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Olfactory hallucinations elicited by electrical stimulation via subdural electrodes: Effects of direct stimulation of olfactory bulb and tract

Gogi Kumar^{1,2}, Csaba Juhasz^{1,2}, Sandeep Sood³, and Eishi Asano^{1,2,*}

¹Department of Pediatrics, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

²Department of Neurology, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

³Department of Neurosurgery, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

Abstract

In 1954, Penfield and Jasper briefly described that percepts of unpleasant odor were elicited by intraoperative electrical stimulation of the olfactory bulb in patients with epilepsy. Since then, few peer-reviewed studies have reported such phenomena elicited by stimulation mapping via subdural electrodes implanted on the ventral surface of frontal lobe. Here, we determined what types of olfactory hallucinations could be reproduced by such stimulation in children with focal epilepsy. This study included 16 children (age range: 5 to 17 years), who underwent implantation of subdural electrodes to localize the presumed epileptogenic zone and eloquent areas. Pairs of electrodes were electrically stimulated and clinical responses were observed. In case a patient reported a perception, she/he was asked to describe its nature. We also described the stimulus parameters to elicit a given symptom. Eleven patients reported a perception of smell in response to electrical stimulation while the remaining five did not. Nine patients perceived an unpleasant smell (like bitterness, smoke, or garbage), while two perceived a pleasant smell (like strawberry or good food). Such olfactory hallucinations were induced by stimulation proximal to the olfactory bulb or tract on either hemisphere but not by that of orbitofrontal gyri lateral to the medial orbital sulci. The range of stimulus parameters employed to elicit olfactory hallucinations was comparable to those for other sensorimotor symptoms. Our systematic study of epileptic children replicated stimulation-induced olfactory hallucinations. We failed to provide evidence that a positive olfactory perception could be elicited by conventional stimulation of secondary olfactory cortex alone.

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*Corresponding Author: Eishi Asano, MD, PhD, MS (CRDSA), Address: Division of Pediatric Neurology, Children's Hospital of Michigan, Wayne State University., 3901 Beaubien St., Detroit, MI, 48201, USA., Phone: 313-745-5547; FAX: 313-745-0955; eishi@pet.wayne.edu.

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Keywords

Pediatric epilepsy surgery; Intracranial electrodes; Electrical stimulation; Functional cortical mapping; Odor; Smell; Orbitofrontal gyrus; Perception; Stimulus parameters; Presurgical evaluation

INTRODUCTION

The ability to perceive odors is important for our life. Smell of smoke, for example, helps us in detecting potential dangers in the environment. Studies of human anatomy and the effect of lesioning have suggested that the primary olfactory system includes the olfactory bulb and tract located on the ventral surface of frontal lobe, as well as the piriform cortex, amygdala and uncus in the anterior-medial temporal lobe [1,2]. Damage involving the primary olfactory system can result in complete or partial loss of odor perception (i.e.: anosmia or hyposmia) [2–4]. The orbitofrontal cortex is considered to be a part of the secondary olfactory cortex [5,6]; damage involving the orbitofrontal cortex can result in deficits in discriminating odor quality or impaired odor memory [7,8].

In 1954, Penfield and Jasper briefly described that intraoperative electrical stimulation of the olfactory bulb elicited transient perception of unpleasant smell (e.g.: burning rubber, stench or manure) in patients with epilepsy [9]; however, patient profile, sample size or stimulus parameters were not reported in detail. Since then, few peer-reviewed studies have reported such phenomena elicited by stimulation mapping via subdural electrodes implanted on the ventral surface of frontal lobe. Conversely, several studies using intracranial depth electrodes reported rare observations of olfactory hallucinations (e.g.: smells like burned wood or something to do with animals) elicited by stimulation of the anterior-medial temporal lobe [10–12]. In the present study, we determined whether and what types of olfactory hallucinations could be reproduced by electrical stimulation via subdural electrodes implanted on the ventral surface of frontal lobes. We also described the stimulus parameters and sites to elicit a given symptom and compared the stimulus intensity eliciting olfactory hallucinations to those eliciting other sensorimotor symptoms.

METHODS

Patients

This study has been approved by the Institutional Review Board at Wayne State University. Written informed consent was obtained by the guardian of each patient. The inclusion criteria consisted of: (i) patients with a history of focal epilepsy who underwent extraoperative subdural electrocorticography (ECoG) recording as a part of presurgical evaluation in Children's Hospital of Michigan in Detroit between 2007 and 2011; (ii) functional cortical mapping via direct cortical stimulation via subdural electrodes implanted on the ventral surface of frontal lobe; (iii) capability to verbally report percepts elicited by electrical stimulation. The exclusion criteria consisted of a documented history of anosmia or hyposmia. This case-series study included a consecutive series of 16 children who satisfied the aforementioned criteria (12 males; age range: 5–17 years; median age: 13 years) (Table 1).

Subdural electrode placement and video-ECoG recording

For extraoperative ECoG recording, platinum grid electrodes (10 mm intercontact distance, 4 mm diameter) were surgically implanted (Figure 1) [13]. All electrode plates were stitched to adjacent plates and/or the edge of dura mater, to avoid movement of subdural electrodes after placement. In addition, intraoperative pictures were taken with a digital camera before

dural closure, to confirm the spatial accuracy of electrode display on the three-dimensional brain surface reconstructed from MRI [14,15]. Chronic subdural ECoG recordings were performed for 2–5 days, and anti-epileptic medications were discontinued or reduced until a sufficient number of habitual seizures were captured. Seizure-onset zones were visually determined (Table 1) [13].

Coregistration of subdural electrodes to the individual three-dimensional MRI

MRI including a T1-weighted spoiled gradient echo image as well as fluid-attenuated inversion recovery image was preoperatively obtained [16]. Planar x-ray images (lateral and anteroposterior) were acquired with the subdural electrodes in place for electrode localization on the brain surface [14, 17–19]; three metallic fiducial markers were placed at anatomically well-defined locations on the patient's head for co-registration of the x-ray image with the MRI. A three-dimensional surface image was created with the location of electrodes directly defined on the brain surface [16,17,19]. The accuracy of this procedure was reported previously as 1.2 ± 0.7 mm with a maximal misregistration of 2.7 mm [17], and was confirmed by intraoperative digital photographs of lateral surface showing in situ locations of the subdural electrodes [14,20,21].

Electrical stimulation protocol

As a component of the clinical management of patients with epilepsy, functional cortical mapping with electrical stimulation was performed using a method similar to those described previously [22–26]. To minimize the risk of stimulation-induced seizures, a loading dose of phenytoin (20 mg/kg) was intravenously administered prior to the mapping session. To minimize the risk of feeling scared or overwhelmed, each patient was informed prior to the stimulation study that she/he might have a transient sensorimotor, auditory, visual, olfactory, gustatory, or language symptom. Each patient was aware of the timing of each stimulation trial but unaware of the location of stimulated sites. A train of repetitive electrical stimuli was delivered to a pair of subdural electrodes using the Grass stimulator (Astro-Med, Inc, West Warwick, RI), and clinical symptoms elicited by stimulation were observed by at least two investigators.

The stimulus frequency was 50 Hz, the pulse duration was 300 μ sec, and the train duration ranged up to 5 sec. To minimize the risk of charge accumulation in the patient's body, biphasic stimulus pulses were used. To determine the presence of after-discharges, video-ECoG was recorded continuously during the entire mapping session. When a clinical symptom was elicited, the train of stimuli was immediately terminated. Stimulus intensity was initially set to 3 mA and was increased to 6 and 9 mA in a stepwise manner until a clinical symptom or after-discharge was observed. Once the after-discharge threshold was determined, stimulus intensity above that threshold was no longer utilized. Sites at which stimulation consistently (at least twice) elicited a clinical symptom were classified as eloquent areas specific to a given symptom. Sites were declared 'not proven to be eloquent' if after-discharges were elicited without a symptom, or a symptom failed to be elicited by maximal stimuli. When both clinical symptom and after-discharges were noted, another train of stimuli with the same or 1 mA smaller intensity was given until either clinical symptom or after-discharges subsided.

RESULTS

The results are summarized in Table 1, Figures 1 and 2. Eleven patients reported a perception of smell in response to electrical stimulation. Nine of the eleven patients perceived a bad or unpleasant smell (like bitterness, smoke, or garbage). The remaining two patients perceived a pleasant smell (like strawberry or good food). A total of 18 out of 22

trials (82%) elicited an olfactory hallucination, when stimulation involved areas medial to the medial orbital sulci (Figure 1). As presented in Table 1, the stimulus intensities employed to elicit olfactory hallucinations ranged 3 to 6 mA. This range was comparable to those for other sensorimotor symptoms in the majority of study patients.

Conversely, none of 39 trials elicited an olfactory hallucination, when stimulation involved areas lateral to the medial orbital sulci alone. The Fisher exact probability test revealed that the probability of a trial eliciting an electrically-induced olfactory hallucination was greater when stimulation involved areas medial to the medial orbital sulci ($p < 0.0001$). In other words, olfactory hallucinations were induced by stimulation proximal to the olfactory bulbs or tracts on either hemisphere but not by that of orbitofrontal gyri lateral to the medial orbital sulci, the structures considered to be a part of the secondary olfactory cortex. Two patients (patients #4 and #9) had seizure onset zones involving the orbitofrontal cortex; neither patient had olfactory aura preceding complex partial seizures.

A total of five patients failed to report any olfactory hallucinations elicited by stimulation (Table 1). In two patients (patients #4 and #16), stimulation did not involve areas medial to the medial orbital sulci. In the remaining three patients (patients #3, #13 and #14), stimulation involved areas immediately medial to the medial orbital sulcus and lateral to the olfactory sulcus.

DISCUSSION

We were able to reproduce olfactory hallucinations elicited by electrical stimulation proximal to the olfactory bulb or tract on either hemisphere (Figure 2). Taking into account the size of subdural electrodes as well as the inherent spread of the stimulus current [27], the positive perception of odors can be explained by the effects of direct stimulation of olfactory bulb or tract. Unlike the previous study of intraoperative stimulation [9], we were able to study children as young as 5 years old and provided the exact stimulus parameters. We found that the range of stimulus parameters employed to elicit olfactory hallucinations was within those for other sensorimotor symptoms. We don't know why the perceived smells in the majority of patients were of unpleasant nature. This could be attributed to the notion that mammalian olfaction is so highly conserved that a predominantly aversive response is built in as a protective reflex to improve the survival [28]. The stimulus parameters could be associated with the unpleasant nature of olfactory hallucinations. In the present study, we used macro-electrodes, which are designed to stimulate a large number of neural cells and fibers. Stimulation using micro-electrodes with very low stimulus intensity might be able to stimulate odor-specific cells or fibers.

When stimulation involved sites lateral to the medial orbital sulci alone, none of 39 stimulation trials elicited an olfactory hallucination. In other words, we failed to elicit positive perception of odors by stimulation of the secondary olfactory cortex alone. This finding does not indicate the lack of olfactory functions in that structure, partly because patients were not assigned an olfactory task during stimulation trials. The present study is not designed to localize the sites of which stimulation causes failure to conduct a given task. A previous study of monkeys using single-neuron recording from the orbitofrontal cortex reported that a small subset of neurons responded to odors, with some differentially responding to different odors [29]. A study of healthy adults using positron emission tomography reported that the orbitofrontal cortices were activated by an odor memory recognition task [30]. Further studies using olfactory tasks involving discrimination or memory of distinctive odors during stimulation trials are warranted to determine the functions of the orbitofrontal cortex. A number of recent studies have indicated that humans have an extraordinary sense of smell [31]. Behavioral studies, for example, reported that

healthy adults detected the scent of fear in human sweat more accurately than chance [32,33].

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Figure 1. Olfactory hallucinations elicited by electrical stimulation in two patients

(A) In patient #5, a 1×6 strip electrode was implanted on the ventral surface of the right frontal lobe. Stimulation of a pair denoted by a red bar (but not pairs denoted by black bars) elicited an olfactory hallucination. (B and C) In patient #12, a 2×5 strip electrode was implanted on the ventral surface of the left frontal lobe. A 1×8 strip electrode was implanted on the medial surface of the left frontal lobe; the anterior end of this electrode was located on the gyrus rectus on the left side. Stimulation of pairs denoted by red bars (but not pairs denoted by black bars) elicited an olfactory hallucination. Circles: electrode sites. Line: medial orbital sulcus. Dotted line: olfactory sulcus where the olfactory tract is located. Broken line: midline.

Figure 2. Summary of electrical stimulation mapping

Circles: electrode sites. Red bars: sites of which stimulation elicited an unpleasant smell. Blue bars: sites of which stimulation elicited a pleasant smell. Black bars: sites of which stimulation failed to elicit an olfactory hallucination. Dotted lines: olfactory sulci where the olfactory tracts lie in. The medial surface of gyrus rectus is not shown. Patient #12 had a single electrode located on the medial surface of gyrus rectus, as presented in Figure 1.

Table 1

Summary

Patient number	Age at surgery (years)	Gender	Medications at the time of surgery	Placement of subdural electrodes	Surgical resection	Pathology	Olfactory symptom elicited by stimulation of the ventral surface of frontal lobe (stimulus intensity)	Motor symptom elicited by stimulation of the Rolandic area (stimulus intensity)	Somatosensory symptom elicited by stimulation of the Rolandic area (stimulus intensity)	Visual symptom elicited by stimulation of the occipital lobe (stimulus intensity)	Auditory or language symptom elicited by stimulation of the temporal and frontal lobes (stimulus intensity)
#1	5	Male	OXC; VPA; LEV	Lt FTPO	Lt F	Cortical dysplasia	Bad smell (6 mA)	Hand twitching (6 mA)	Mouth tingling (6 mA)	Eye deviation without reporting a visual perception (6 mA)	Receptive aphasia (6 mA)
#2	8	Male	OXC	Lt FTPO	Lt T	Tumor	Garbage like bad smell (4 mA)	Mouth twitching (3 mA); Hand twitching (3 mA); Leg twitching (3 mA)	Mouth tingling (3 mA); Hand tingling (3 mA)	Phosphene (3 mA)	Receptive aphasia (4 mA); Expressive aphasia (4 mA)
#3	8	Male	CBZ; LCM	Rt FTPO	Rt FT	Cortical dysplasia	Not reported (6 mA)	Mouth twitching (6 mA); Hand twitching (3 or 6 mA); Leg twitching (3 mA)	Not reported (6 mA)	Eye deviation without reporting a visual perception (6 mA)	Not reported (6 mA)
#4	9	Female	VPA; VGB	Lt FTPO	Lt F	Cortical tubers	Not reported (9 mA)	Mouth twitching (9 mA); Hand twitching (9 mA); Leg twitching (9 mA)	Mouth tingling (6 or 9 mA)	Phosphene (9 mA)	Expressive aphasia (9 mA)
#5	10	Male	VPA; LCM	Rt FTPO	Rt PT	Cortical dysplasia	Bad smell (3 mA)	Hand twitching (3 or 6 mA); Leg twitching (3 mA)	Hand tingling (3 mA); Leg tingling (3 mA)	Phosphene (6 mA)	Not reported (6 mA)

Epilepsy Behav. Author manuscript; available in PMC 2013 June 01.

Patient number	Age at surgery (years)	Gender	Medications at the time of surgery	Placement of subdural electrodes	Surgical resection	Pathology	Olfactory symptom elicited by stimulation of the ventral surface of frontal lobe (stimulus intensity)	Motor symptom elicited by stimulation of the Rolandic area (stimulus intensity)	Somatosensory symptom elicited by stimulation of the Rolandic area (stimulus intensity)	Visual symptom elicited by stimulation of the occipital lobe (stimulus intensity)	Auditory or language symptom elicited by stimulation of the temporal and frontal lobes (stimulus intensity)
#6	10	Male	OXC	Rt FTPO	MSTs on Rt FP	Arachnoid cyst	Smells like smoke (3 mA)	twitching (3 mA) Mouth twitching (6 mA); Hand twitching (3 or 6 mA)	Mouth tingling (3 or 6 mA); Hand tingling (6 mA)	Phosphene (3 mA)	Not reported (6 mA)
#7	11	Female	OXC; LEV	Rt FTPO	Rt FT	Cortical dysplasia	Smells like sweet strawberries (6 mA)	Hand twitching (3 mA); Leg twitching (6 mA)	Mouth tingling (6 mA); Hand tingling (3 mA)	Phosphene (6 mA)	Hearing sounds (6 mA)
#8	12	Male	VPA; LEV	Lt FTPO	Lt T	Gliosis	Smelling of smoke (3 mA)	Hand twitching (6 mA); Eye deviation (6 mA)	Mouth tingling (6 mA); Hand tingling (3 or 6 mA)	Phosphene (3 mA)	Receptive aphasia (6 mA)
#9	14	Male	OXC; PHT	Lt FTP; Rt FTPO	Rt T	Gliosis	Bad smell (3 mA)	Mouth twitching (6 mA); Hand twitching (3 or 6 mA); Eye deviation (6 mA)	Mouth tingling (6 or 9 mA)	Phosphene (6 mA)	Expressive aphasia (6 mA)
#10	14	Female	OXC	Lt FTPO	Lt T	Gliosis	Bad smell (6 mA)	Mouth twitching (6 mA); Hand twitching (3 or 6 mA); Eye deviation (6 mA)	Mouth tingling (6 mA)	Phosphene (3 mA)	Hearing sounds (6 mA); Receptive aphasia (6 mA); Expressive aphasia (6 mA)

Patient number	Age at surgery (years)	Gender	Medications at the time of surgery	Placement of subdural electrodes	Surgical resection	Pathology	Olfactory symptom elicited by stimulation of the ventral surface of frontal lobe (stimulus intensity)	Motor symptom elicited by stimulation of the Rolandic area (stimulus intensity)	Somatosensory symptom elicited by stimulation of the Rolandic area (stimulus intensity)	Visual symptom elicited by stimulation of the occipital lobe (stimulus intensity)	Auditory or language symptom elicited by stimulation of the temporal and frontal lobes (stimulus intensity)
#11	14	Female	OXC; TPM	Lt FTPO	Lt T	Tumor	Smells like good food (6 mA)	Mouth twitching (3 mA); Hand twitching (3 mA)	Mouth tingling (3 mA); Hand tingling (3 or 6 mA)	Phosphene (6 mA)	Hearing sounds (6 mA); Receptive aphasia (6 mA); Expressive aphasia (3 or 6 mA)
#12	14	Male	OXC; LEV	Lt FTP	Lt F	Gliosis	Bad smell (6 mA)	Mouth twitching (6 mA); Hand twitching (3 mA)	Mouth tingling (6 mA); Hand tingling (3 mA)	Not stimulated	Receptive aphasia (6 mA); Expressive aphasia (6 mA)
#13	15	Male	LTG; LEV	Lt FTP	Lt T	Tumor	Not reported (6 mA)	Mouth twitching (3 mA)	Not reported (6 mA)	Not stimulated	Hearing sounds (3 mA); Receptive aphasia (3 mA); Expressive aphasia (3 mA)
#14	15	Male	VPA	Lt FTPO	Lt T	Gliosis, Hippocampal sclerosis	Not reported (6 mA)	Mouth twitch (3 mA); Eye deviation (6 mA)	Mouth tingling (3 mA)	Phosphene (3 mA)	Receptive aphasia (3mA); Expressive aphasia (3mA)
#15	17	Male	OXC; LEV	Lt FTPO	Lt T	Cortical dysplasia	Unpleasant, bitter smelling (3 mA)	Mouth twitching (3 mA); Hand twitching (3 mA); Eye deviation (6 mA)	Not reported (6 mA)	Phosphene (3 mA)	Hearing sounds (6 mA); Receptive aphasia (6 mA); Expressive aphasia (6 mA)

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Patient number	Age at surgery (years)	Gender	Medications at the time of surgery	Placement of subdural electrodes	Surgical resection	Pathology	Olfactory symptom elicited by stimulation of the ventral surface of frontal lobe (stimulus intensity)	Motor symptom elicited by stimulation of the Rolandic area (stimulus intensity)	Somatosensory symptom elicited by stimulation of the Rolandic area (stimulus intensity)	Visual symptom elicited by stimulation of the occipital lobe (stimulus intensity)	Auditory or language symptom elicited by stimulation of the temporal and frontal lobes (stimulus intensity)
#16	17	Male	OXC; LTG	Lt FTPO	Lt F	Gliosis	Not reported (6 mA)	Hand twitching (3 mA); Leg twitching (3 mA)	Mouth tingling (3 mA); Leg tingling (3 mA)	Not reported (6 mA)	Expressive aphasia (3 mA)

LEV: Levetiracetam. LTG: Lamotrigine. LCM: Lacosamide. CBZ: Carbamazepine. OXC: Oxcarbazepine. TPM: Topiramate. VPA: Valproate. VGB: Vigabatrin. Lt: Left. Rt: Right. F: Frontal. T: Temporal. O: Occipital. P: Parietal. MSTs: Multiple subpial transactions.