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Olfactory stimulation induces delayed responses in epilepsy

Mariana S. Lunardi [a], Katia Lin [a,b,c,*], Rūta Mameniškienė [d,e], Sandor Beniczky [f,g], Alicia Bogacz [h], Patricia Braga [h], Mirian S.B. Guaranha [i], Elza M.T. Yacubian [i], Rūta Samaitienė [j,k], Betül Baykan [l], Thomas Hummel [m], Peter Wolf [b,f]

[a] Centro de Epilepsia de Santa Catarina (CEPESC), Hospital Governador Celso Ramos (HGCR), Florianópolis, SC, Brazil
[b] Serviço de Neurologia, Departamento de Clínica Médica, Hospital Universitário, Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil
[c] Centro de Neurociências Aplicadas (CeNAp), Hospital Universitário, Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil
[d] Epilepsy Centre, Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania
[e] Clinic of Neurology and Neurosurgery, Medical Faculty, Vilnius University, Vilnius, Lithuania
[f] Danish Epilepsy Centre, Dianalund, Denmark
[g] Aarhus University, Aarhus, Denmark
[h] Instituto de Neurología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay
[i] Hospital São Paulo, Universidade Federal de São Paulo, São Paulo, Brazil
[j] Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania
[k] Clinic of Children's Diseases, Medical Faculty, Vilnius University, Vilnius, Lithuania
[l] Department of Neurology and Clinical Neurophysiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[m] Smell & Taste Clinic, Department of ORL, TU Dresden, Germany

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ABSTRACT

Precipitation and inhibition of seizures and epileptic discharges by sensory stimuli are receiving increasing attention because they provide insight into natural seizure generation in human epilepsies and can identify potential nonpharmacological therapies. We aimed to investigate modulation (provocation or inhibition) of epileptiform discharges (EDs) in mesial temporal lobe epilepsy (MTLE) versus idiopathic generalized epilepsy (IGE) by olfactory stimulation (OS) compared with standard provocation methods. The underlying hypothesis was that any response would be more likely to occur in MTLE, considering the anatomical connections of the temporal lobe to the olfactory system. This multicenter, international study recruited patients with either MTLE or IGE who were systematically compared for responses to OS using an EEG/video-EEG protocol including a 30-min baseline, twice 3-min olfactory stimulation with ylang-ylang, hyperventilation, and intermittent photic stimulation. The 95% confidence interval (CI) for the baseline EDs in each patient was calculated, and modulation was assumed when the number of EDs during any 3-min test period was outside this CI. A total of 134 subjects (55 with MTLE, 53 with IGE, and 26 healthy controls) were included. Epileptiform discharges were inhibited during OS in about half the patients with both MTLE and IGE, whereas following OS, provocation was seen in 29.1% of patients with MTLE and inhibition in 28.3% of patients with IGE. Olfactory stimulation was less provocative than standard activation methods. The frequent subclinical modulation of epileptic activity in both MTLE and IGE is in striking contrast with the rarity of reports of olfactory seizure precipitation and arrest. Inhibition during OS can be explained by nonspecific arousal. The delayed responses seem to be related to processing of olfactory stimuli in the temporal lobe, thalamus, and frontal cortex.

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1. Introduction

Modulation of epileptic activity by sensory stimuli has long been known and can be either provocative or inhibitory. It can be used for nonpharmacological treatments and provides insight into mechanisms of natural seizure generation. Habitual precipitation of seizures by such stimuli is called reflex epilepsy, which in the majority of cases is related to the visual system including photosensitivity [1]. Olfactory reflex epilepsy has never been described although olfactory auras are known since Gowers [2] and related to dreamy states by Jackson [3]. They occur in approximately 6% of patients with temporal lobe epilepsy (TLE) [4]. In addition, it is known that patients with TLE have impaired olfactory function and reduced olfactory bulb volume [5]. Stevens studied the influence of external factors on epileptiform discharges (EDs) in 100 patients, 61 of whom were exposed to olfactory stimulation (OS) [6]. Sixteen patients with TLE (26.2%) demonstrated "exaggerated

* Corresponding author at: Departamento de Clínica Médica, 3º Andar, Hospital Universitário Polydoro Ernani de São Thiago, Rua Prof. Maria Flora Pausewang S/Nº, Caixa Postal 5199, Campus Universitário, Trindade, 88040-900 Florianópolis, SC, Brazil. Tel.: +55 48 37219149; fax: +55 48 37219014.
E-mail address: linkatia@uol.com.br (K. Lin).

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spiking during or immediately after exposure to perfumed air", whereas no response was observed in the EEG of 22 patients with idiopathic generalized epilepsy (IGE) [6]. However, no seizures were provoked in any of these patients, and there are only a few case reports where seizures were triggered by aromatic oils [7] or by the inhalation of a paint thinner [8]. The counterpart of seizure precipitation, i.e., seizure inhibition by OS, has also been reported [2,9–12]. However, targeted investigations are scarce. We therefore undertook a systematic comparison of EEG responses to OS in patients with a well-established diagnosis of either mesial TLE (MTLE) or IGE, the underlying hypothesis being that any responses would be more likely to occur in MTLE, considering its functional anatomical relations to the olfactory system.

2. Materials and methods

2.1. Study description, approvals, and consents

This multicenter, international study was conducted between June 2009 and February 2015 at seven enrolling sites in Brazil, Lithuania, Denmark, Uruguay, and Turkey. It was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2014) [13] and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Institutional review boards and ethics committees for each site approved the study protocol and informed consents. All subjects signed an informed consent form and voluntarily agreed to participate.

We consecutively included patients with a definite diagnosis of either MTLE with hippocampal sclerosis (HS) or IGE. Diagnosis was based on clinical history and seizure semiology supported by EEG or video-EEG and magnetic resonance imaging (MRI) or computed tomography (CT) scan consistent with these diagnoses and without evidence of progressive structural lesions in the central nervous system or progressive encephalopathy. All patients were on treatment with standard antiepileptic drugs. A control group comprised 26 healthy volunteers with no history of any neurological or psychiatric disease or complaints, with normal intellect, and with no family history of epilepsy. None of the patients and controls had any clinically relevant nasal condition or complaints of smell or taste dysfunction. Patients with olfactory auras were excluded because these were considered as potential confounders. A previous internationally validated questionnaire – the Multi-Clinic Smell and Taste Questionnaire (MCSTQ-SC) – was given to all participants in order to systematically evaluate the presence of any nasal, smell, or taste dysfunction [14].

Patients were excluded if they were below 13 years of age; were smokers; were pregnant women; had any nasal, smell, or taste dysfunction as assessed with the MCSTQ-SC; had cardiovascular and pulmonary disease or other clinically relevant conditions that might interfere with hyperventilation; had a history of ylang-ylang essential oil allergy; or had nonepileptic events, including psychogenic seizures.

2.2. EEG/VEEG protocol

Noninvasive EEG or video-EEG was recorded using 19–32 EEG electrodes placed according to the International 10–20 or 10–10 electrode system, with an inferior temporal electrode chain and/or sphenoidal electrodes when applicable (MTLE-HS). All patients and controls were submitted to the protocol summarized in Table 1. The recording started with the subject lying awake and relaxed on a bed, with eyes closed. The EEG during the entire protocol was continuously monitored to ensure that drowsiness or sleep did not occur. After baseline and olfactory stimulation, intermittent photic stimulation (IPS) and hyperventilation (HV) were performed according to standard protocols [15,16], adjusted to a total duration of 5 min. According to local standard procedures, IPS was not performed in all patients with MTLE-HS. Each test condition was separated by 15-minute intervals. The total duration of the recording was 1.5–2 h per patient.

Table 1
Video-EEG protocol.

1. Baseline — 30 min of EEG recording (awake, relaxed state, eyes closed). Epileptiform discharges (EDs) were counted in each 3-minute time window, and a mean number of EDs of the total of 10 time windows was obtained.
2. First olfactory stimulus (OS) — OS1 — 3 min normally breathing with the odorant stimulus (EDs counted) — adaptation of olfactory cells was avoided by approaching and distancing the cotton ball containing the essential oil slowly toward and from the nostrils.
3. Post-OS1 — 15 min of recording — EDs were counted for each 3-minute time window, and a mean number of EDs of the total 5 time windows was obtained.
4. Second OS — OS2 — 3 min normally breathing with the odorant stimulus (EDs counted).
5. Post-OS2 — 15 min of recording — EDs were counted for each 3-minute time window, and a mean number of EDs of the total 5 time windows was obtained.
6. Hyperventilation (HV) — 5 min of hyperventilation (inspiring and expiring through the mouth) — ED occurrences in the last 3 min were counted.
7. Post-HV — 15 min of recording — EDs were counted for each 3-minute time window, and a mean number of EDs of the total 5 time windows was obtained.
8. Intermittent photic stimulation (IPS) — photic stimulation with frequencies of 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 60, 50, 40, 30, 25, and 20 Hz (eyes opened for 5 s and closed for 5 s in each frequency and interval between flashes of 7 s).
9. End of protocol.

The olfactory stimulus consisted of ylang-ylang essential oil (*Cananga odorata*) as suggested by Betts [11]. Ylang-ylang has a pleasant fragrance and produces little or no trigeminal activation [17]. Its essential oil is obtained by steam distillation from fresh matured ylang-ylang flowers and is used in the cosmetic and pharmaceutical industries as an active component of antibacterials and in aromatherapy. Its chemical composition is predominantly of volatile terpenes and benzenoid and phenylpropanoid components [18–20]. An odorant solution at 10% was obtained by diluting 0.5 ml of the essential oil (stored in 20-ml yellow glass bottles) in 4.5 ml of an odorless solvent (glycerine, paraffin, or mineral oil) immediately before use. Afterwards, 1 ml of this odorant solution was dropped on a cotton ball and applied near patients' both nostrils simultaneously. All subjects received this stimulation for 3 min twice (first olfactory stimulus — OS1, second olfactory stimulus — OS2), with each stimulation followed by 15 min of rest (post-OS1 and post-OS2 periods, respectively) to account for any late response. Because of its volatility, the solution was used just once. Great attention was paid to ensure that all subjects during stimulation kept a constant quiet breathing rate. All EDs fulfilling established criteria [21] were visually identified and counted in the recordings under each test condition (Table 1): spike, spike-and-slow wave, sharp wave, sharp-and-slow wave, polyspike, and polyspike-and-slow wave. All EEGs of each group were recorded and read by one experienced and board-certified clinical neurophysiologist according to the International Federation of Clinical Neurophysiology [22] and American Clinical Neurophysiology Society [23] guidelines and consensus statements. Foreseeable difficulties were discussed between the raters beforehand in a virtual session. If any doubts arose during individual evaluations, the traces were referred to one of the authors (S.B.) for final rating.

2.3. Statistical analysis

A sample size of 43 patients in each group (MTLE-HS and IGE) was considered necessary to detect a significant difference in olfactory modulation of epileptic discharges between groups with a power of 80% and a two-sided test at a significance level of 5%. Statistical analysis was performed using IBM® SPSS® software package for Mac (standard version 21.0) and Microsoft Excel® software package for Windows (2014). Descriptive analysis was made to characterize the sample. Quantitative variables were expressed as mean ± standard deviation (SD), and qualitative variables were expressed as percentage values. The normality of the data distribution was assessed using the Kolmogorov–Smirnov test. Wilcoxon test was used to compare the occurrences of EDs between the baseline period and testing periods within each group (MTLE-HS and IGE). To compare individual responses (provocative × inhibitory) between MTLE-HS

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