Title: Differences in the conectivity between hippocampi in patients with drug resistant epilepsy of the temporal lobe a resting-state fMRI study.

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Abstract

Introduction: Drug-resistant temporal lobe epilepsy is used to be treated through surgical interventions which resect the epileptogenic focus which is usually found in the hippocampus and/or the amygdala. Sometime this intervention produces some episodic memory loss, for this reason the functionality of this structures must be assessed. The objective from the present research is to observe the connectivity between both hippocampi, their functionality and evaluate their implication before the surgical process.
Methodology: The sample was formed by 24 patients, all of them with temporal lobe epilepsy who completed a fMRI resting-state procedure. The images obtained from the fMRI were analysed with the software SPM12.
Results: We have found the existence of slight but significative differences between the connectivity of both hippocampi, with les connectivity in patients with lesions in the left hemisphere tan lesions in the right hemisphere, as well as intragroup differences.
Conclusions: The differences in connectivity inside of each group, are due to the functionality of the hippocampus, since the disconnection of one hippocampus from the other could indicate a lack of functionality. The pattern of greater affection in patients left-handed is coherent with the greater prevalence of lack in episodic memory in this group. Neuropsychological studies with memory tasks could be useful to establish the functional connectivity in resting-state as a valid index to predict the hippocampal functionality.

Keywords: hippocampus, epilepsy, episodic memory, functional magnetic resonance, resting-state fMRI.

INTRODUCTION

The epilepsy of temporal lobe (ELT) is one of the most common forms of epilepsy resistant to drugs. According to the classification of the international epileptic syndromes, we can differentiate two subtypes of epilepsy, first one would be the medial type and the one which is the objective of our interest is the temporal type, due to a higher prevalence (Bartolomei, et al., 1999).

In fact, is been estimated that the 30% of the patients who suffer epilepsy, have the type which is resistant to drugs, this prevents from receive the needed treatment. Here in Spain, we are talking about, from a total of 240000 patients of epilepsy, 80000 present the drug resistant variation. (Rufo-Campos et al., 2008).

For this reason, the only alternative of treatment for those patients who present the drug resistant variation of epilepsy is a surgical intervention. This intervention consists in the resection of the focus of the lesion, normally placed in the hippocampus and/or the amygdala. In fact, in the most actual views aim to reduce the size of the resection, taking off only the anterior temporal lobe with extension of 4,5 cm of the neocortex. The fact that the patient doesn't stop having seizures may be due to an insufficient resection of the epileptogenic structures from the mesial temporal (Rugg-Gunn et al., 2020).In spite of this, several studies demonstrate that this interventions produce some deficit in the episodic memory, in particular the autobiographical (Miró et al.,2019; Addis et al., 2007). In addition, these surgical interventions, can affect in the task of naming (Drane, 2018; Kendall, et al 2016). Also, we can find some affection in verbal fluency, due to the circuit of language is been affected, in the dominant hemisphere, having to reorganize itself. In a longitudinal study could be observed the reorganisation or recruitment of the contralateral frontal lobe demonstrating that there are several systems which gives support to the language, these mechanisms go in to action when the principal circuit of talk is affected (Bonelli et al 2012; Sanjuan et al., 2013).

Thus, to give a higher understanding about how affects the damage in some brain structures to episodic memory, in addition of how the brain works with the damage and the compensatory mechanisms which are used, we consider very important the use of fMRI (Denkova, 2014). Many are the studies which tried to map the hippocampus due to his straight relationship with the memory, the objective of this is to avoid the amnesia after the surgical intervention. To do it correctly, this mapping must be reliable in every single and particular case. We can find studies like (Ávila et al. 2006), where two tasks were performed, the first one was the image remembering (Detre et al. 1998) and the second one was an adaptation of «Roland's hometown- walking task» (Jokeit et al. 2001). However, this tasks only could map the posterior hippocampus. Other studies concentrated their efforts in developing a method of fMRI which could be able to predict the deficits in verbal memory after the surgical process of the resection of the anterior temporal lobe, this is the case of (Sidhu et al., 2015). In this one, is been demonstrated the intervention of extratemporal structures to anticipate the memory deficit, in addition of the inverse relationship between the amount of hippocampus to be resected and the preserved memory capacity. For this, they used a task where 10 blocks of 10 words were presented, where each word was presented for 3 seconds, making a total of 30 seconds per block, leaving 15 seconds between each block. Nevertheless, this study couldn't evaluate the functionality of the hippocampus at an individual level, here is where our interest resides.

Due to, in some cases, the patients of fMRI, have some difficulties in the moment of doing the tasks needed to evaluate the memory is important to look after other methods. In this case we are talking about the Resting-state fMRI, which principle is that the functional connectivity between areas in rest reproduce the structural connectivity of the brain. This technique substantiates in the measure of the fluctuations of low frequency in BOLD (Blood oxygen level dependent) to study the functional architecture of the brain. This technique is considered of special interest due to the high resolution it has, this allows to map in a simpler way some nets and epileptogenic focuses (Lee et al.,2013). Moreover, the study of (Bettus et al., 2010) found an increase of the basal functional connectivity between amygdala and the anterior and posterior hippocampus, being this a specific marker of the epileptogenic zone in 22 patients with epilepsy of the mesial temporal lobe. In other studies, like (Barnett et al., 2019) with a seed-based analysis or ROI (Region of interest) have demonstrated that the hippocampus can be parcellated in anterior and posterior region. Moreover, the epileptogenic hippocampus shows a lesser connectivity with the mPFC (medial prefrontal cortex) and the PCC (posterior cingulate cortex) two central nuclei in the default mode network. This connectivity has a medium and positive correlation with the memory capacity and this one correlates in the same way with the connectivity of the anterior hippocampus and the verbal memory in the subjects with LTE (left temporal epilepsy). In addition, (Bettus et al., 2010), shows that the connectivity observed in patients with temporal lobe epilepsy had a reduced functional connectivity of the anterior hippocampus in comparison with the controls.

So, with the previous context, the aim of this study, is to observe the connectivity between the right and left hippocampus and determine if there is any relationship with the hemisphere affected with temporal love epilepsy

Finally, we raise our hypothesis: 1) we could observe some connectivity between both hippocampus and 2) The connectivity between both hippocampi in patients with the lesion in the left hemisphere would be lower.

METHOD

Participants

The sample was obtained from a group of patients with brain lesions from “Hospital Universitario y Politécnico la Fe” (Valencia). All patients submitted to a pre-surgical functional neuroimaging test. The sample was formed for 24 subjects with temporal lobe epilepsy (10 men and 14 women).

The mean age is 38,50 years (DE 13,70). Additionally, 8 had brain lesions located in temporal areas of the right hemisphere and 16 in the left hemisphere.

From the 24 subjects, 23 were categorized as right-handed and 1 as ambidextrous, according to “Edinburgh Handedness Inventory” (Oldfield, 1971).

Image Acquisition

The images were obtained through a scanner Philips Achieva 3T. The participants were situated in a supine position inside the scanner of magnetic resonance and their heads were immobilized with cushions to reduce the artifacts produced for movement. The anatomical image were performed with a T1w MPRAGE sequence ((TR=8,15ms; TE= 3,73ms; matrix 256x256; voxel size = 1x1x1 mm; flip angle =8º; 150 volumes); to the functional data (resting-state sequence) a T2* EPI sequence was used (TR=2000 ms; TE=30 ms; matrix =80x80; voxel size =3x3x4 mm; flip angel =85º; 150 volumes).During this sequence.

Image preprocessing

For the processing of the images we used the software DPARSFA (Data Processing Assistant for Resting-State, version 5.0200301 (Yan, Wang, Zuo & zang, 2016)) based in SPM12, under MATLAB R2018b. For this we followed the recommended procedure, including “slice timing”; movement correction; anatomical-functional co-registry (to the mean functional image); segmentation of the structural images using “unified segmentation”; elimination of spurious variances through linear regression, including the 24 parameters of head movement, volume spikes with FD > 0.5, the signal from white matter and the cerebrospinal fluid, and possible quadratic linear effects; normalization to MNI space (3mm X 3mm X 3mm); smoothing (4mm); and band pass temporal filtering (0.01-0.1 Hz).

Resting-state functional connectivity analysis

A ROI to ROI analysis was performed to investigate the connectivity between both hippocampi. In this methodology, the functional connectivity depends on the correlation between the BOLD signal from the ROI, also called seed, and the BOLD signal from other regions of the brain (or ROIs). Due to our interest was to study the connectivity between both hippocampi, we raised a ROI to ROI analysis. The ROIs chosen were the left hippocampus and the right hippocampus from the Automated Anatomical Atlas (AAL, Tzourio-Mazoyer et al., 2002, see Figure 1)

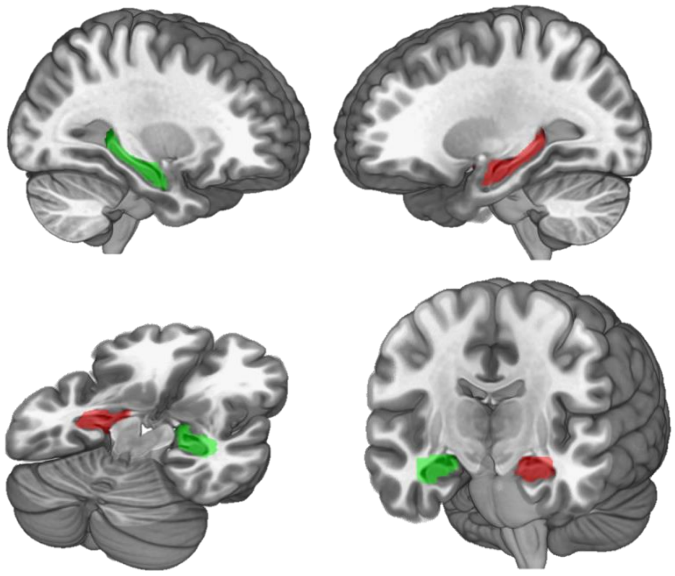

Figure 1: Hippocampi seeds (Tzourio-Mazoyer et al., 2002)

The statistical analysis was performed through the software SPSS statistics for windows, version 25.0 (IBM corp., Armonk, NY, USA). A t test was performed for independent samples using Z punctuations of Fisher as index of connectivity between hippocampi. This was made to observe the differences in connectivity between hippocampi in patients with the lesion in the left hemisphere in comparison with who had the lesion in the right hemisphere.

RESULTS

The punctuations of connectivity (Fisher Z) were computed through the SPSS software, afterwards were converted to r punctuations of Pearson, observing a higher connectivity between both hippocampi in the subjects where the lesion was localized in the right hemisphere in comparison with a lower connectivity in the subjects where the lesion was localized in the left hemisphere (see figure 2 and figure 3)

N= 8

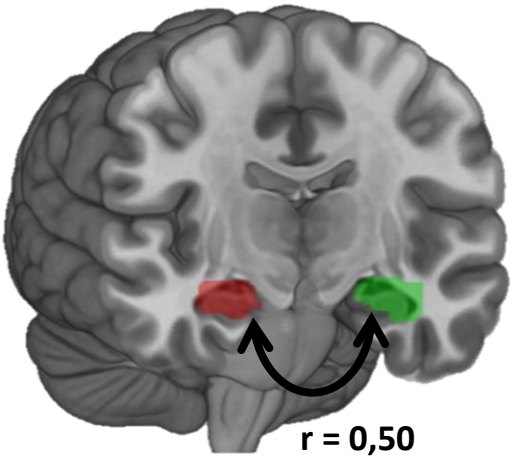

Figure 2: Connectivity in the group with lesion in the right hemisphere

N= 16

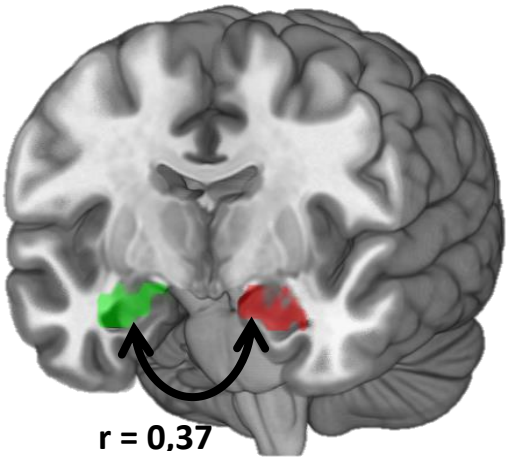

Figure 3: : Connectivity in the group with lesion in the left hemisphere

In the table 2 we have the results for the analysis for two independent samples. Here we can observe the correlation between both hippocampi in both groups has a punctuation of p = 0,08 one tailed. This value isn't very significant; however, the value of the G of Hedge is 0,65 indicating a moderate-high size effect. In our case we decided to use this parameter because the G of Hedge takes into account the size of the sample.

Table 2: Results to t test of independent samples

		Levene test of equality of variances		T test for mean equalities					95 % confidence interval of the difference	
		f	sig.	t	gl	sig	mean difference	standard error difference	inferior	superior
hippo_izquierdo_corr_hippo_derecho	equal variances are assumed	1,002	0,328	1,449	22	0,08	0,16154	0,11149	-0,06969	0,39276
	equal variances are not assumed			1,533	16,402	0,07	0,16154	0,10536	-0,06138	0,38445

The individual analysis for each one of the participants (see figure 4) shows the connectivity of the hippocampi for each individual, indexing in which hemisphere is located the lesion.

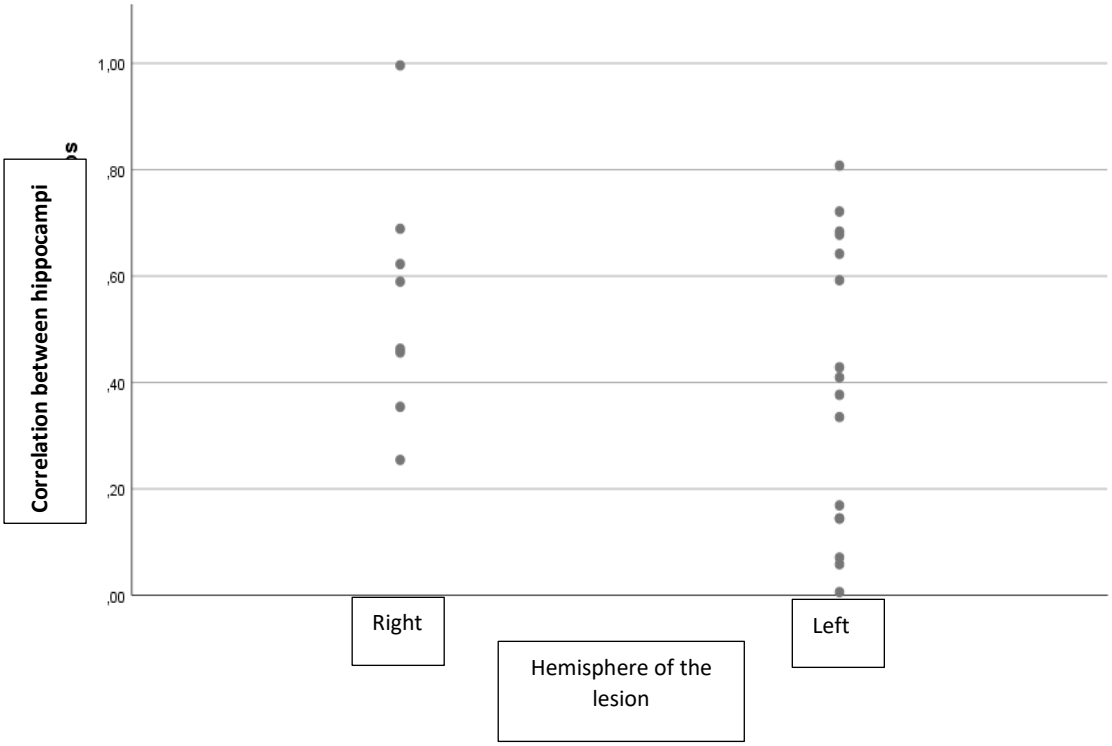

Figure 4: Connectivity of every subject

DISCUSION AND CONCLUSIONS

The aim of this study, is to observe the connectivity between the right and left hippocampus and determine if there is any relationship with the hemisphere affected with temporal love epilepsy. In this way, we raise our hypothesis: 1) we could observe some connectivity between both hippocampus and 2) The connectivity between both hippocampi in patients with the lesion in the left hemisphere would be lower.

Confirming our first hypothesis, we could observe the presence of connectivity between hippocampi and it variates slightly, in other words, those who have the lesion in the right hemisphere have a tendency to have a higher connectivity at a group level, in comparison, those who have in the left hemisphere have a lower connectivity, confirming the second hypothesis. This matches with a previous study of (Barnet et al., 2019) where the connectivity of the epileptogenic focus is specially reduced when its located in the dominant hemisphere.

These findings could suggest, that inside of one group of patients, the connectivity's are characterized to individual differences. For this reason, is important to make fMRI studies before a surgical procedure, due to, when higher is the connectivity between hippocampi more susceptible is the patient to suffer deficits in the memory after the intervention.

This investigation has some limitations; the lac of a control group; the small size of the sample and the absence of randomisation of the sample. However, we can consider the results of this study could be useful for future investigation. For example, studies with memory tasks could be useful to stablish the functional connectivity in resting-state fMRI as a valid index to predict the hippocampal functionality, reducing the risk of amnesia after the surgery.

In conclusion, this investigation led us to observe the reduced connectivity between hippocampi when the epileptogenic focus is localized in the left hemisphere.

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