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What do brain oscillations tell about the human sense of smell?

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Abstract

Brain activity may manifest itself as oscillations which are repetitive rhythms of neuronal firing. These local field potentials can be measured via intracranial electroencephalography (iEEG). This review focuses on iEEG used to map human brain structures involved in olfaction. After presenting the methodology of the review, a summary of the brain structures involved in olfaction is given, followed by a review of the literature on human olfactory oscillations in different contexts. A single case is provided as an illustration of the olfactory oscillations. Overall, the timing and sequence of oscillations found in the different structures of the olfactory system seem to play an important role for olfactory perception.

KEYWORDS

iEEG, intracranial EEG, olfaction, rhythms, SEEG, stereoelectroencephalography

1 | INTRODUCTION

Around 20% of the population has an olfactory impairment due to different causes, with approximately 5% being anosmic (Brämerson et al., 2004; Landis et al., 2004; Vennemann et al., 2008). Because existing treatment options are limited (Mattos et al., 2021; Walliczek-Dworschak & Hummel, 2017), the development of olfactory implants has been discussed (Gunder et al., 2023). The required technology for such implants is available, with sensors that detect and differentiate odors (Bierling et al., 2021; Chiu & Tang, 2013). Despite research in this field since the 1880s (Aronsohn, 1884; Bérard et al., 2021; Holbrook et al., 2019; Mazzola et al., 2017), it is unclear which neuronal structures should be stimulated in which way to induce adequate olfactory sensations.

Brain activity may manifest itself as oscillations which are repetitive rhythms of neuronal firing. They are the focus of the current review. In *in vivo* human research, the measurement techniques are for most of them not precise enough to record single-neuron potentials; thus, they are usually recorded as local field potentials (LFP) (Gupta et al., 2020). These LFP can be measured via magnetoencephalography, surface electroencephalography, or intracranial electroencephalography (iEEG). The periodicity of the LFP can be constant over time independently of external stimuli, but they can also be entrained by external events and change in phase (shift of the pattern over time), frequency (faster or slower pattern), or amplitude (Thut et al., 2012). These changes are determined by the manner the electrical membrane responds to the synaptic currents (Jensen et al., 2019). In this regard, the different rhythms are often measured

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within specific canonical frequency bands; their boundaries may vary from study to study but are overall quite similar. According to the Organization for Human Brain Mapping, Committee on Best Practices in Data Analysis and Sharing (OHBM COBIDAS) (Pernet et al., 2020), these frequency bands are infra-slow: <1 Hz, delta: .1 to <4 Hz, theta: 4 to <8 Hz, alpha: 8 to <13 Hz, beta: 13–30 Hz, and gamma: >30 to 80 Hz.

iEEG provides a unique access to human brain function as intracranial activations can be displayed with a high temporal and spatial resolution without artifacts from muscle activity or eye movements at the cost of higher invasiveness (see Lachaux et al., 2003 for a review about iEEG). It is mainly done in patients suffering from medically intractable epilepsy to probe the epileptogenic zones. Due to its predisposition to be an epileptic focus, the temporal lobe is often targeted. Sometimes also Parkinsonian patients and some patients with brain tumors receive iEEG. The clinical question regarding the diagnosis determines the selection of the electrode sites, as well as the duration of the implantations. At the same time, these recordings offer valuable input to understand how our brain processes information when undergoing different states, tasks, or stimulations.

This review focuses on iEEG used to map human brain structures involved in olfaction. After presenting the methodology of the review, a summary of the brain structures involved in olfaction will be given, followed by a review of the literature on human olfactory oscillations in different contexts. A single case will be provided as an illustration of the olfactory oscillations. Some perspectives and limitations will be finally discussed.

2 | METHODOLOGY

For the research of literature, the databases PubMed, Web of Science, Scopus, and Google Scholar were screened. The keyword selection was based on the following criteria: search in title + abstracts + keywords when possible. The included keywords were...

The included keywords were one of the following:

Intracranial EEG, SEEG, sEEG, iEEG, stereoelectroencephalography, oscillations, oscillation, local field potential, local field potentials, LFP.

They were associated with one of the following keywords in different combinations (**AND**):

Olfaction, olfactory, smell, scent, odor, odour, anosmia, hyposmia, normosmia.

The following keywords were excluded:

Rat, rats, mice, mouse, rodent, rodents, insect, insects, monkey, monkeys, cat, cats, animal, slug, honeybee, honey bee, drosophila, limax, catfish, catfishes, frog, frogs, moth, crayfish, crayfishes, elephant, elephants, mollusk, turtle, turtles, salamander, salamanders, gastropod, gastropods, terrestrial, terrestrials, antenna.

These prerequisites led to 169 results in PubMed, 408 results in Web of Science, 1 result in Scopus, and 77 results in Google Scholar.

Significance

Brain activity may manifest itself as oscillations which are repetitive rhythms of neuronal firing. These local field potentials can be measured via intracranial electroencephalography (iEEG). This review focuses on iEEG used to map human brain structures involved in olfaction. Studies show that breathing organizes oscillations in the cerebral olfactory pathway and acts as a baseline for olfactory processing. Theta, beta, and gamma oscillations are found in the primary olfactory cortex during olfactory processing. Attentional states and cognitive tasks shape the olfactory oscillations. The dynamic of the oscillations might play a role for preparing olfactory network communication and multisensory integration.

All of these abstracts were screened manually with further exclusion criteria: animal research, in vitro research, surface EEG, computational models.

The review focuses on intracranial EEG used to map human brain structures involved in olfaction. Even so, some rodent work has been included when needed to draw hypotheses or explain a specific concept. For more details about the main research studies included in this review, see [Table 1](#).

3 | OVERVIEW OF THE OLFACTORY PATHWAY

The olfactory mucosa in the olfactory cleft of the nasal cavity is composed of different cell types. One of them are the olfactory sensory neurons (OSN), bipolar cells that are responsible for the transduction of chemical information into neural olfactory information sent to central structures. The OSN are activated through receptors located on protrusions, the olfactory cilia. Axons of these OSN project to the ipsilateral olfactory bulb, on the ventral surface of the forebrain. As shown in rodent and human work, the olfactory bulb has a complex organization with six circular cell layers including interneurons (Nagayama et al., 2014). Axons of OSN form synapses with the mitral cells that are organized into round spherical structures named glomeruli. Each of the glomeruli receives projections from OSN expressing the same receptor types (Axel, 1995). The pattern of activation of the glomeruli in the olfactory bulb determines odor quality or percept (Mori et al., 1999). The mechanisms driving such pattern formations have still not been fully uncovered; however, the dynamics driven by different layers of interneurons seem to be the base for specific rhythms forming the olfactory percept.

In humans, after passing through the olfactory bulb, the neural impulses are sent through the lateral olfactory tract to a group of brain structures that are commonly described as the primary olfactory cortex or secondary olfactory structures. These include the

TABLE 1 Summary of studies included in the present review.

First author (Year)	Topic	Brain structures	N	Mean age/age range	Sex	Stimuli	Procedure	Results
Hughes and Andy (1979)	Olfaction, breathing	Amygdala	9	N.C.	N.C.	D,L-beta-phenylethylmethylcarbinol (floral) 1,2-dichloroethane (etheral) 1,8-cineole (camphoraceous) D,L-menthone (minty) Cyclopentadecanone (musk) Formic acid (pungent) Dimethyl disulfide (putrid) Ethyl butyrate Methanol Camphor Moskene Eugenol Pulegone Acetic acid Acetylcholine bromide	Odors presented via olfactometer 1000mL/min airflow, ISI 2-3 min. Patients instructed to take series of sniffs	Beta and gamma appear specifically during odor condition but synchronized with inspiration. Differences in amplitudes of these oscillations depending on odorant nature. Similar odorant classes were represented by similar patterns
Ganzha (1986)	Olfaction, breathing	Amygdala	3	N.C.	N.C.	N.C.	Not detailed. Applied a 15-80Hz frequency, masking very low or very high frequencies	Beta spindles seemed produced by odor, lasting 1-3 s and occurring at the end of inhalation and beginning of exhalation. Amplitude of these bursts depends on the degree of stimulation

(Continues)

TABLE 1 (Continued)

First author (Year)	Topic	Brain structures	N	Mean age/age range	Sex	Stimuli	Procedure	Results
Hudry et al. (2001)	Olfaction	Amygdala	7	32.9, 24–48	6F/1M	Passive test: lily, pizza, caramel, bitter almond, butyric acid, isoamyl phenylacetate, lavender, guaiacol, mustard, apricot, chewing gum, isovaleric acid. Suprathreshold detection test: butanol	Odors presented monorhinally (ipsilateral to amygdala) in a glass bottle. Duration 3–5 s, inspiration phase considered as stimulus duration. ISI 1 min. Passive presentation or suprathreshold test. Suprathreshold test: repeated stimulations, patients responding whether odor was present or not	Passive test: odors induced ERP with positive peak 300 ms post-stimulus, negative peak 450 ms post-stimulus, followed by slow reversion to baseline. No effect of type of odor on amplitudes and latencies. Suprathreshold test: repeated stimulations decreased positive peaks latencies only
Hudry et al. (2003)	Olfaction	Amygdala	18	35.8, 23–56	13F/5M	24 different smells, see Royet et al. (1999) for details. Smells are unfamiliar but with similar intensity and hedonicity	Odors presented monorhinally (ipsilateral to amygdala) in a glass bottle. Duration 3–5 s, inspiration phase considered as stimulus duration. Specific breathing technique. Matching-to-sample task: sixteen pairs of odorants, successive trials, 30 s ISI between odors within the pair, and 120 s ISI between pairs. 8 matching and 8 mismatching pairs	Repetition suppression effect: Amplitudes of ERP reduced for matching odors whatever if hit or miss. Patients who incorrectly judged odors as similar also had repetition suppression effects. Latencies of responses to target odor shorter than for sample odor

TABLE 1 (Continued)

First author (Year)	Topic	Brain structures	N	Mean age/age range	Sex	Stimuli	Procedure	Results
Jung et al. (2006)	Olfaction	Amygdala	9	N.C.	N.C.	24 different smells, see Royet et al. (1999) for details. Smells are unfamiliar but with similar intensity and hedonicity	Same procedure than previous study, Hudry et al. (2003)	Beta and low gamma found specifically during odorous stimulation, lasting for 4–5 s during inspiration. Gamma modulated by repetition or similitude of odorants in each pair. Reflects repetition suppression effect
Zelano et al. (2016)	Breathing	Piriform cortex, amygdala, hippocampus	7 or 8	29–59	3F/4 or 5M	N.A.	N.A.	In piriform cortex and limbic system, natural breathing might synchronize the electrical activity. The power of oscillations peaks during inspiration. This pattern is dissipated when breathing is directed from nose to mouth. Breathing phase might enhance fear discrimination and memory retrieval
Jiang et al. (2017)	Olfaction	Mainly posterior piriform cortex (PPC, medial contact of electrode in 5/7 patients) and anterior amygdala (close to posterior piriform cortex) in 2/7 patients	7	19–61	6F/1M	Almond, baby powder, banana, cheese, garlic, gasoline, jasmine, orange, peanut butter, pine, rose, sesame, and strawberry	Patients received 4 odors out of the set of 13. They were instructed verbally to sniff. They had to report whether they detected an odor. 20–40 stimuli of each odor	Odor condition was correlated to an increase of theta, at the beginning of odor onset with maximum during inspiration. This effect was higher in posterior piriform cortex (especially medial and anterior locations of it) than other structures but also present in amygdala, and coupled between PPC and anterior hippocampus but not parahippocampal gyrus. No gamma activity

(Continues)

TABLE 1 (Continued)

First author (Year)	Topic	Brain structures	N	Mean age/age range	Sex	Stimuli	Procedure	Results
Zhou et al. (2019)	Olfaction, multisensory	Superior temporal gyrus (STG, auditory), superior temporal sulcus (STS, auditory), piriform cortex (PC, olfactory)	7	32.9, 25–47	4F/3M	Mint, rose	Spoken cue about whether the following odor is rose or mint. Squeezing bottles for odor presentation. Patients instructed to sniff when smell delivery. Followed by a question to ask whether the auditory cue and odor matched	Following spoken cues, low-frequency oscillations in auditory cortex were synchronized with those from piriform cortex. When gamma was present, it was modulated by the low-frequency phase dynamics in both auditory and olfactory cortices.
Arabkheradmand et al. (2020)	Olfaction	Piriform cortex	13	32, 20–61	10F/3M	N.C.	Retrospective data. Anticipatory or non-anticipatory conditions. Some odors delivered manually by squeezing bottles, some through a computer controlled olfactometer. Some patients had identification tasks or not, some had detection tasks or not. 15–20s ISI	When anticipating odor delivery (around .5 s before inhaling), significant intertrial phase coherence in delta at group and individual levels. Anticipation of odors seems to reset the phase of low frequencies. The strength of this reset correlates to the increase in odor response magnitude
Yang et al. (2021)	Olfaction	Piriform cortex, hippocampus	8	27–57	5F/3M	Anise oil, cinnamon, coffee, honeysuckle, mint, orange, peanut butter, pine, strawberry, vanilla	Working memory task with sequences of three distinct odors	Oscillations are embedded into each other, theta driving some higher frequencies. During encoding, gamma is greater in some distinct theta phases, and this exact sequence is reinstated in the piriform cortex during maintenance. Replay events were associated with enhanced piriform-hippocampal theta-phase synchrony

TABLE 1 (Continued)

First author (Year)	Topic	Brain structures	N	Mean age/age range	Sex	Stimuli	Procedure	Results
Zhou et al. (2021)	Olfactory networks during resting state	Connectivity between piriform cortex and hippocampus or Heschl's (auditory) and hippocampus	8 (fEEG) and 25 (fMRI)	36.9, 25–54 (fEEG) and 25.5 (fMRI)	3F/5M (fEEG) and 14W/11M (fMRI)	No smell, resting state	Measured connectivity between two structures with the fEEG data by measuring phase locking of signals	Olfactory cortex has stronger functional connectivity with hippocampus than auditory cortex. Respiratory rhythms may organize olfactory networks by modulating connectivity between the piriform cortex and hippocampus
Yang et al. (2022)	Olfaction	Piriform cortex	7	N.C.	N.C.	Mint, rose	Spoken cue about whether the following odor is rose or mint. Squeezing bottles for odor presentation. Patients instructed to sniff when smell delivery. Followed by a question to ask whether the auditory cue and odor matched	Theta oscillations appear first during inspiration and disappear quickly. Then beta and gamma appear, beta stays through exhalation and gamma peak at the transition between inhalation and exhalation. Beta and gamma amplitudes are correlated with odor identification. Theta phase modulates beta and gamma in the piriform cortex, this is called nested oscillations
Dikeçligil et al. (2023)	Olfaction, breathing	Piriform cortex	10	30.9, 23–47	8F/2M	Coffee, banana, eucalyptus	Cue to sniff followed by one of the three odors or odorless air. Either monorhinal stimulation (left or right nostril) or birhinal. Identification task with forced choice among four alternatives. Also asked about which side was stimulated	In case of monorhinal stimulation, the ipsilateral nostril stimulation led to faster processing in the piriform cortex followed by a distinct pattern coming from the contralateral nostril. In case of birhinal stimulation, the dominance of the ipsilateral nostril remained apparent at the central level

Note: Studies reported in this table were conducted in humans only. The studies are focused on neural oscillations measured by intracranial EEG that are related to olfaction or on the influence of the respiratory function on olfaction.

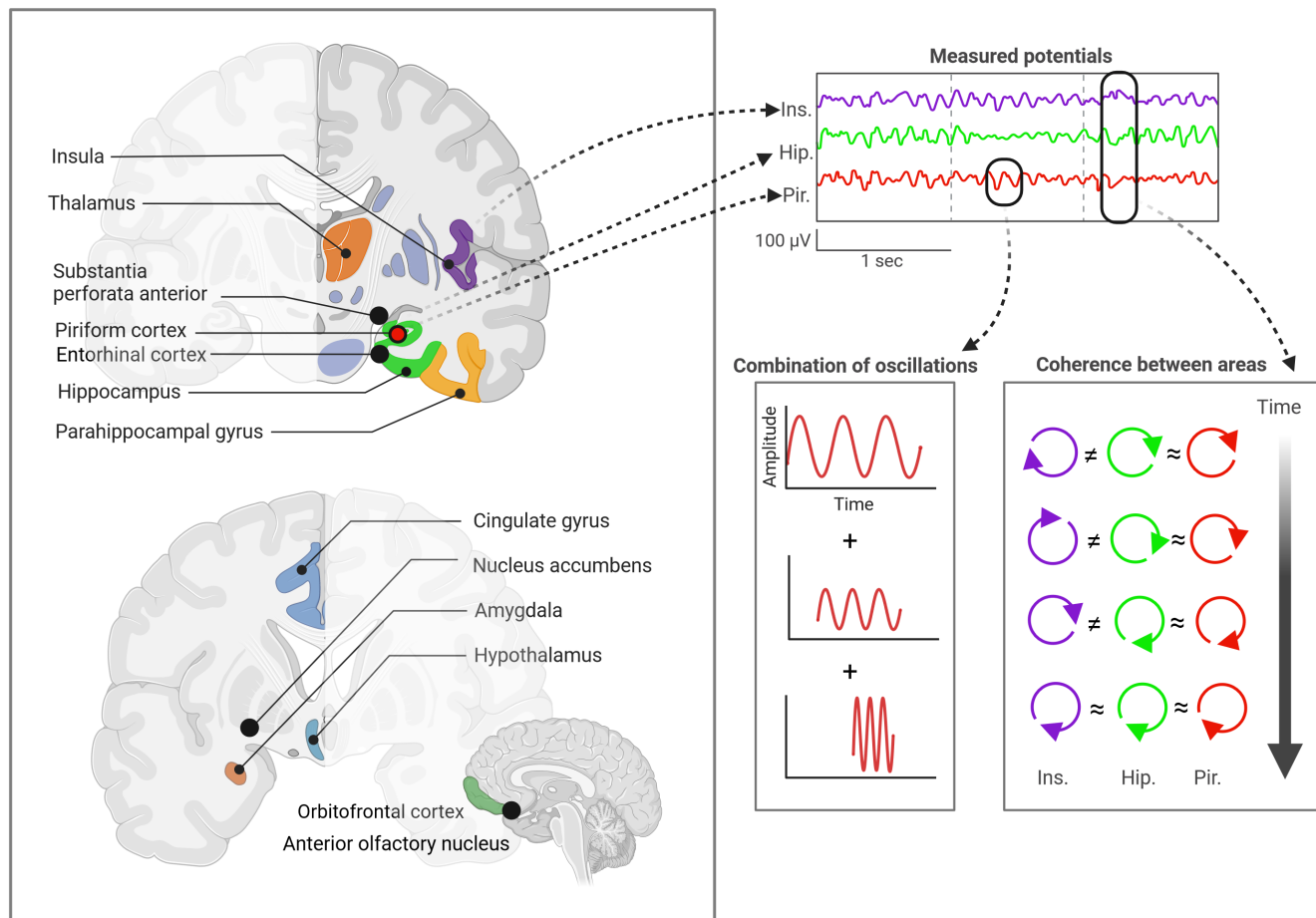


FIGURE 1 Summary of the brain structures involved in olfaction, and of the different oscillatory features to take into account when considering the olfactory processing. Created with BioRender.com. Hip, Hippocampus; Ins, Insula; Pir, Piriform cortex. The piriform cortex, the substantia perforata anterior (human homolog of the olfactory tubercle (Witt, 2020)), entorhinal cortex, anterior olfactory nucleus, and nucleus accumbens are slightly anterior to the brain slice depicted here, that is why they are represented with specific bold dots on the figure. The odor percept is shaped by encoding olfactory features in different networks, some of them having nodes in common. Certain structures are invariably part of the main olfactory pathway (left panel). By placing intracranial electrodes in these structures, local field potentials can be recorded (“measured potentials” panel) to understand how they influence the networks dynamics. For example, they can entrain other structures to oscillate in synchrony with them. This relies on a specific sequence of neuronal events. The measured potentials can be roughly considered as a sum of recurrent signals of different frequencies (low frequencies for slower oscillations over time or high frequency for faster oscillations over time), see the “combination of oscillations” panel. The amplitude of each frequency and its temporal dynamic in combination with other types of frequencies (or phase) determines the communication with other structures (see “combination of oscillations” panel). The coherence (or synchronicity of oscillatory patterns over time) across different brain structures can be evaluated (see “coherence between areas” panel, where the circular arrows represent oscillations over time). Just as an arbitrary example, in this figure, the neural oscillations in the insula are faster than the ones in the hippocampus or piriform cortex, that is, there is probably more high-frequency content in the insula. The piriform cortex and the hippocampus seem to elicit the same frequencies over time although with a little shift in phase (little delay). Thus, they could be functionally connected. After a while (see the last row in this coherence graph corresponding to the last time point), the phase is identical for the three structures. This alignment in the signal could be the starting point for processing specific olfactory features by bringing different networks together. In summary, not only the structures where these processes happen but also the sequence order in which the neurons fire, the frequency content of their oscillations, and their phase shape the olfactory perception.

anterior olfactory nucleus, the piriform cortex, the cortical nuclei of the amygdala, and the entorhinal cortex. The following structures receive projections from the primary olfactory cortex: the hippocampus, the parahippocampal gyrus, the thalamus (especially its mediodorsal part), the hypothalamus, the insula, or the orbitofrontal cortex (Gottfried, 2006; Witt, 2020). The olfactory information also reaches the substantia perforata anterior (the human equivalent of the olfactory tubercle), the nucleus accumbens, the cingulate cortex,

and the cerebellum (Witt, 2020), see Figure 1, left panel, for a summary of some brain structures involved in olfaction. Importantly, the role of the thalamus is debated in olfaction. Indeed, the olfactory pathway was believed to not project initially to the thalamus, contrary to other senses, but is distributed to areas of the limbic system before passing through the mediodorsal thalamus (Shepherd, 2005). More recently, imaging studies have shown a structural connection between the mediodorsal thalamus and the piriform cortex that

might serve the olfactory processing (Behrens et al., 2003; Thaploo et al., 2022).

In fact, it seems that the olfactory pathway is more complex than stated above, as structures interact with each other at a local scale or simultaneously as networks. Based on functional magnetic resonance imaging studies with various designs, authors agree on the point that there are distinct olfactory networks for purely sensory processing or cognitive and conceptual aspects of olfaction (Arnold et al., 2020; Karunanayaka et al., 2014). The sensory networks comprise primary olfactory cortices while cognitive networks encompass also association and frontal cortices.

But the way the different structures influence each other at the level of a structural or functional connectivity is still not fully uncovered. Neural oscillations might help to understand these dynamics and how the synchronization through different brain structures and at specific timing entrains brain networks to process olfactory features. For this purpose, our review provides an overview of the different studies carried out in humans on the topic of olfactory brain oscillations. It summarizes important features to pay attention in this area of research.

4 | NEURAL OSCILLATIONS IN RELATION TO OLFATORY PROCESSING

4.1 | Breathing organizes oscillations in the cerebral olfactory pathway

There are differences between nasal and oral breathing. On the one hand, nasal respiration includes adjustment of air temperature and humidity, as well as air filtering (Recinto et al., 2017). In addition, breathing through nasal airways induces higher diaphragmatic amplitude than oral breathing (Trevisan et al., 2015). Moreover, in humans, the activity in structures of the olfactory system is synchronized to the natural breathing cycle, in the piriform cortex, the amygdala and the hippocampus (Zelano et al., 2016). In addition, the connectivity between the piriform cortex and the hippocampus seems to be modulated by this breathing cycle (Zhou et al., 2021). Interestingly, the power of these oscillations peaks during inspiration and dissolves as breathing is diverted from the nose to the mouth (Zelano et al., 2016).

The natural respiratory rate in humans is usually 10–20 breaths per minute, corresponding to .16–.33 Hz (Russo et al., 2017) while in rodents and other small animals, the rate of breathing is around 2–12 Hz (Zelano et al., 2016). Thus, when referring to canonical EEG frequency bands, the respiratory signal falls into delta (.1 to <4 Hz) and theta (4 to <8 Hz) bands, which are relatively slow rhythms. These are precisely the rates of brain oscillations that are propagated in olfactory structures.

The tracking of respiration in the primary olfactory cortex may be of particular importance for the sampling of the incoming air in order to detect potential olfactory cues of interest as fast and as accurately as possible. In addition, in humans, the breathing phase

seems to enhance the performance on some cognitive olfactory-related tasks, namely fear discrimination, memory retrieval (Zelano et al., 2016), and even cognitive tasks unrelated to olfaction (Perl et al., 2019).

4.2 | Theta, beta, and gamma oscillations are found in the primary olfactory cortex during olfactory processing

An early study on olfactory brain oscillations in humans already reported beta (12–24 Hz) and gamma (40–70 Hz) oscillations in the amygdala during sniffing of odors (Hughes & Andy, 1979). In particular, the beta rhythm was synchronized with inspiration. A few years later, similar beta (20–30 Hz) band enhancement was found in the amygdala during odor delivery; but occurring at the transition between inhalation and exhalation, with the amplitude of these spindles correlated to the degree of olfactory stimulation (Ganzha, 1986). Since then, several studies have shown that not only beta but three main frequency bands are represented during olfactory processing in the primary olfactory cortex: theta, beta, and gamma (Arabkheradmand et al., 2020; Jiang et al., 2017; Jung et al., 2006; Paulsen & Sejnowski, 2006; Yang et al., 2022; Zhou et al., 2019).

As stated in the previous section, some neural oscillations are linked to the respiratory rhythm. This seems to serve as an internal clock to potentiate incoming odor processing (Haehner et al., 2011). Indeed, when smelling an odor, there is a specific sequence of events in the piriform cortex: theta oscillations occur first with the inspiration and disappear quickly (Yang et al., 2021), followed by beta and gamma oscillations. Beta waves stay through the exhalation, while gamma peaks at the transition between inhalation and exhalation and remains for longer. As theta is also partly represented during non-odorous trials, it is presumably involved in respiration, while beta and gamma happen specifically more during olfactory processing. In addition, beta and gamma rhythm amplitudes are correlated to the smell identification ability (Yang et al., 2021). Moreover, beta and gamma amplitudes are entrained by theta only if an odor is present, which overall points to the idea that respiration is tracked in order to potentiate the olfactory performance (Yang et al., 2022).

4.3 | Attentional states shape the olfactory oscillations

Olfaction is, among others, an alert sense, which means tracking potential threats, saliency, or novelty of olfactory stimuli. These abilities hinge on the attentional and memory systems. In this regard, it has been shown that anticipating an odor resets the phase of the low-frequency bursts in the piriform cortex, especially in the delta band (Arabkheradmand et al., 2020). This reset induces the coupling of low-frequency oscillations. The strength of this phase

reset correlates to the odor response magnitude (Arabkheradmand et al., 2020). In general, theta reset has been shown to happen during encoding and retrieval in a working memory task (Kahana, 2006).

Another important mechanism is the habituation effect that translates into a decrease in some perceptual components following repeated or prolonged stimulation. This decrease is driven by adaptation either at the level of the olfactory mucosa or within the different brain areas of the olfactory cortex (Pellegrino et al., 2017). It helps prioritize incoming stimuli according to their novelty or importance. Similar observations have been reported using iEEG. In the amygdala, odors induce olfactory event-related responses (ERPs); the latency of their early positive peak decreased over repetitive exposure (Hudry et al., 2001, 2003). Some authors also used a match-to-sample task to investigate olfactory discrimination. This task consists in the delivery of two odors, the first being the cue (or sample) and the following being the target odor. Participants have to indicate whether the target matches the sample. It appeared that the amplitude of the target ERPs decreased in matching pairs and when the unmatched stimuli were incorrectly recognized as similar (Hudry et al., 2003). In addition, the low gamma frequency (25–35 Hz) elicited during the olfactory stimulation decreased in the amygdala over repetitions and was modulated by the similarity of odors within pairs of stimuli (Jung et al., 2006). These effects have been called repetition suppression and could reflect olfactory short-term memory or top-down attentional processing (Hudry et al., 2001, 2003; Jung et al., 2006; Kahana, 2006). This would result in a decrease in attentional load serving selective attention.

In short, the anticipation of smell and habituation seems to be reflected in the brain oscillations to facilitate the processing of odors. A hypothesis would be that the reset and long-range coherence of low-frequency oscillations (delta, theta) during smell anticipation prepare the brain networks to evaluate the relevance of the stimulus. The higher frequency bursts (gamma in particular) could reflect higher cognitive processing in this context.

4.4 | Cognitive tasks related to olfaction: Discrimination, identification

Hughes and Andy remarked that the amplitudes of beta (12–24 Hz) and gamma (40–70 Hz) were different in the amygdala for the 15 different odorants they used in their experiment, with a similar amplitude pattern for odors of the same odor classes (floral, ethereal, camphoraceous, minty, musk, pungent, putrid) (Hughes & Andy, 1979). However, when investigating the ERPs produced in response to 12 or 24 odorants, Hudry and colleagues did not find any differences between them (Hudry et al., 2001, 2003). Thus, it was difficult at that time to conclude whether odor discrimination or identification is reflected in the local field potentials. Still, as discussed in the previous section, the same studies provided insights concerning adaptation effects taking place in the amygdala when investigated with a match to sample task, both on amplitudes of an

early positive peak of the olfactory response and on its correlated gamma power (Jung et al., 2006). This reflects attentional processes that could play a role in olfactory short-term memory, and thus indirectly in odor discrimination.

Since then, it has been shown that beta and gamma (Kahana, 2006; Paulsen & Sejnowski, 2006) are involved in a variety of cognitive functions, and are also present in an olfactory context (Jiang et al., 2017; Kay, 2015; Yang et al., 2021, 2022; Zhou et al., 2019). In particular, beta is the most coherent rhythm across brain structures and also seems to be associated with odor learning (Kay, 2015). It has been hypothesized that gamma is absent from the posterior piriform cortex and the anterior amygdala when the olfactory tasks are not cognitively demanding (Jiang et al., 2017). Both beta and gamma power have been found to be correlated with odor identification ability (Yang et al., 2021, 2022). Moreover, the patterns of theta-coupled gamma activity in the piriform cortex are reinstated after an olfactory memory task to probably subserve maintenance of the memory trace, and its strength correlates to the recall accuracy on a signal trial basis (Yang et al., 2021). In addition, Dikeçliçil and colleagues (2023) reported a differential timing of olfactory patterns in the piriform cortex depending on the nostril side dynamic (ipsilateral response first followed by contralateral). The robustness of this coding improved with the olfactory identification ability.

4.5 | Oscillations: Network communication features and multisensory integration

Not only the frequencies themselves but also the spatial and phasic aspects of oscillations are important. As suggested previously, the oscillatory phase might affect behavior and vice versa (Thut et al., 2012). According to the communication-through-coherence theory, when two distant brain areas have their oscillations synchronized, the excitability of their neuronal assemblies is modified, which affects their spike discharging and their sensitivity to inputs (Thut et al., 2012). This may play a key role in brain networking. The synchronization might not be just a pure correlation: The different frequency bands are not necessarily independent from each other. In fact, some oscillations might be entrained by others, an interaction called cross-frequency coupling.

In this context, it seems that a recurrent temporal reference allows brain oscillations to be modified, acting like an internal baseline resting state (Thut et al., 2012). In the case of the olfactory system, it is possible that low frequencies such as theta assume this function. In fact, in the primary olfactory cortex, theta is partly a reflection of breathing (Zelano et al., 2016) which helps organizing the olfactory brain networks by modulating connectivity between piriform cortex and hippocampus (Zhou et al., 2021).

In an olfactory context, theta also modulates beta and gamma amplitudes (Yang et al., 2021), which authors refer to as nested oscillations, a phenomenon in which low frequencies' phases entrain the amplitude of higher frequencies. As beta and gamma amplitudes

are also correlated to odor identification abilities (Yang et al., 2021, 2022), theta might play the role of a conductor for higher olfactory tasks by modulating these two frequency ranges. In a working memory task, theta resets after both stimulus encoding and memory retrieval (Kahana, 2006). It also serves a long-range coherence between prefrontal and posterior sites during the retention interval of verbal and visuospatial working memory tasks (Kahana, 2006). The same has been observed during an olfactory memory task: Specific enhancement of gamma frequencies was embedded into theta oscillations during the encoding phase (Yang et al., 2022). This pattern is reinstated during maintenance and replaying olfactory events synchronizing the theta band between the piriform cortex and the hippocampus to possibly improve odor discrimination accuracy (Yang et al., 2022). It has also been shown that the multisensory integration in the olfactory system depends on phase shifts of low-frequency rhythms in the primary olfactory cortex (Zhou et al., 2019).

It is important to consider work in other species to understand the generation and function of these interlocked rhythms. In fact, the oscillatory activity in the olfactory system seems to be evolutionary conserved within vertebrates, and the functions of gamma oscillations in particular exhibit similarities across phyla (Kay, 2015). In the olfactory bulb of rodents for example, this involves local inhibitory interneurons, with reciprocal dendrodendritic synapses between glutamatergic tufted or mitral cells and GABAergic granule cells (Kay, 2015; Paulsen & Sejnowski, 2006). Fast gamma arises at an early stage (related to sniffing) from tufted cells that share short lateral dendrites with each other in nearby glomeruli (Mori et al., 2013). They are followed by slow gamma that may depend on mitral cells' communication relying on long dendrites (Mori et al., 2013), and the two tufted and mitral systems can adapt to each other. Granule cells enhance fast oscillations (gamma and beta), serving as a synchronizing mechanism. Inputs (top down and likely local GABAergic) to granule cells desynchronize gamma (Gray & Skinner, 1988; Nusser et al., 2001). Similarly, in humans, early gamma in the olfactory bulb has been described using the non-invasive electro-bulbogram technique. Indeed, theta and gamma are involved to the exchange of information from the olfactory bulb to the piriform cortex; while a top-down feedback from the piriform cortex to the olfactory bulb is facilitated by delta and theta oscillations (Iravani et al., 2021). Feedback from the amygdala or from other higher central structures to the olfactory bulb is necessary to adjust the activity of inhibitory interneurons and modify the frequency. For example, it has been shown in rodents that feedback via the GABAergic granule cells desynchronizes the gamma oscillations (Mori et al., 2013). The feedback to the olfactory bulb is also necessary to maintain beta bursts as being the most coherent rhythm across areas of the olfactory system (Mori et al., 2013). Thus, this balance between short- and long-distance synapses, excitatory or inhibitory connections and feedback shape the frequencies and phase of oscillations, such that they can be nested and/or synchronized across brain structures. In sum, the hypothesis in humans is that theta and beta oscillation rhythms would be in charge of grouping information at the level of

the olfactory bulb and prepare olfactory networks (Kay, 2015) while faster gamma bursts would reflect higher cognitive processing. This fits with the idea that slow oscillations might coordinate integrated computations, while fast oscillations might reflect local network computations (Buzsáki, 2006).

5 | CASE DESCRIPTION

This case description aims to illustrate oscillations linked to the olfactory processing that were mentioned previously, and raise questions on some of its features. None of the analyses was statistically significant. The purpose of the case description is purely descriptive. It illustrates the different concepts described in previous sections, raises hypotheses to be investigated in future work, and underlines the points to pay attention to when investigating olfactory oscillations in humans.

5.1 | Methods

We describe one case of a 39-year-old male with pharmaco-resistant temporal lobe epilepsy (ICD-10 G40.2, "focal partial symptomatic epilepsy and epileptic syndromes with complex partial seizures"). This patient underwent SEEG for identification of the epileptogenic zone as part of presurgical evaluation at the Carl Gustav Carus University Hospital Dresden, Germany. He was presented with odors with different hedonic valences ("fish" as an unpleasant odor and "peach" as a pleasant odor). This procedure was approved by the Ethics Committee of the TU Dresden (GVOEK) under the application number BO EK 400082021. The patient provided his written informed consent.

SEEG was recorded from 96 contacts in the right hemisphere, located among others in the amygdala (for one of them very close to the piriform cortex), hippocampus, and parahippocampal gyrus. The selection of the electrode sites and the duration of implantation were made solely for clinical reasons. The recordings were performed 2 days after electrode implantation.

The odors were delivered 20 times and for 3s each with a face mask using a computer-controlled olfactometer (Sommer et al., 2012) which allows for precise timing of the stimuli and constant airflow (2L/min). The patient received the odors passively, that is, he was not primed about the odor presentation with an auditory or visual cue. Respiration was monitored to align the stimulus onset with the following inspiration. This respiratory signal was measured using a plethysmographic belt, which provides information of changes of tidal volume. The belt was divided into two parts, one placed around the abdomen and the other one on the chest of the patient. The chest respiration was preferred for the analysis. The realignment of onsets to the inhalation phase was manually performed. The inhalation following the odor onset was selected and the marker was placed at the crossover between the inhale curve and the zero line (y-axis).

Using time–frequency analysis (continuous wavelet transform (Bajaj, 2020)), oscillations in different frequency bands were analyzed. For this purpose, the following steps were implemented: The data were processed with a low pass filter at 235 Hz (FIR filter two-pass, zero phase lag), then notch filtered at 50 Hz. They were resampled at 500 Hz. The signal was re-referenced to the common average reference of SEEG contacts. It was again band-pass filtered 1–200 Hz (FIR filter two-pass, zero phase lag, with 2 Hz width the first time and 50 Hz width the second). The trials were baseline-corrected via Z-score transformation ($(x - \mu)/\sigma$ where x is the data point value, μ is the mean of the dataset, and σ is the standard deviation) using -2 to 0 s as a baseline. Epochs were visually inspected and discarded when signs of muscular artifacts or interictal activity were found. After that, continuous wavelet transform (CWT) was applied on each trial and the subsequent power was baseline-corrected again with Z-score transformation using -1.8 to -0.2 s as a baseline interval. Then, trials were averaged by condition (i.e., peach or odorless) and these two averages were subtracted from each other (i.e., peach minus control).

In addition, olfactory performance was assessed using the validated and reliable Sniffin'Sticks olfactory test battery (Hummel et al., 1997), a standardized test which allows to diagnose people as normosmic, hyposmic, or anosmic (Oleszkiewicz et al., 2019). This is based on tests for odor threshold, odor discrimination, and odor identification, resulting in a combined “TDI-score”.

5.2 | Results and discussion

5.2.1 | Olfactory pattern

The patient was normosmic when tested birhinally, as indicated by his TDI score of 38.5. A specific olfactory pattern was observed for peach from the closest contact to the piriform cortex in the amygdala. This pattern was composed of an early theta/beta oscillations linked to the inspiration phase, followed by beta and few gamma oscillations, as described in the literature (Figure 2, see also Section 4.2). This illustrates the importance of timing of oscillatory events and phase dependency on the breathing pattern.

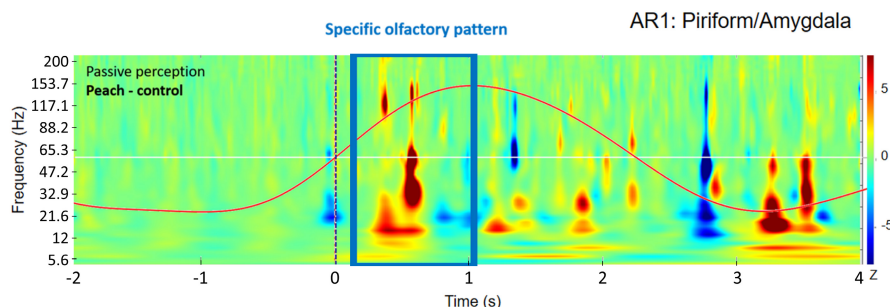


FIGURE 2 Time–frequency analysis of the olfactory response to the peach odor in the amygdala (close to the piriform cortex). The map shows the contrast between odor and odorless conditions. Time point 0 (dotted line) reflects the onset of stimulation realigned on the inspiration phase (red line). Frequencies are displayed in a logarithmic way. The color map is expressed as a Z-score derived from the power ($\mu\text{V}^2/\text{Hz}$).

This pattern disappeared gradually when moving away from the closest contact to the piriform cortex (Figure 3). In fact, the reference chosen (common average reference of SEEG contacts) being for most of it outside of the amygdala might drive the data at this electrode contact to come from the piriform cortex. This tends to confirm the specific feature of the amygdala/piriform cortex in the olfactory processing compared to other structures. In this regard, it would be interesting to employ methods that decipher the cross-coherence and correlation of patterns between the amygdala/piriform cortex and various other brain locations. This would give insight about the involvement of these locations in olfactory networks.

As discussed in Section 4, the low-frequency oscillations are linked to the breathing pattern, and are believed to reflect pure sensory aspects of the smell. We cannot exclude that it represents some other periodic event. However, as the odor presentation was completely passive (no sounds, visual or verbal cues, no instructions to count the stimulations, jittered odor presentation) and the odor condition was subtracted to the control (odorless) one, we do not assume that the low-frequency boost represents attentional processes or preparation mechanisms. It is yet more likely to be linked to olfaction or breathing. These low-frequency oscillations also are a predominant feature in networks preparation. If we refer to the olfactory pathway described in Section 3, we would then expect that the structures of the primary olfactory cortex (piriform cortex, amygdala, entorhinal cortex) elicit a high coherence in between them whatever the frequency band; while the coherence of these with secondary olfactory cortices would be present for low frequencies but less for beta and gamma.

5.2.2 | Differences of patterns between peach and fish odors: A pleasantness evaluation?

Unlike the pleasant peach odor, the unpleasant fish odor produced an early and sustained reinforcement of the delta band. The question is whether the difference in delta band between fish and peach odors could reflect an early shift in the networks prepared for higher cognitive olfactory processes. This deviation could reflect the difference in pleasantness between these two odors. It could also reflect the odor quality. It has been shown, for example, that activity of the

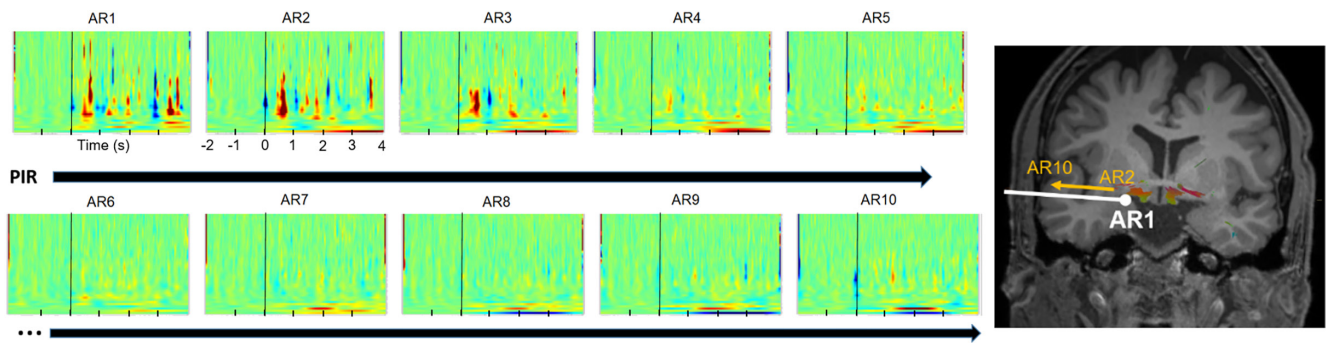


FIGURE 3 Time–frequency analysis of the olfactory response to the peach odor at different electrode contacts in the amygdala. The maps correspond to the contrast between odor and odorless conditions. AR1 is the closest contact to the piriform cortex (PIR), and AR10 the most distant from the piriform cortex (Figure 2).

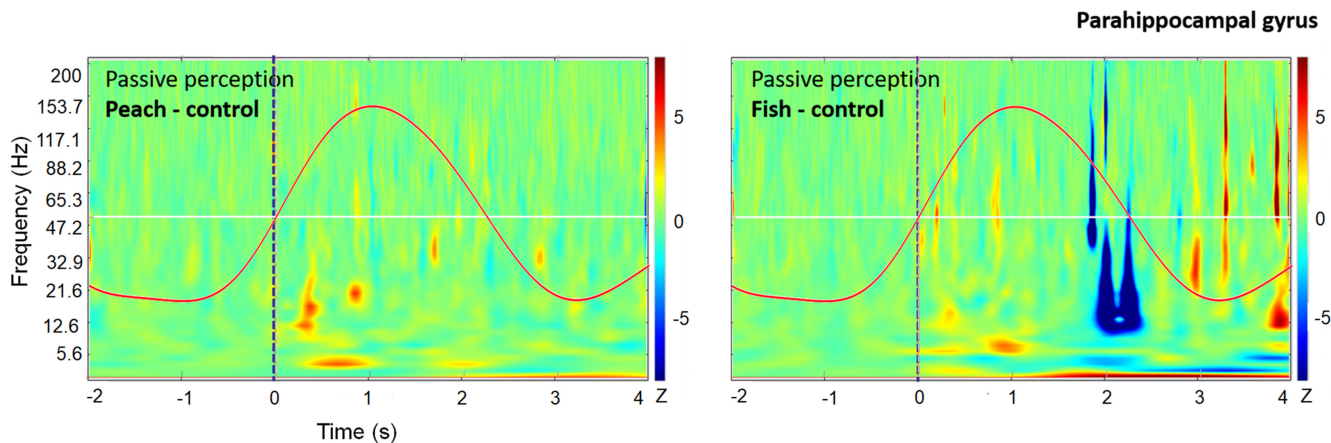


FIGURE 4 Time–frequency analysis of the olfactory response to peach or fish odors in the parahippocampal gyrus. The maps show the contrast between odor and odorless conditions. Time point 0 (dotted line) reflects the onset of stimulation realigned to the inspiration phase (red line). Frequencies are displayed in a logarithmic way. The color map is expressed as a Z-score derived from the power ($\mu\text{V}^2/\text{Hz}$).

posterior portion of the piriform cortex is correlated with the odor quality (Gottfried et al., 2006), and similar fMRI patterns reflect similar odor perception (Howard et al., 2009). In addition, perception of odor quality seems to be refined from the piriform and amygdala to the orbitofrontal cortex (Sagar et al., 2023).

Thus, more investigations are needed in order to check that these differences are not just odor specific, or related to differences in inhalation amplitudes or duration.

In addition, the parahippocampal gyrus showed different oscillations for fish and peach in the exhalation phase (Figure 4). This illustrates the complexity of a phase dependency that might also rely on contextual information.

These results provide some insights into differential oscillation patterns in the human primary olfactory cortex for pleasant and unpleasant odors, which has to be further studied.

5.2.3 | A lack of sustained gamma band: Context dependent?

For both odors, the gamma oscillations were present only very briefly. This contradicts the literature described in Sections 4.2

and 4.4 where the gamma band was quite dominant and long-lasting. However, the studies reported sniff-induced olfactory processing where patients were cued about the odor delivery. As discussed in Section 4.3, gamma is hypothetically modulated by the attentional status and expectations. Thus, gamma may be less pronounced when the task is completely passive, as it was the case here.

Taken together, these results illustrate hypotheses that need to be proven also at a group level. They point at different features that have to be considered in this field of research.

6 | GENERAL DISCUSSION

6.1 | Hypotheses and future perspectives

The timing and sequence of oscillations found in the different structures of the olfactory system seem to play an important role for olfactory sensations. Possibly, the respiration-triggered sequence of oscillations (gamma, theta) combined with specific electrical stimulation could evoke reproducible olfactory percepts. That could be seen as an alarm clock that starts when the appropriate baseline is

entrained by respiration. The simultaneous activation of different structures could also be considered, combining different oscillations in a specific sequence and the coherence of these events between the different brain structures.

6.2 | Limitations

Conducting experiments involving invasive brain recordings in humans requires special attention when it comes to interpreting results. Firstly, because it usually entails very low sample sizes. For example, the studies reported here present results from 3 to 18 patients.

On the methodological side, the patients undergoing intracranial recordings sessions suffer from pharmacoresistant epilepsy typically originating from the temporal lobe. Thus, the placement of the electrodes is not led by research but clinical needs, which means that the brain structures from which recordings are taken vary from patient to patient and from study to study (see [Table 1](#)). The literature dealing with olfaction and intracranial recordings in humans indexed here mostly provides insights from the piriform cortex (7/13 studies), the amygdala (7/13 studies), and the hippocampus (3/13 studies). Consequently, it is challenging to investigate the spatial propagation of neural oscillations through various brain structures and secondary olfactory areas in particular.

Moreover, the variety of procedures does not allow us to draw strict conclusions. For instance, the cognitive load required for the olfactory tasks was not the same across studies (see [Table 1](#) for more information about the procedures). Some patients received odors in a passive way, while others had to count the number of stimulus presentations, some were cued in advance while some were not. Some had to perform matching-to-sample tasks, others not. This could have an impact on the dynamics of the different networks involved and the coherence or reinstatement of the oscillatory patterns across structures.

Second, epilepsy is a disease in which signals from neural assemblies are overly synchronized. The epileptogenic zones can be located in olfactory brain structures (Khurshid et al., 2019). In addition, if any, the type of medication used to prevent seizures might affect the oscillatory patterns of the brain (Zijlmans et al., 2009). Thus, findings in the context of dynamics of brain rhythms elicited by olfaction have to be interpreted carefully. Yet, it is to note that the treatment of most of the patients that receive iEEG indication is toned down during the time of iEEG assessment. Long-time side effects of epileptogenic medication should also be taken into account.

Thirdly, and more specifically patients are implanted in the above discussed areas mostly have long-standing lesions in these areas that had altered the normal function of this tissue. Temporal lobe epilepsy patients typically encounter difficulties in discriminating and identifying smells properly (Desai et al., 2015; Hwang et al., 2020; Kohler et al., 2001). However, it remains unclear to

what degree they abnormally detect odors (Hwang et al., 2020; Kohler et al., 2001; Türk et al., 2020) as studies on this point report inconsistent results. The abnormalities in odor discrimination and identification might arise from general cognitive deficits further to the local effects. It has indeed been shown that these two specific olfactory performances reflect the integrity of some cognitive abilities (Hedner et al., 2010; Sabiniewicz et al., 2021; Willander & Larsson, 2007), some of which are impaired in epileptic patients, namely emotion recognition and social cognition (Amlerova et al., 2014; Edwards et al., 2017; Hixson & Kirsch, 2009; Jiang et al., 2014; Monti & Meletti, 2015). In particular, negative emotions such as anger, disgust, sadness, and fear are affected (Edwards et al., 2017; Monti & Meletti, 2015), which might be reflected in the pleasantness assessment of an odor. Possibly also as a result of the decreased olfactory function, epileptic patients exhibit decreased olfactory bulb volumes (Hummel et al., 2013; Inal et al., 2021) and changes in the piriform cortex (Young et al., 2019).

7 | CONCLUSION

Olfaction has complex functions related to warning of dangers, communication, and eating and drinking. It involves different levels of processing, from breathing patterns by way of intensity, pleasantness, or higher cognitive tasks in various brain structures. Olfactory brain networks integrate internal and external stimuli, and contextual information. This is accomplished, at least in part, via specific dynamics in the frequencies of neural oscillations in the different olfactory structures.

DECLARATION OF TRANSPARENCY

The authors, reviewers, and editors affirm that in accordance with the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

AUTHOR CONTRIBUTIONS

Coralie Mignot was involved in conceptualization, methodology, formal analysis, investigation, writing—original draft, visualization. Susanne Weise was involved in conceptualization, investigation, writing—original draft. Dino Podlessek was involved in resources, writing—review & editing. Georg Leonhardt was involved in resources, writing—review & editing. Moustafa Bensafi: was involved in writing—review & editing, supervision, project administration, funding acquisition. Thomas Hummel was involved in conceptualization, methodology, resources, writing—review & editing, supervision, project administration, funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interests.

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DATA AVAILABILITY STATEMENT

The dataset described in the current manuscript is available from the corresponding author on reasonable request.

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