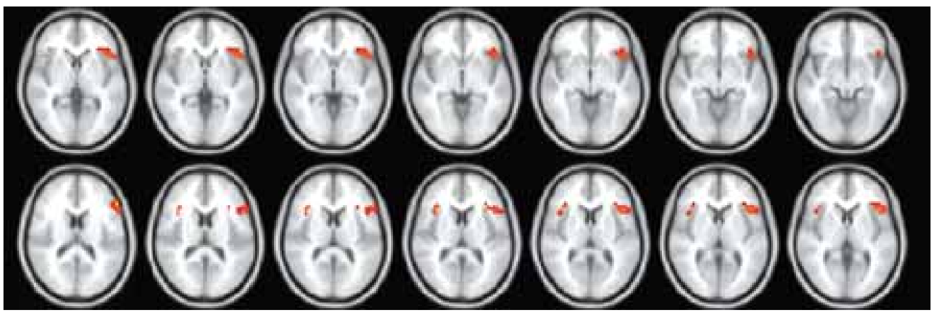

Figure 3. Activation under the word generation paradigm in control group subjects.

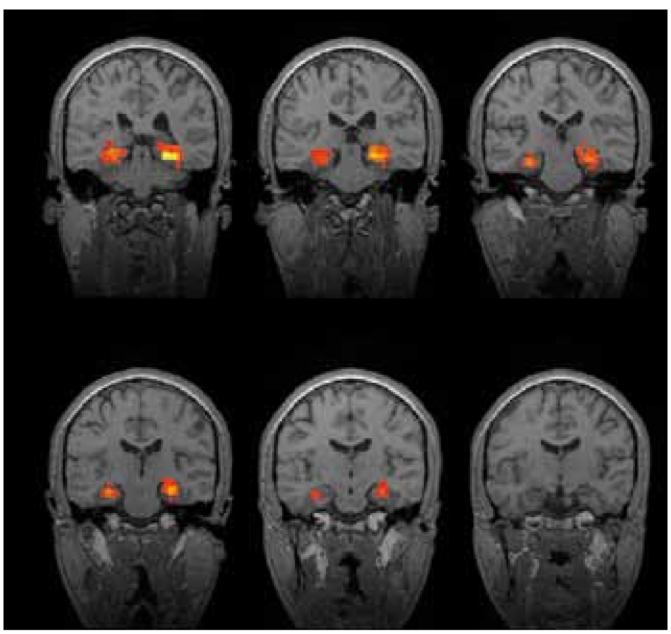

Figure 4. Activation under the complex scenes coding paradigm in patients with right hippocampal sclerosis (Case 1)

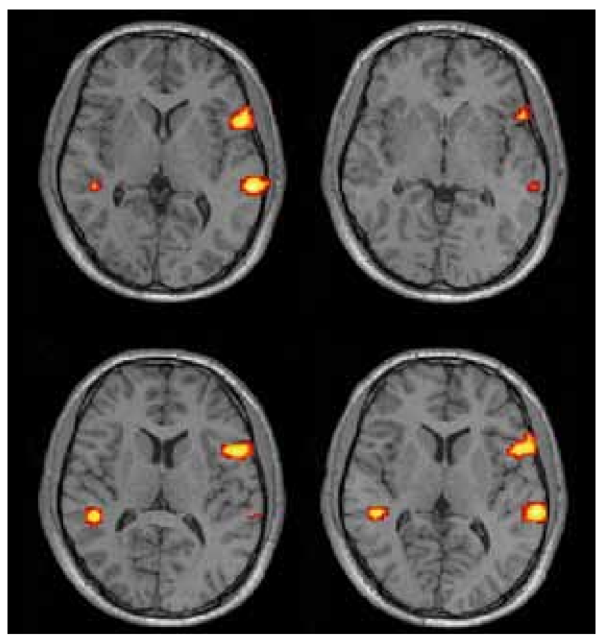

Figure 5. Activation under the semantic decision paradigm in patients with right hippocampal sclerosis (Case 1).

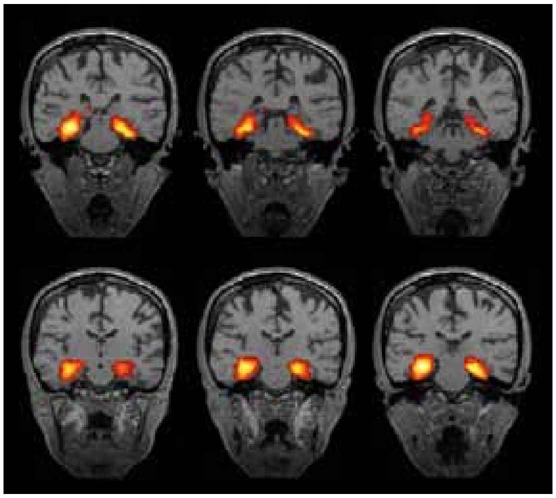

Figure 6. Activation under the complex scenes coding paradigm in patient with temporal epilepsy (Case 2).

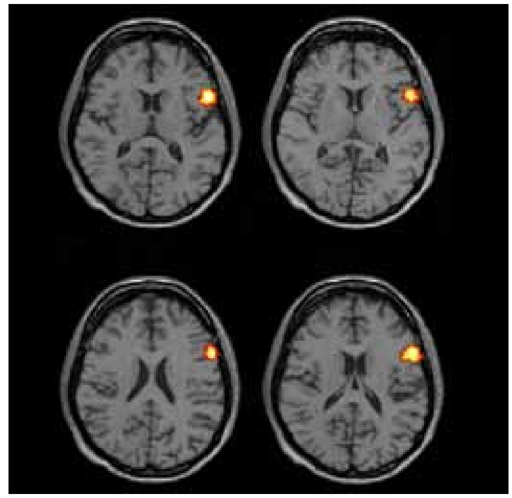

Figure 7. Activation under the word generation paradigm in a patient with non-lesional temporal epilepsy (Case 2).

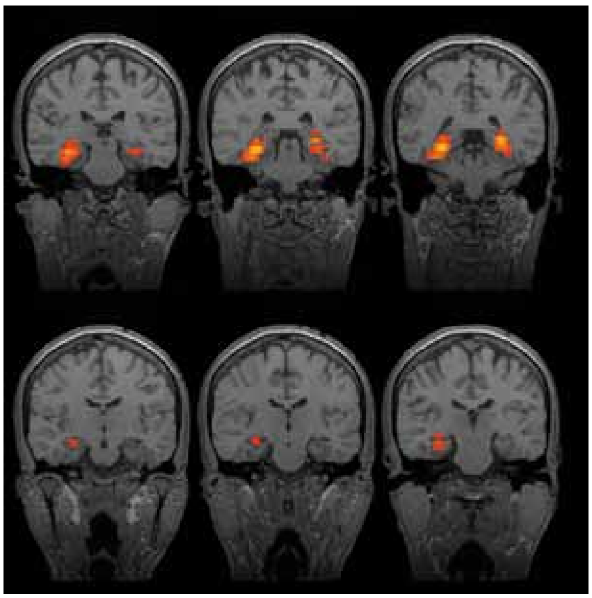

Figure 8. Activation under the complex scenes coding paradigm in a patient with epilepsy due to left hippocampal sclerosis (Case 3).

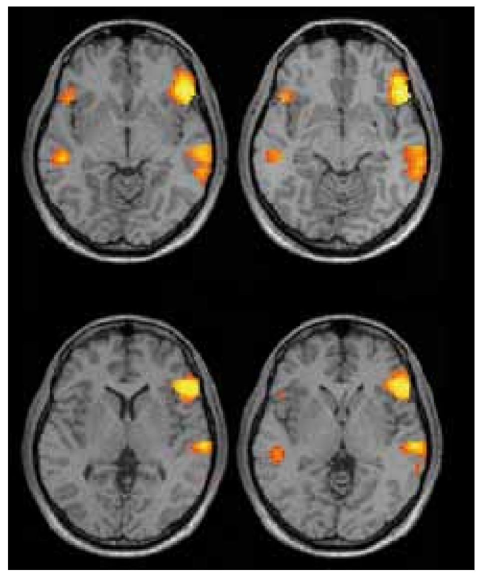

Figure 9. Activation under the semantic decision paradigm in a patient with epilepsy due to left hippocampal sclerosis (Case 3).

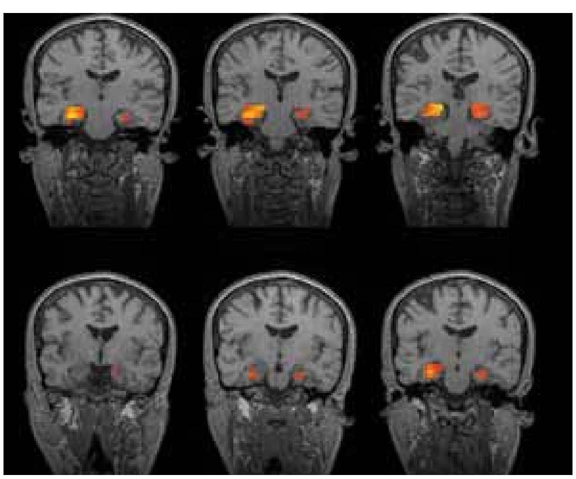

Figure 10. Activation under the complex scenes coding paradigm in a patient with epilepsy due to left hippocampal sclerosis (Case 4).

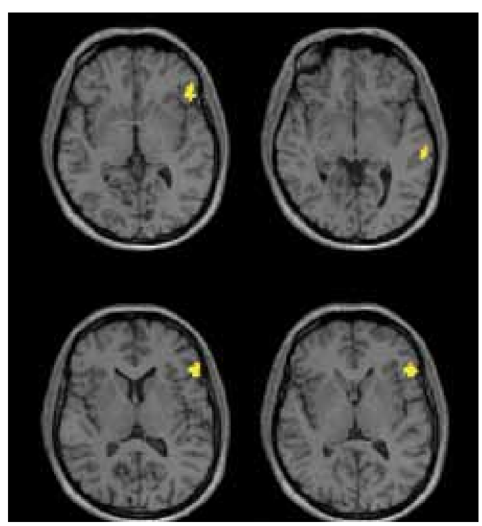

Figure 11. Activation under the semantic decision paradigm in a patient with epilepsy due to left hippocampal sclerosis (Case 4).

Discussion

Results from patient 4 indicate language lateralization, consistent with the hippocampus' degree of functionality as evaluated by the fMRI and the Wada test, and unrelated to its size. Although the size of the hippocampus is determines the maximum amount of active voxels possible, the activation in the anterior portions of the hippocampus may be a determinant factor regarding function.

When the quantity of active voxels is adjusted in accordance with the size of the hippocampus, an asymmetry consistent with the Wada test is evidenced. This indicates that the interpretation of the memory tests benefits from the introduced adjustment, although higher number of subjects is required to define ranges for a proper interpretation of the IAC.

Previous results agree with proposals of the existence of file language network involving the hippocampus, lateralized toward the left hemisphere in most people and that is modified by plasticity mechanisms when the hippocampus is affected on a functional level rather than a structural level (6-8). This proposal is best reflected in cases such as patient 1, where I a is not affected by his right sclerosis, and patient 3, in whom a people camp was dysfunction diminishes IA and shows a more pronounced bilateral representation in regions involving expressive as well as receptive language.

Limitations

Protocol implementation was performed in a small group of control subjects and patients, but its use in epileptic patients is still widespread. The situation of the patients analyzed in this work was only discussed prior to their surgeries; in order to access the protocol in a better way, a follow-up of patients after surgery is necessary to enable acquiring data on the prognostic value of the protocol and to assess possible changes generated by plasticity mechanisms.

Age of onset and intensity of the crises are highly valuable in the study of epileptic patients. This information will be included in future statistical analyses, aiming to increase patient sample and achieve better modeling of these variables' effects.

Conclusions

Results of the implementation of the fMRI memory and language protocol for patients with temporal lobe epilepsy are presented in this work. We have tested the protocol in the chosen control group and in patients with various levels of cognitive ability, finding consistency among control subjects, and a significant level of correspondence in patients in whom a Wada test was performed.

Evidence obtained through fMRI techniques on the role of the hippocampus in the language network and the effect of the left hippocampus on language migration patterns towards the contralateral hemisphere is highlighted.

A proposal for the future is to expand the number of cases and to include left-handed control subjects. Likewise, it is important to assess the prognostic value of fMRI of language in patients who are candidates to epilepsy surgery, taking into account the increase in the possibility of performing a noninvasive technique in a large group of the population with minimal risk.

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