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Intracranial Investigation of Piriform Cortex Epilepsy During Odor Presentation

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Abstract

The piriform cortex (PC) is part of the olfactory system, principally receiving input from the lateral olfactory tract and projecting to downstream components of the olfactory network, including the amygdala. Based on preclinical studies, PC is vulnerable to injury and can be easily kindled as an onset site for seizures. While the role of PC in human epilepsy has been studied indirectly and the subject of speculation, cases of demonstrated PC seizure onset from direct intracranial recording are rare. We present a pediatric patient with drug-resistant focal reflex epilepsy and right mesial temporal sclerosis with habitual seizures triggered by coconut aroma. The patient underwent stereoelectroencephalography with implantation of olfactory cortices including PC, through which we identified PC seizure onset, mapped high frequency activity associated with presentation of olfactory stimuli and performance on cognitive tasks, and reproduced habitual seizures via cortical stimulation of PC. Coconut odor did not trigger seizures in our work with the patient. Surgical workup resulted in resection of the patient's right amygdala, PC, and mesial temporal pole, following which she has been seizure free for 20 months

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Ethics Approval: This study was performed in line with the principles of the Declaration of Helsinki.

Consent to Participate: Verbal and written informed consent were obtained from the patient and parents.

Consent to Publish: The authors affirm that our research participant provided informed consent for publication of the images in Figures 1 and 2.

without functional decline in cognition or smell. Histological findings from resected tissue showed astrogliosis and subpial gliosis.

Keywords

piriform cortex; stereoelectroencephalography; high frequency activity; epilepsy surgery; focal epilepsy; olfaction

1. Introduction

The human piriform cortex (PC) is a phylogenetically ancient three-layered allocortex (Vaughan and Jackson 2014) and divided into frontal and temporal subregions (Lane et al. 2020). The PC is a key component of the olfactory system (Gottfried and Zald 2005) receiving input from the olfactory bulb and anterior olfactory nucleus, with principal efferent connections to the lateral amygdala nucleus, entorhinal cortex, orbitofrontal cortex, and mediodorsal nucleus of the thalamus (Gottfried and Zald 2005; Ray and Price 1993; Zhou et al. 2019) and is involved in feedforward and feedback inhibitory processes (Suzuki and Bekkers 2012).

Piriform cortex is vulnerable to excitotoxic injury and can be a seizure onset site in preclinical models. In humans, vulnerability of PC is seen in the context of status epilepticus (Vaughan and Jackson 2014). Olfactory dysfunction in medial temporal lobe epilepsy is suggestive of injury to olfactory networks and highlights the effect of mesial temporal lobe (MTL) structures, especially the amygdala, and its impact and connectivity to the piriform area and olfactory cortices (Vaughan and Jackson 2014), which may also account for some olfactory auras (Chen et al. 2003; Taşcı et al. 2021). Temporal lobectomy and amygdalectomy are used to treat drug-resistant MTL epilepsy (Hamasaki et al. 2014) and likelihood of seizure freedom increases when PC is included (Borger et al. 2020; Galovic et al. 2019) and with greater amount of PC destroyed (Hwang et al. 2022; Kim et al. 2022). Targeting PC for therapeutic seizure intervention using deep brain stimulation is also underway (Kurada et al. 2020; Young et al. 2018).

Despite PC’s vulnerability to seizures, few studies have investigated its role as a seizure onset zone in humans (Vaughan and Jackson, 2014) and interest in the role of the PC in human epilepsy has increased relatively recently. Most available research on PC has been animal focused but with emerging neuroimaging techniques there is growing opportunity to investigate human PC. Most existing neuroimaging studies examining epilepsy involving human PC have used extracranial methods (Vaughan and Jackson 2014) and intracranial studies are rare. In one such study, Vaughan and Jackson (2014) reported on a 37-year-old female patient undergoing intracranial EEG monitoring for drug-resistant epilepsy that included a depth electrode in frontal PC. Electrode recordings showed subclinical seizure activity in PC described as 1-to-2-minute runs of rhythmic sharp waves. Recordings during the patient’s habitual clinical seizure captured attenuation and gamma frequencies in PC. Surgical resection included destruction of right temporal lobe structures, including frontal and temporal PC, but was incomplete due to proximity to the middle cerebral artery. Surgery resulted in reduced seizure burden without seizure freedom.

Our study adds to available research examining epilepsy involving human PC. We present novel data on a pediatric patient with drug-resistant, focal epilepsy and right mesial temporal sclerosis who underwent intracranial monitoring and mapping that included PC using stereoencephalography (SEEG) in our epilepsy center.

2. Case Report

The patient was a 17-year-old, right-handed female at the time of presentation to our epilepsy center. She had a history of acute disseminating encephalomyelitis (ADEM) in the setting of mononucleosis at age 14 years old that presumably led to seizures and right hippocampal sclerosis. Seizures were treated unsuccessfully with oxcarbazepine. At age 16, she underwent laser ablation of right mesial temporal structures at an outside hospital (OSH) (Figure 1) without notable improvement in seizure control. Medical history was otherwise noncontributory. During repeated inpatient stays at OSH for epilepsy-related treatment, her mother used a strong-smelling coconut shampoo. Subsequently, patient's aura included coconut smell and a metallic taste in her mouth.

During surgical workup at our center, coconut odor was reported to be a seizure trigger. A brain MRI at that time showed remnant amygdala from her initial laser ablation. A video EEG demonstrated interictal discharges in the right temporal region and one electrographic seizure with onset from the right temporal lobe. The patient underwent SEEG implantation targeting remnant amygdala, temporal pole, prefrontal cortex, anterior insula, anterior cingulate, orbitofrontal cortex, and frontal and temporal PC (Figure 1). Interictal SEEG showed frequent discharges with superimposed fast activity in PC, temporal greater than frontal, and remnant amygdala. Numerous subclinical electrographic seizures were recorded from the temporal PC with propagation into frontal PC and amygdala. A single habitual seizure was elicited during cortical stimulation of the most mesial contacts of the temporal PC (5 second train at 50 Hz, 0.3 msec pulse width, 3 mA intensity) showing propagation across various temporal and frontal lobe structures. Electrocortical stimulation of PC did not affect performance on cognitive mapping tasks.

The patient also underwent high frequency activity (HFA) mapping via SEEG with presentation of a range of odors including orange, banana, vanilla, and coconut (Figure 2). Each odor produced an independent and highly reproducible burst ranging from 40–150 Hz activity, often with embedded spikes (see Figure 2 for specific frequency bands). Habituation to odors was observed, with activity becoming briefer and lower in amplitude over the course of mapping. Stimulation of the frontal piriform and remnant amygdala elicited the metallic taste described in the patient's typical aura. Based on findings, she underwent an uncomplicated resection that included remnant right amygdala, temporal and frontal PC, and temporal pole. Histology showed widespread astrogliosis and subpial gliosis. There were no reported changes in cognition or olfaction following surgery. She has been seizure free postoperatively (approximately two years) (Engel Class 1) and was weaned off oxcarbazepine. She has since graduated high school and is pursuing college.

3. Discussion

Here we present a case with validated PC seizure onset along with passive mapping of the effects of an olfactory stimulus. Few intracranial studies exist examining seizures originating from human PC. The PC's primary role is processing olfactory information and its contribution to cognitive function has yet to be elucidated. To our knowledge, ours is the first published study to document human focal epilepsy originating from PC, to map HFA associated with olfaction and cognition, and to use cortical stimulation to reproduce habitual seizures and risk-stratify functional deficit from directly within PC. Though Vaughan and Jackson (2014) identified subclinical and habitual seizure activity involving PC in their adult patient with drug-resistant epilepsy, they did not test piriform reactivity to odors nor produce a PC seizure. Findings from our study of increased HFA in response to odor presentation are consistent with results from Vaughan's and Jackson's (2014) case study, and recent research showing theta, beta, and gamma HFA during odor presentation in groups of patients with drug-resistant epilepsy (Jiang et al. 2017). Although seizures have been triggered by odors as reported by our patient (Vaughan and Jackson 2014), coconut presentation did not result in seizure during our work with her.

Like Vaughan's and Jackson's (2014) case study, findings from our patient's surgical workup resulted in partial resection of her frontal and temporal PC. In contrast to their patient, however, our patient has been seizure free since surgery, which is likely because her resection included all targeted epileptogenic tissue. These findings are consistent with previous research indicating surgical destruction of PC in patients with drug-resistant MTL epilepsy is associated with seizure freedom (Borger et al. 2020; Galovic et al. 2019; Hwang et al. 2022; Kim et al. 2022).

Histological findings from our patient's resected tissue showed astrogliosis and subpial gliosis. These findings support existing research showing reactive gliosis, including hypertrophy and proliferation, associated with drug-resistant seizures (Khurgel and Ivy 1996). Repeated seizure activity leads to pathological structural changes in glial cells that alter their function, including type and amount of neuroproteins produced (e.g., glial fibrillary acidic protein), thereby increasing immunoreactivity, seizure susceptibility, and resistance to antiseizure medication (Khurgel and Ivy, 1996; Kim et al. 2015).

Our patient did not experience postsurgical functional decline in cognition or olfaction, completed high school without issue, and is pursuing college, although preserved olfaction may be due to the patient's intact left-sided PC. No cognitive decline was expected based on findings from intracranial cognitive mapping that showed no disruption in performance during task completion.

As has been reported in previous research, our patient quickly habituated to odors, likely out of adaptive necessity to rapidly detect, and respond to environmental changes (Pellegrino et al. 2017). Regarding the cause of our patient's seizures, olfactory auras are frequently found in patients with history of encephalitis (Lehrner et al. 1997) and she was diagnosed with ADEM at age 14 years old, shortly before onset of seizures. This association is further supported by research indicating human PC is highly vulnerable to injury (Cheng et al.

2020; Sakurai et al. 2018; Vaughan and Jackson 2014; Vismer et al. 2015; Young et al. 2019).

4. Conclusion

Our study used SEEG to monitor and map human PC epilepsy and showed PC HFA associated with odor presentation and induced a typical seizure using cortical stimulation to PC. Cognitive mapping suggested PC cortex could be resected without affecting patient function. Results guided surgical resection that included PC and resulted in seizure freedom without olfactory or cognitive changes.

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Data Availability:

The data analyzed during the current study are not publicly available due to reasons of confidentiality of protected health information but are available from the corresponding author on reasonable request.

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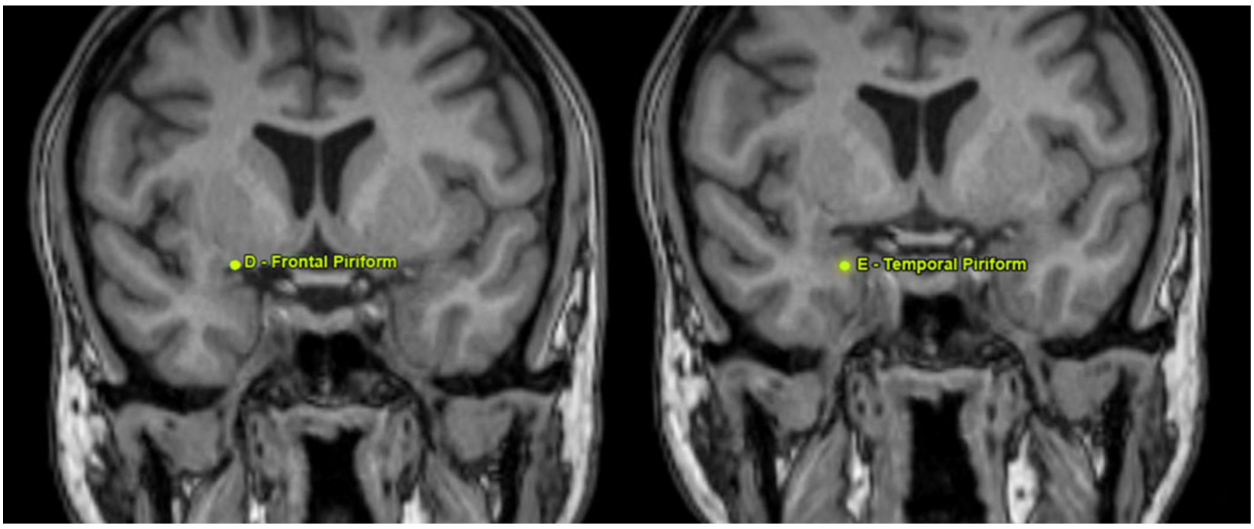

Figure 1.
MRI reconstruction of most mesial contacts of right frontal (D) and temporal (E) piriform electrodes marked in green.

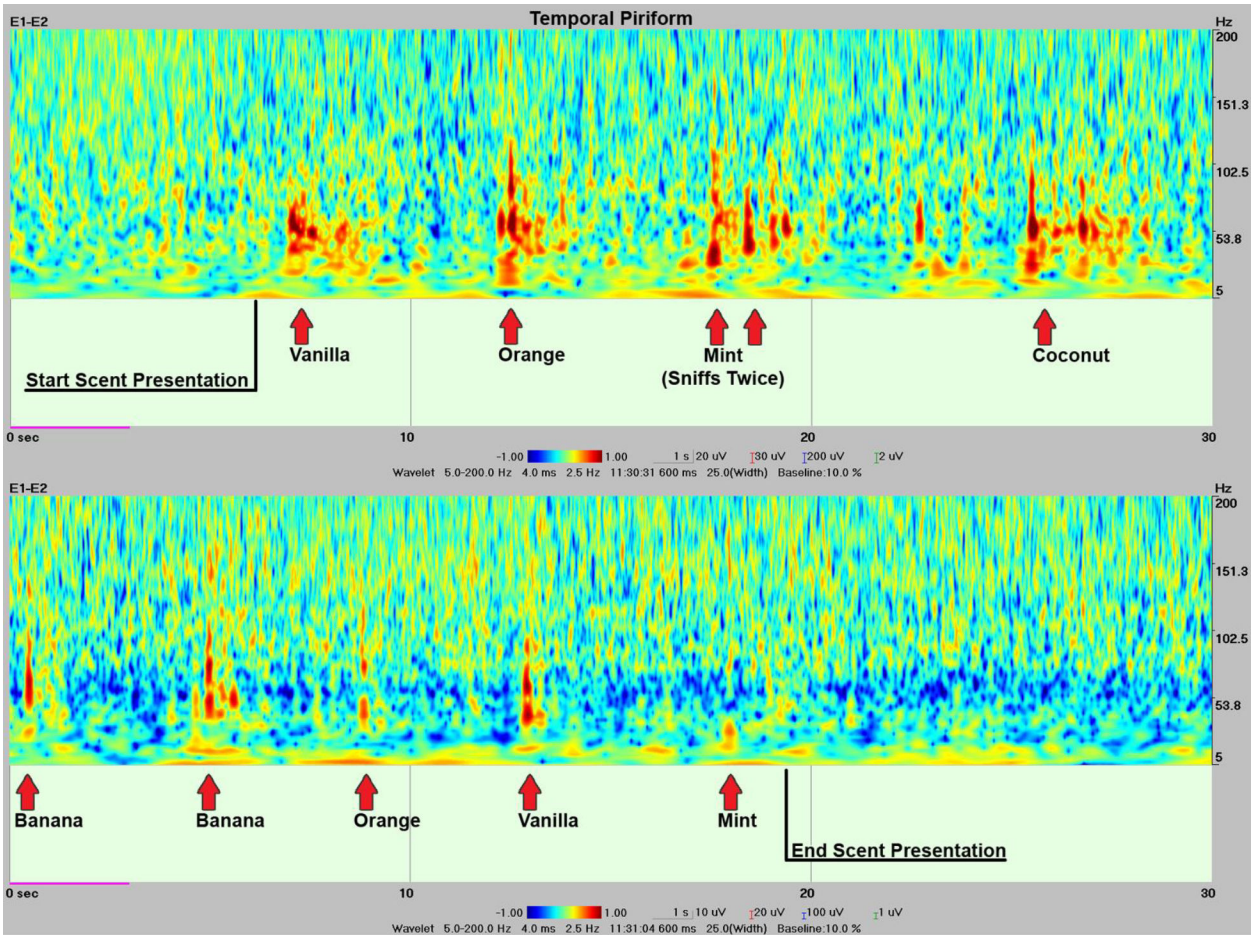

Figure 2.

Wideband amplitude analysis of temporal piriform contacts over approximately 45 seconds of odor presentation. Highest amplitude (deep red) bands generally appear between 30 Hz and 120 Hz. Note the decrease in response intensity over the testing interval. There are qualitative similarities in response characteristics of successive odor trials, but progressive reduction in amplitude makes identification of specific odors difficult using this analysis tool.