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SHORT RESEARCH ARTICLE

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Olfactory function in focal epilepsies: Understanding mesial temporal lobe epilepsy beyond the hippocampus

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Abstract

Several lines of research have linked olfactory regions with the pathophysiology of focal epilepsies. Among those regions, the piriform cortex represents the major part of the primary olfactory cortex. According to these data, we raised the hypothesis that in patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis exists an interictal dysfunction of olfactory processing that could be more significant compared to patients with extra-hippocampal focal epilepsy and healthy controls. This could be the consequence of a dysfunctional epileptogenic network that extends beyond the hippocampus and affects other structures, including the piriform cortex. To test this hypothesis, we evaluated the olfactory function with the Sniffin' Sticks test in 32 patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis, 30 patients with extra-hippocampal focal epilepsy, and 22 healthy controls. Compared to the other study groups, patients with temporal lobe epilepsy due to hippocampal sclerosis showed a basal olfactory dysfunction characterized by an impairment in odor discrimination and odor identification. We also found that high seizure frequency had a strong correlation with the evaluated olfactory tasks. Our results are consistent with neuroimaging and neuropathological data that establish a link between olfactory regions and the pathophysiology of temporal lobe epilepsy.

KEYWORDS

epilepsy, hippocampal sclerosis, olfaction, piriform cortex, temporal lobe

1 | INTRODUCTION

Compared to other sensory-perceptual functions and unlike some neurodegenerative disorders, olfactory function in epilepsy has not been thoroughly studied. Some studies have linked temporal lobe epilepsy with olfactory dysfunction, and their results show a variable impairment in olfactory threshold, odor identification, and odor discrimination.[1–4] These olfactory functions depend mainly on the primary olfactory regions, which include the piriform cortex, the olfactory bulb, the anterior olfactory nucleus, the olfactory tubercle, the periamygdaloid cortex, and the anterior part of the entorhinal cortex.[5,6] Beyond these regions, the olfactory network includes the orbitofrontal cortex, the thalamus, and the

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insula.[5,6] All of these structures may be affected in temporal lobe epilepsy and could explain the interictal olfactory dysfunction. However, the piriform cortex remains the most important region related to olfactory processing and represents the major part of the primary olfactory cortex.[6,7]

As well as the hippocampus, the piriform cortex has a three-layered allocortical structure, is vulnerable to cell dysfunction induced by excitotoxicity, and is highly susceptible to secondary epileptogenesis induced by electrical and chemical stimulus.[8,9] The piriform cortex is located at the junction of the temporal and frontal lobes.[10] The temporal aspect of the piriform cortex is related to the amygdala and the entorhinal cortex, the frontal aspect is related to the olfactory tubercle and the olfactory tract, and the lateral aspect merges into the insula.[9,10] The strategic anatomical location of the piriform cortex allows it to be a common pathway for the propagation of epileptiform discharges in focal epilepsies.[11] This is in line with some neuroimaging studies that have shown that in patients with mesial temporal lobe epilepsy, the dysfunction of anatomical circuits goes beyond the hippocampus and affects other structures such as the piriform cortex.[12]

According to these data, we raised the hypothesis that in patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis, there could exist an interictal olfactory dysfunction, which could be more significant compared to patients with extra-hippocampal focal epilepsy and healthy controls. To test this hypothesis, we evaluated the olfactory function with the Sniffin' Sticks test in the three study groups previously mentioned.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

A comparative case series study with consecutive sampling was performed. We recruited patients aged 18-65 years who had an epilepsy diagnosis and were treated at the epilepsy units of Hospital Ruber Internacional, Hospital Ramon y Cajal, or Hospital Clinico San Carlos, in Madrid, Spain. The patients were classified into two study groups: patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis and patients with extra-hippocampal focal epilepsy. In addition, we recruited a third group of healthy controls among the relatives of the patients that were age- and sex-matched. We excluded subjects with a history of smoking, physical and/or mental limitations, epilepsy surgery, seizures in the previous week to evaluation, traumatic brain injury, neurodegenerative disorders associated with olfactory dysfunction, upper respiratory infection in the previous week to evaluation, allergic rhinitis, and diseases of the paranasal sinuses. Patients with dual pathology or extensive lesions on MRI were also excluded. The etiology and classification of each group was based on clinical history, semiology, video-EEG, and brain MRI. To evaluate the olfaction, the extended version of the Sniffin' Sticks test (n-Butanol version) was applied. This is a validated and commonly used tool for assessment of olfactory function in subjects with normal sense of smell and in individuals with smell loss.[13] Compared with other tests, the Sniffin' Sticks test explores three different components of olfaction: odor perception threshold, odor discrimination, and odor identification. Each olfactory function can be evaluated separately, and the sum of these three components corresponds to a global TDI score.

2.2 | Case definition

- *Mesial temporal lobe epilepsy associated with hippocampal sclerosis (HS):* patients with focal epilepsy in whom seizure semiology suggests a mesial temporal lobe onset and is associated with hippocampal atrophy and abnormalities of the hippocampal signal intensity on MRI studies, as well as interictal/ictal epileptiform activity located at the temporal lobe.
- *Extra-hippocampal focal epilepsy (EH):* patients with focal epilepsy in whom seizure semiology does not suggest a mesial temporal lobe onset and is associated with an extra-hippocampal lesion on MRI studies, as well as interictal/ictal epileptiform activity congruent with that lesion, and normal hippocampus on brain MRI.
- *Healthy control (HC):* healthy subjects aged 18-65 years who do not meet any of the exclusion criteria.

2.3 | Statistical analysis

The data were analyzed with the R software (version 3.2.1) using the packages epicalc, robust, and relaimpo.[14] A description of each variable, based on the median and interquartile range for quantitative variables and absolute and relative frequency for categorical variables, was made. The association between the study group (HS, EH, and HC) and the clinical and demographic variables was assessed with one-way analysis of variance, the Pearson chi-square test, or the Fisher exact test, as appropriate. The association between the study group and the olfactory variables was evaluated with both crude and adjusted tests. Given the data distribution, crude analyses were performed with the Kruskal-Wallis test, and adjusted analyses were performed with robust multiple linear regression. The adjustment variables were age, sex, seizure frequency, and duration of disease. Due to high collinearity, the number of antiepileptic drugs and the laterality of the lesion were excluded from the models. Post hoc analyses were performed with the Tukey HSD (honestly significant difference) test. In all cases, we applied bilateral tests and considered significant P values less than 0.05. Finally, we also investigated the relative importance of the study group and other

clinical variables on their ability to predict the TDI score. To this end, we calculated the lmg values of each variable with the relaimpo package. The lmg value indicates the portion of the total variability of the dependent variable explained by the model corresponding to each of the predictor variables.

3 | RESULTS

Eighty-four participants were included. Thirty-two patients were in the group of HS, 30 were in the group of EH, and 22 were HC. Table 1 summarizes the demographic and clinical variables of the three groups. The crude and adjusted tests of association between the study group and the olfactory variables are shown in Table 2 and Figure S1. In the crude analyses, we found a significant association with all olfactory variables. However, after adjusting by age, sex, seizure frequency, and duration of disease, only odor discrimination ($P < 0.001$), odor identification ($P < 0.001$), and TDI score ($P < 0.001$) remained statistically significant. In the post hoc analyses, we found that patients with HS showed a statistical difference in the three olfaction tests as compared with patients with EH and HC. In the adjusted analyses, in addition to study group, we also found that high seizure frequency

TABLE 1 Demographic and clinical variables.

	Hippocampal epilepsy	Extra-hippocampal epilepsy	Healthy controls	Test	P value
Total	32	30	22	–	–
Age, median (IQR)	44.5 (37.5-52)	32.5 (25-46)	42.5 (34.5-46)	ANOVA	0.004
Duration of disease, median (IQR)	28.5 (15.8-38.2)	13.5 (10-22.8)	-	*t* test	0.001
Sex frequency (percentage)					
Female	14 (43.8)	12 (40)	11 (50)	Chi-square test	0.772
Male	18 (56.2)	18 (60)	11 (50)		
Type of seizures, frequency (percentage)					
Focal without impairment of consciousness	8 (25)	17 (56.7)	-	Fisher's exact test	0.019
Focal with impairment of consciousness	23 (71.9)	13 (43.3)			
Generalized	1 (3.1)	0 (0)			
History of status epilepticus, frequency (percentage)					
Yes	1 (3.1)	5 (16.7)	-	Fisher's exact test	0.099
No	31 (96.9)	25 (83.3)			
Febrile seizures, frequency (percentage)					
Yes	8 (25)	0 (0)	-	Fisher's exact test	0.005
No	24 (75)	30 (100)			
Seizure frequency in the last year, frequency (percentage)					
No seizures	(6.2)	4 (13.3)	-	Fisher's exact test	0.88
1-3	7 (21.9)	4 (13.3)			
4-6	4 (12.5)	4 (13.3)			
7-9	2 (6.2)	2 (6.7)			
≥10	17 (53.1)	16 (53.3)			
Laterality of the lesion, frequency (percentage)					
Left	19 (59.4)	19 (63.3)	-	Fisher's exact test	0.99
Right	11 (34.4)	10 (33.3)			
Bilateral	2 (6.2)	1 (3.3)			
Number of antiepileptic drugs, frequency (percentage)					
1	4 (12.5)	8 (26.7)	-	Fisher's exact test	0.008
2	18 (56.2)	10 (33.3)			
3	5 (15.6)	12 (40)			
≥4	5 (15.6)	0 (0)			

TABLE 2 Association between study group and olfactory variables

	Hippocampal epilepsy	Extra-hippocampal epilepsy	Healthy controls	Crude *P* value (Kruskal-Wallis)	Adjusted *P* value (robust multiple linear regression)	Post hoc analysis *P* value (Tukey's HSD)
Olfactory threshold, median (IQR)	6.5 (5.6-6.7)	7.5 (6.3-8.4)	8.5 (7.1-10)	<0.001	0.12	–
Odor discrimination, median (IQR)	9 (8-10.2)	11 (10-12)	14 (13.2-15)	<0.001	<0.001	EH-C = 0.76 H-C = 0.001 H-EH = <0.001
Odor identification, median (IQR)	10 (10-11)	12 (11-12)	14 (13-14)	<0.001	<0.001	EH-C = 0.705 H-C = 0.057 H-EH = 0.002
TDI score, median (IQR)	26.1 (22.6-28.3)	29.8 (28.3-32.2)	36.5 (35.5-37.8)	<0.001	<0.001	EH-C = 0.64 H-C = <0.001 H-EH = <0.001

Adjustment variables: age, sex, seizure frequency, and duration of disease. Variables excluded due to high collinearity: laterality of the lesion and number of antiepileptic drugs.
Abbreviations: C, healthy control; EH, extra-hippocampal epilepsy; H, hippocampal epilepsy.

(≥10 in the last year) showed a strong statistical association with odor discrimination ($P < 0.001$), odor identification ($P = 0.0011$), and TDI score ($P < 0.001$). Concerning the relative importance of the clinical variables on their ability to predict the TDI score, the variables with the highest Img values were seizure frequency (0.284) and study group (0.277), followed by duration of disease (0.036), history of febrile seizures (0.025), and history of status epilepticus in the last 5 years (0.018). The proportion of the total variance explained by the model was 67%.

4 | DISCUSSION

Compared to patients with extra-hippocampal focal epilepsy and healthy controls, patients with HS show an interictal olfactory dysfunction characterized by an impairment in odor discrimination, odor identification, and TDI score. As we mentioned before, these olfactory functions depend on several frontal, temporal, and limbic anatomical structures. In particular, the entorhinal cortex is involved in odor identification and memory tasks,[15] the orbitofrontal cortex is involved in the odor identity and offers a multisensory integration of olfaction,[16] the amygdala is involved in the emotional aspect of olfaction, and the inferior frontal gyrus is important for naming odors.[17–19] Another important region is the olfactory bulb, since it represents one of the first anatomical structures of olfactory processing and has a unique morphological configuration that exhibits a strong connectivity with a high number of synapses that can only be compared with the cerebellar cortex or the hippocampus.[19,20] In addition, the olfactory bulb serves as the main afferent to mesial temporal structures and is involved not only in the olfactory processing, but also in the pathophysiology of some temporal lobe epilepsies.[18–20]

All the structures mentioned above may be part of the epileptogenic network in HS[12] and could explain the interictal olfactory dysfunction that we have found; however, the piriform cortex remains the most important region related to olfactory processing and represents the major part of the primary olfactory cortex.[6,7] Besides that, it has a strong connectivity with anatomical structures involved in the epileptogenic network of HS, and its activation has been documented in all olfactory tasks, mainly in odor discrimination and olfactory working memory tasks.[21,22] This is consistent with some imaging and neuropathological studies that have shown that the piriform cortex seems to be an important modulator in the pathophysiology of temporal lobe epilepsy.[11,23–25] In this regard, an EEG-fMRI study conducted by Fahoum et al showed that patients with temporal lobe epilepsy had an ipsilateral activation of the piriform cortex, the insula, the claustrum, and the amygdala.[25] Flanagan et al found similar results, supporting the idea that the piriform cortex is a

common pathway for the propagation of epileptiform discharges in focal epilepsies.[11]

Our findings further support the hypothesis that the olfactory dysfunction observed in the group of patients with HS is the consequence of a dysfunctional epileptogenic network that extends through the piriform cortex and nearby structures. In the same line, a recent publication by Galovic et al revealed the importance of the resection of the piriform cortex in the postoperative seizure outcome of patients with temporal lobe epilepsy.[26] They found that the removal of at least half of the piriform cortex increases the odds of becoming seizure-free by a factor of 16 (95% CI, 5-47).[26]

In our series, we also found that high seizure frequency had a strong correlation with the evaluated olfactory tasks. This finding is consistent with some animal and neuroimaging studies that have shown that the piriform cortex is highly susceptible to electrical kindling.[8,27] In the same line, Laufs et al evaluated two separate groups of patients with focal epilepsies using either simultaneous EEG-fMRI or [11C]flumazenil PET.[28] They found that $GABA_a$ receptor binding near the frontal piriform cortex ipsilateral to the presumed cortical focus was reduced in patients with more frequent seizures.[28] These data suggest that altered GABAergic inhibition in the piriform cortex may be a consequence of increased seizure frequency, which is congruent with our results showing that patients with high seizure frequency have a tendency to exhibit a lower performance in odor discrimination, odor identification, and TDI score. We are aware of several methodological limitations of our study, including a lack of repeated testing, a relatively small sample size, and a lack of pathological confirmation. In addition, this study was based on a medical record of consecutive patients, which limits its direct application to the general population. However, our findings are consistent with several studies that have found similar results,[1–4] and are congruent with previous neuroimaging and neuropathological data showing an association between olfactory regions and the pathophysiology of temporal lobe epilepsy. The selective involvement of olfactory functions in patients with HS raises the possibility of using unified olfactory tests in the noninvasive evaluation of these subjects.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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