Electrical stimulation of the medial orbitofrontal cortex in humans elicits pleasant olfactory perceptions

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A B S T R A C T

Background: Olfactory hallucinations can be part of epileptic seizures of orbitofrontal origin. Olfactory hallucinations, however, are rare and therefore the semiology, localization and lateralization characteristics are underdetermined. In addition, many discrepancies are found in the literature regarding olfactory processing and orbitofrontal (OF) functions and olfactory function. Particularly, the questions of laterality and affective component in coding of odors in the OF cortex remain controversial.

Aims: This study explored whether cortical electrical stimulation of the OF and mesiotemporal brain can trigger olfactory hallucinations with special focus on olfactory percepts in terms of laterality and hedonics.

Materials and methods: Eight patients with temporal lobe epilepsy participated in the study, at the time of invasive exploration of their epilepsy. The most distal contact of the OF and anterior hippocampus depth electrodes were stimulated (50 Hz, 0.2 ms biphasic pulse; maximal stimulation 4 mA). Patients were instructed to report any kind of sensation they might experience. Intracranial depth electrodes were localized (iElectrodes): subject-specific brain mask, subcortical segmentation and cortical parcellation based on the Destrieux atlas (FreeSurfer) were superposed to the coregistered T1-weighted MRI and CT images (SPM). The center of mass of each electrode-artifact cluster determined the electrode localization. The electrode labeling was done in patient space. To obtain the electrode coordinates in Montreal Neurological Institute (MNI) space, the images obtained previously in the patient space were first segmented and normalized (SPM). Then, the localization procedure (iElectrodes) was run again with these new normalized images in MNI space.

Results: No hallucination was evoked by stimulation, neither of the right nor the left hippocampus (8/8 patients). Pleasant olfactory hallucinations were evoked by OF stimulation in 5/8 patients in either hemisphere. Patients named the percept as the smell of lemon or coffee for example. Among those 5 patients, electrodes were localized in the cortex of the olfactory sulcus, medial orbital sulcus or medial OF gyrus. Increasing stimulation amplitude changed the olfactory percept identification in 3 out of those 5 patients. No affective judgement or change in perceived odor intensity was reported by the patients. No hallucination was evoked by the stimulation of the white matter of the medial OF brain in 3/8 patients independently of the hemisphere stimulated.

Conclusions: This study demonstrated that stimulation of the cortex of the medial OF brain and not of its white matter elicits specific pleasant olfactory hallucinations independently of the hemisphere stimulated, supporting one symmetrical olfactory processing in human.

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1. Introduction

Divergent determinations of brain areas of the primary or secondary olfactory cortices are found in the literature. It is generally accepted that the piriform cortex and the amygdala are part of the primary olfactory cortex and that the secondary olfactory cortex
includes the orbitofrontal cortex (OFC) [1]. The OFC, on which the present study has been focused, receives fibers from the primary areas [2] and is also most commonly subdivided into its medial and lateral parts [3].

Previous studies highlight the critical role of the olfactory bulb, the pole of the temporal lobe and the OFC in olfactory functions [4–7]. Lesions in these areas are frequently observed in hyposmic or anosmic patients, i.e. patients with respectively reduced smell perceptions or complete loss of smell. Those patients had smaller activation of the primary and secondary olfactory areas in response to odors than patients with normal olfaction [4]. It was reported that most severe olfactory losses are associated with olfactory bulb and temporal lobe damages bilaterally. Only a single study focused on the differences in the location of lesions in anosmic, phantomastic, or parosmic (distorted smell perception) patients, who showed more frequently lesions of the right olfactory bulb, of the left frontal lobe, or of the right lateral or medial OFC, respectively [5]. Damage to the OFC is associated with odor identification and discrimination deficits [8–13].

Functional neuroimaging studies of olfactory processing have analyzed brain activations with regard to presentation of pleasant or unpleasant olfactory stimuli (also named as “negatively or positively valenced” by Anderson et al. [14], or as “negative or positive hedonic valued” by Rolls et al. [15]). Whether with positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), inconsistent or contradictory results about the brain laterality of valence of odors were found. Focusing on the OFC activation, right OFC activation was found for pleasant odors [14,16,17] and left OFC activation for unpleasant odors [14,15,18]. No functional laterality was reported by others [19–21]. In terms of subregions of the OFC, pleasant smells were shown to activate the medial OFC, while unpleasant smells were shown to activate the lateral OFC [14,15,21,22]. In the study of Nigri et al. [20], results suggested that lateral OFC relays unpleasant olfactory perceptions to the medial OFC, where olfactory stimuli are integrated and processed, on either hemisphere (note that no pleasant odor was tested). Odor identification tasks were shown to activate the OFC [12,23]. Another important dimension of odor is its intensity, which was observed to be not associated with OFC but associated with amygdala [14] or pyriform and entorhinal cortex [15] activities.

Eliciting olfactory perceptions with direct electrical stimulation of olfactory relevant structures has been done only very rarely. Penfield and Jasper [24] were the first to briefly describe that unpleasant smell were elicited by intraoperative electrical stimulation of the olfactory bulb in epileptic patients. Only a handful of observations have since then been reported. Three other cases of olfactory hallucinations and one “ill-defined smell” were vaguely reported by Munari and Bancaud [25] and by Smith et al. [26] by stimulation of the posterior OF using depth electrodes. Kumar et al. [27] in a more recent study induced unpleasant olfactory hallucinations by stimulating sites associated with the olfactory bulb or tract in children via subdural electrodes.

Finally it emerges from the literature that no general agreement is yet established about laterality and hedonic olfactory processing of the OFC. We report here a series of eight patients where deep OF stimulation at various positions were done and olfactory symptoms could be gathered and compared to the electrode location.

2. Materials and methods

2.1. Patients

Eight patients participated to the study within the context of the invasive exploration of their temporal lobe epilepsy performed because of conflicting scalp clinical, EEG and radiological data (Table 1). Depth electrodes were positioned based on clinical and radiological evidence and previous scalp EEG. Patients were instructed to freely report any kind of sensations they might feel. This work was conducted according to the recommended ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospitals of Geneva (CER 14-076). Individually signed consent of patients was collected.

2.2. Intracerebral electrodes and electrical stimulation

Stereo tactic depth electrodes (Spencer probe depth electrodes, Ad-Tech, Racine, USA) were used and implanted using a stereotactic headframe (Leksell coordinate frame G, Elekta, Sweden) that was affixed to the patients’ skull with pins and the corresponding Leksell stereotactic arc. The stereotactic coordinates and angles of the targets and trajectories were planned and calculated on a high-resolution 3D T1-weighted MRI fused on a stereotactic CT, using BRAINLAB iPlan 3.0 Stereotaxy.

Stimulation was applied on the depth electrodes in the OF brain and hippocampus. Only the most distal contact of the electrode shaft was stimulated. Stimulation was biphasic charge balanced pulses, 60 μs/phase, delivered at a frequency of 50 Hz (NimEclipse system, Medtronic, Minneapolis, MN, USA). The stimulation was monopolar, using one surface skin electrode as the return electrode (Neuronile ground, Ambu, Ballerup, Denmark). Stimulation amplitude was increased progressively up to a maximum of 4.0 mA.

3. MRI and CT data acquisition

Patients were scanned in a Siemens 1.5 T Magnetom Aera (patient S0), 3.0 T Magnetom Prisma (patients S2–3, S6–7) (Siemens, Erlangen, Germany), or in a Philips Ingenia (patients S1, S4–5) (Philips, Amsterdam, Netherlands) prior to electrode implantation. High-resolution 3D, T1-weighted MRI MP2RAGE or TFE were performed with approximately 1 mm³ resolution and slice thickness about 1 mm.

Postoperative CT images were acquired with a Siemens Somatom Definition Flash (patients S0, S5–6), Somatom Force (patient S7) or with a GE Healthcare Light Speed VCT (patient S1), Discovery CT750HD (patient S2) (GE Healthcare, Chicago, USA). Slice thickness was 1 mm for all patients except patients S2 and S3, whose slice thicknesses were 2.5 mm and 1.5 mm, respectively.

3.1. Electrode localization

Intracranial depth electrodes were localized and labeled using validated freely available software (Fig. 1). First the preoperative T1-weighted DICOM MRI images were automatically processed in order to obtain a subject-specific reliable ribbon brain mask, pial surfaces, a subcortical segmentation and cortical parcellation based on the Destriex atlas [28] (FreeSurfer v6.0 Software Suite [29]; http://surfer.nmr.mgh.harvard.edu; NIfTI format). Secondly, the postoperative CT images were co-registered onto the preoperative MRI images (SPM12, v6906 software; http://www.fil.ion.ucl.ac.uk/spm; NIfTI format). Once these pre-processing steps were done, the brain mask, pial surfaces, subcortical segmentation and cortical parcellation were superposed to the coregistered MRI and CT images (iElectrodes_v1.010 toolbox [30]; https://sourceforge.net/projects/ielectrodes). The center of mass of each electrode-artifact cluster determined the depth-electrode localization within a precision of 0.56 mm [30]. Electrodes were automatically labeled using the Destrieux atlas information. Note that the
Destrieux atlas marks as gyrus, only the cortex visible on the pial view, and as sulcus, the hidden cortex, i.e. the banks of sulci [31]. To obtain the electrode coordinates in the Montreal Neurological Institute (MNI) space, segmentation and normalization procedures (SPM12) were first applied to the images obtained previously in the patient space (MRI, coregistered MRI and CT, brain mask, subcortical segmentation and cortical parcellation). Then, the localization procedure (iElectrodes) was run again with these new normalized images in MNI space.

### 4. Results

The occurrence of olfactory hallucinations with thresholds of stimulation at which olfactory hallucinations were perceived and the localization of the stimulated electrodes are summarized in Tables 2–4.

### Table 1

Characteristics of patients who participated to the study. F: female; M: male; L.: left; R.: Right; hipp.: hippocampus.

| Patients | Age at surgery/Gender | Seizure type | Cerebral abnormality | Seizure onset zone (iEEG) | Aura |
|----------|-----------------------|--------------|----------------------|---------------------------|------|
| S0       | 42/F                  | Focal to bilateral tonic-clonic | L. hipp. sclerosis | L. hipp. | None |
| S1       | 28/F                  | Focal impaired awareness | L. frontal dysplasia | L. frontal | None |
| S2       | 54/F                  | Focal impaired awareness | R. amygdala dysplasia | R. amygdala | None |
| S3       | 22/M                  | Focal to bilateral tonic-clonic | None | L. mesial structures | Epigastric |
| S4       | 32/M                  | Focal to bilateral tonic-clonic | None | L. mesial structures | None |
| S5       | 19/F                  | Focal to bilateral tonic-clonic | None | Bilateral mesial structures | None |
| S6       | 35/F                  | Focal to bilateral tonic-clonic | None | L. mesial structures | None |
| S7       | 50/M                  | Focal to bilateral tonic-clonic | R. hipp. sclerosis | Bilateral mesial structures | Olfactory |

None of the 8 patients reported any perception of smell elicited by stimulation of the anterior hippocampus of either hemisphere (Table 2).

For OF stimulations, 5/8 patients perceived a pleasant smell, such as food or plant, whatever was the hemisphere (Tables 3). Electrodes were localized in the cortex of the olfactory sulcus (S0, S1, S6), medial orbital sulcus (S2), or medial OF gyrus (S4). The intensity of stimulation eliciting an olfactory hallucination was in the range of 0.5–3.5 mA. For patient S0, the amplitude of stimulation was not available. Three of these 5 patients (S1, S2 and S6) perceived different olfactory hallucinations in function of stimulus intensity. No hallucination was perceived in 3/8 patients (S3, S5 and S7) neither of the right nor of the left hemisphere (Table 4). Electrodes were localized in the white matter of the olfactory sulcus (S3), medial orbital sulcus (S5), or medial OF gyrus (S7). The amplitude of stimulation was increased gradually up to a

### Table 2

Description of patients’ anterior hippocampus electrode stimulations and hallucinations. L: left; R: Right. NA: Not available.

| Anterior hippocampus electrodes | Laterality | Stimulation amplitude (mA) | Olfactory hallucinations | Others hallucinations |
|--------------------------------|------------|-----------------------------|--------------------------|-----------------------|
| S0                             | R          | NA                          | None                     | None                  |
| S1                             | L          | 2.0                         | None                     | None                  |
| S2                             | R          | 2.5                         | None                     | None                  |
| S3                             | R          | 2.1                         | None                     | Feels like vomiting   |
| S4                             | L          | 3.0                         | None                     | None                  |
| S5                             | L          | 4.0                         | None                     | None                  |
| S6                             | L          | 1.0                         | None                     | None                  |
| S7                             | R          | 2.6                         | None                     | None                  |
maximum of 2.1 mA, 2.6 mA and 4.0 mA for patient S3, S7, and S5 respectively. Higher values could not be tested for patients S3 and S7 due to sick feeling and feeling of oppression, respectively.

The regions of interest found for olfactory hallucinations are summarized and schematized in Fig. 2. The localization of the contacts stimulated in all patients can be visualized in Fig. 3.

5. Discussion

The main findings of our study are that we could elicit olfactory perceptions with deep medial OFC stimulation at the various sites that were exclusively pleasant and not lateralized in terms of OFC side. No olfactory hallucination was induced either with OF white matter stimulation nor with hippocampal stimulation.

Indeed, all medial OFC stimulations were associated with pleasant hallucinations, which is in agreement with previous findings of fMRI studies [14,15,21,22]. Electrode localizations assigned with pleasant hallucinations were either in the cortex of the olfactory sulcus, medial orbital sulcus, or medial OF gyrus. In this study no unpleasant hallucination was reported. This is also in agreement with the fact that unpleasantness would be associated with lateral left OFC [14,15], which we did not stimulated. The present observation of pleasantness evoked by OFC stimulation does not dispute the suggestion of Nigri et al. [20] that the medial OFC is involved in integrative olfactory processing even if they tested only unpleasant odors. A very recent fMRI paper comparing patients with olfactory impairment with versus without parosmia, a condition where unpleasant odorous percepts are elicited by normal odors, showed that parosmia patients had higher activations in the putamen and thalamus but not in the OFC [33]. This goes in line with the present data that the OFC is probably not the main generator of unpleasant olfactory symptoms.

Secondly, in terms of laterality, this study comforts that the OFC does not present laterality of the positive hedonic value of olfaction, as already reported [15,19–21]. Pleasant olfactory hallucinations were elicited by stimulation of sites in the medial OFC independently of the hemisphere stimulated. No unpleasant odor
perception was elicited, even by stimulation of the left medial OFC. The laterality of stimulation was not correlated to the laterality of seizure onset both in the group with responses to stimulation and absence of response.

Stimulation of the white matter of the OF brain did not elicit any olfactory hallucination. This observation suggests that the white matter stimulation would be too diffuse or rough to be interpreted by OF connected cortices and consequently to induce any hallucination, similarly to speech arrest due to disruption of natural speech processing with stimulation of white matter [34].

No patients suffered from olfactory aura except patient S7. It is to be noted that patient S3 suffered from epigastric aura explaining its nausea sensation.

The present study could suggest that odor perception might change with stimulus intensity of the OFC electrode stimulation. For example, the first olfactory hallucination perceived by patient S1 was a smell of coffee. The odor of coffee was not interpreted as more intense with higher stimulation but was associated with another olfactory hallucination: a smell of lemon. Thus, the interpretation of the hallucination could be related with the intensity of the stimulation but not with the intensity of the hallucination in itself, in agreement with Anderson et al. [14] and Rolls et al. [15], who claimed that odor intensity was not associated with OFC activity.

The accuracy of the electrode localization achieved by the semi-automatic workflow applied here was expected to be of 0.56 mm in comparison to the manual localization method [30]. This gold standard manual method is dependent on the experience of neuroradiologists. Recent semi-automatic imaging techniques available now allow to obtain an accurate and reproducible localization, independently of the user expertise.

The precise localization of the stimulated electrodes allowed extending the actual knowledge by demonstrating evidence that stimulation of the cortex of the medial OF brain and not of its white matter elicit pleasant olfactory hallucinations.

Fig. 3. Stimulated contacts in all patients. The localization of the contacts of the orbitofrontal (OF) electrode stimulated in all patients is displayed on a T1-weighted MRI template in MNI space provided by SPM12. The contacts that evoked pleasant olfactory hallucinations are indicated by green dots or crosses, and those which did not elicit any hallucination are indicated by red dots or crosses.
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This is to certify that the above-named is the author of the manuscript and that we have neither conflicts of interest nor ethical conflict.

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