NEUROCASE
https://doi.org/10.1080/13554794.2021.1921221

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CASE STUDY

Consequences of gaining olfactory function after lifelong anosmia

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ABSTRACT

We present a rare case in which a patient has gained her smell after lifelong anosmia. The patient was objectively tested and diagnosed with functional anosmia at age 13 and reported they were experiencing a new sensation of smell at age 22. Our results show an electrophysiological signal for two unimodal odorants. The patient had a retronasal score in the hyposmic range and self-reported the ability to smell non-trigeminal odors, but reported being disturbed by the presence of the new sense and co-occurrence of phantosmia. We discuss our case in routes of neurogenesis and non-forming memory association with odors.

ARTICLE HISTORY
Received 5 February 2021
Accepted 16 April 2021

KEYWORDS
Ansomia; olfactory recovery; neurogenesis; congenital; new sense; memory; phantosmia

Introduction

The loss of smell can lead to changes in behavior and quality of life. Many individuals only experience these changes in an acute phase with even more people experiencing a gradual decrease in olfactory function, for example, with aging or with the course of a chronic rhinosinusitis (Hummel & Lötsch, 2010; London et al., 2008; Pellegrino, Walliczek-Dworschak et al., 2017; J. Reden et al., 2007; Schwob et al., 2017). A certain portion of these people will recover from the olfactory loss, for example, with recovery from acute infections of the upper respiratory tract possibly based on gradual regeneration of olfactory receptor neurons. However, a segment of those losing the sense of smell will not recover and may make adjustments to live a life without smells (Croy et al., 2014). In fact, those who do not notice their smell loss may never experience an impairment to the quality of life and thus make no adjustments (Oleszkiewicz et al., 2020).

Adjustments, or lack of them, may be different with those that never had olfactory function since they do not know the benefits associated with a functioning sense of smell. This scenario can be seen in congenital anosmia. Additionally, a similar result may appear with those who have lost their sense of smell at an early age or have forgotten what it is like to have this sense functioning, for example, in patients with chronic rhinosinusitis without a sense of smell since years. To date, most reports have dealt with adjusted behaviors from long-term smell loss and failure to recover.

In post-infectious olfactory loss, the chances of recovery diminish after the first 1– 2 years (Hendriks, 1988; Ogawa et al., 2020; J. Reden et al., 2006). Yet, recovery after 5, 7, and 9 years has been previously reported for patients losing their smell after a traumatic brain injury (Mueller & Hummel, 2009; Sumner, 1964; Zusho, 1982). Similarly, reports of late recovery after surgery and/or steroids exist for patients with chronic rhinosinusitis (Heilmann et al., 2004; Jafek et al., 1987). However, there has not been reports of someone with lifelong anosmia being able to smell in adulthood. Regaining smell without ever having it might result in a very different experience as learned association with smells would not exist. Here, we present a rare case in which a patient has gained her smell after lifelong anosmia.

Case presentation

A female patient (age of 25 years; right-handed) presented herself for the first time in our outpatient consultation in November 2020 with suspected congenital olfactory disorder that would have existed in the first 25 years of life. Medical history confirms the olfactory dysfunction which was tested at age 13 with a psychophysical odor identification test performed in a manner not applying forced-choice odor selections (Sniffin' Sticks; (Hummel et al., 2001)), in which the patient was unable to perceive any of the 12 odors presented separately to the left and right nostrils. A detailed otorhinolaryngological examination showed no nasal pathologies. The MR scans performed at the time showed absence of olfactory bulbs and a bilaterally shallow olfactory sulcus (Figure 1). At age 12, she was diagnosed with hypothyroidism and has been taking hormones since this time and this coincided with severe depression between ages 12 and 22. She experienced spinal issues since elementary school (and was diagnosed with scoliosis) and at 18 she experienced a triple herniated disc. At visit time, she claimed her back pain and depression have not bothered her in several years.

From an age of 24 years she was able to perceive more and more fragrances with occasional new smell impressions every few weeks. During an interview process, she emphasized that her "new sense" is an annoyance to her with most odor sensations being unpleasant. Only a few fragrances are perceived as pleasant (e.g., lavender or curry). To the former, she has experienced more and more unpleasant smells (e.g., manure, onion, garlic) than pleasant ones which has increased her anxiety.

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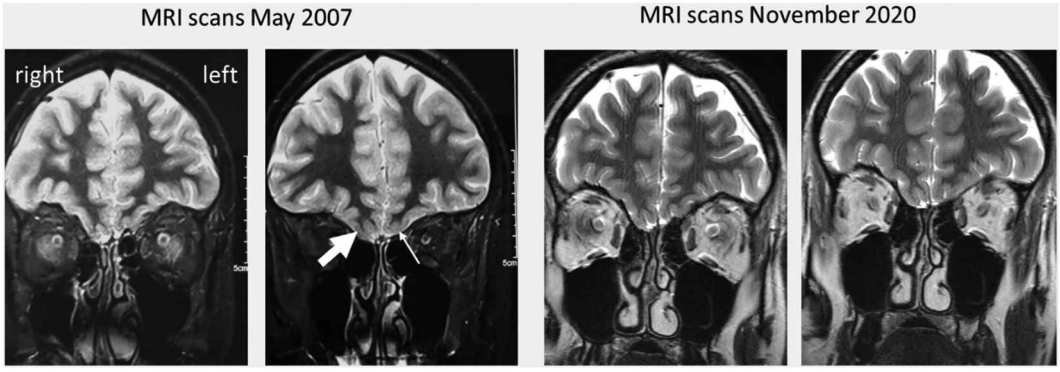

Figure 1. Patient MRI scans at age 12 and a recent visit after regaining smell function (age 25). Clear, but flattened olfactory sulcus on the right hemisphere is visible while the sulcus is flattened on the left. At both occasions, no clearly defined olfactory bulbs could be detected.

During the last months, she fainted and connected this collapse to the olfactory stress. Additionally, during the recent olfactory recovery period (~18 months), there have been a few olfactory phantoms (phantosmia II°: intense [8/10], unpleasant [−2 on a scale from −5 to +5], lasting minutes to hours, not daily but constant frequency, extremely annoyed by the odor phantom (Hummel et al., 2013)). From a follow-up interview (10 days after November visit), the patient reported on the odor phantoms "I often cannot tell whether the smell is real or not. It usually feels just as strong and real as when I actually smell something" and "smells stay in the nose for hours which is stressful". On a third interview (4 months after November visit), following an odor presentation, a pinch of the nose did not make the smell disappear. Gustatory function has remained unchanged over the years although retronasal aromas have mostly become more pleasant.

The patient underwent an ENT medical examination which showed the following: mucosa free of irritation/reddening, no secretion, no polyps, olfactory cleft on both sides free, slight septal deviation to the right, and no pronounced turbinate hyperplasia. Orthonasal olfactory function was checked with the "Sniffin 'Sticks" test, consisting of threshold (T), discrimination (D) and identification (I) tests (Hummel et al., 1997). The composite score (TDI value) of all three tests allows a classification into normosmia (>30.5 points), hyposmia (>16 points, ≤30.5 points) and functional anosmia (≤16 points) for the age range of the patient (Oleszkiewicz et al., 2019). The smell test showed a TDI score of 12 points (T-1, D-6, I-5), and she claimed that she could smell some of the odors very clearly during testing. Still, based on the TDI score she was diagnosed with orthonasal functional anosmia. However, in a test measuring retronasal olfactory function with taste powders (Heilmann et al., 2002), the patient reached a score of 15/20 which suggests hyposmia. Both tests were repeated 4 months later with similar results such that TDI was in the functional anosmic range (T-1, D-5, I-6) while retronasal function was again in the hyposmic range (12/19 correct). Additionally, at follow-up, she was asked for perception of 32 odorants regarding detection (yes/no) and pleasantness (11-point Likert-type scale, "extremely like" to "extremely dislike", Table 1). The patient claimed that she could smell half (16) of these odors which included mostly trigeminal (e.g., peppermint, clove), but also non-trigeminal odorants (e.g., coffee, lilac). Many pleasant ratings for spices were lower than what is commonly found (e.g., clove, anise, ginger; (Dravnieks et al., 1984)) and some similar odors were given opposite ratings of liking (low peppermint, but high mint). Supra-threshold taste sprays showed normal taste function (e.g., normogeusia) for sweet, bitter, sour, and salty (4/4 correct; (Hummel et al., 2013)).

Table 1. Common odorants assessed for detection and hedonics.

Odorant	Smell	Hedonics	Odorant	Smell	Hedonics
Orange	Yes	7	Pear	No	-
Peppermint	Yes	3	Cocoa	No	-
Turpentine	Yes	1	Lilac	Yes	5
Clove	Yes	3	Grapefruit	Yes	5
Leather	No	-	Grass	No	-
Banana	No	-	Strawberry	No	-
Garlic	Yes	2	Honey	No	-
Rose	No	-	Ginger	Yes	3
Fish	Yes	1	Coconut	No	-
Citrus	Yes	4	Lavender	Yes	8
Coffee	Yes	10	Melon	No	-
Anise	Yes	3	Peach	No	-
Mint	Yes	11	Mushroom	No	-
Licorice	No	-	Smoke	Yes	1
Apple	No	-	Chocolate	No	-
Pineapple	No	-	Onion	Yes	1

Electrophysiological tests were performed to further understand underlying olfactory functioning. Objective olfactometry using electroencephalography–derived olfactory event-related potentials showed clear cerebral responses for left and right-sided stimulation with hydrogen sulfide ("rotten eggs-like" odorant) and phenylethyl alcohol ("rose-like" odorant) which suggests an intact olfactory system (Figure 2) (Lötsch & Hummel, 2006). In the follow-up interview, the patient reported that the 'rotten egg smell' stayed with her for hours after the testing. Magnetic resonance imaging (MRI) structural scans revealed that the olfactory sulcus in the plane behind the eyeballs was of almost normal depth on the right side, but clearly flattened on the left. The olfactory bulbs were not clearly distinguishable on either side (Figure 1). There were no other structural abnormalities in the brain.

Discussion

The medical history of the patient points to congenital, possibly isolated, anosmia. As typical with congenital loss, the patient

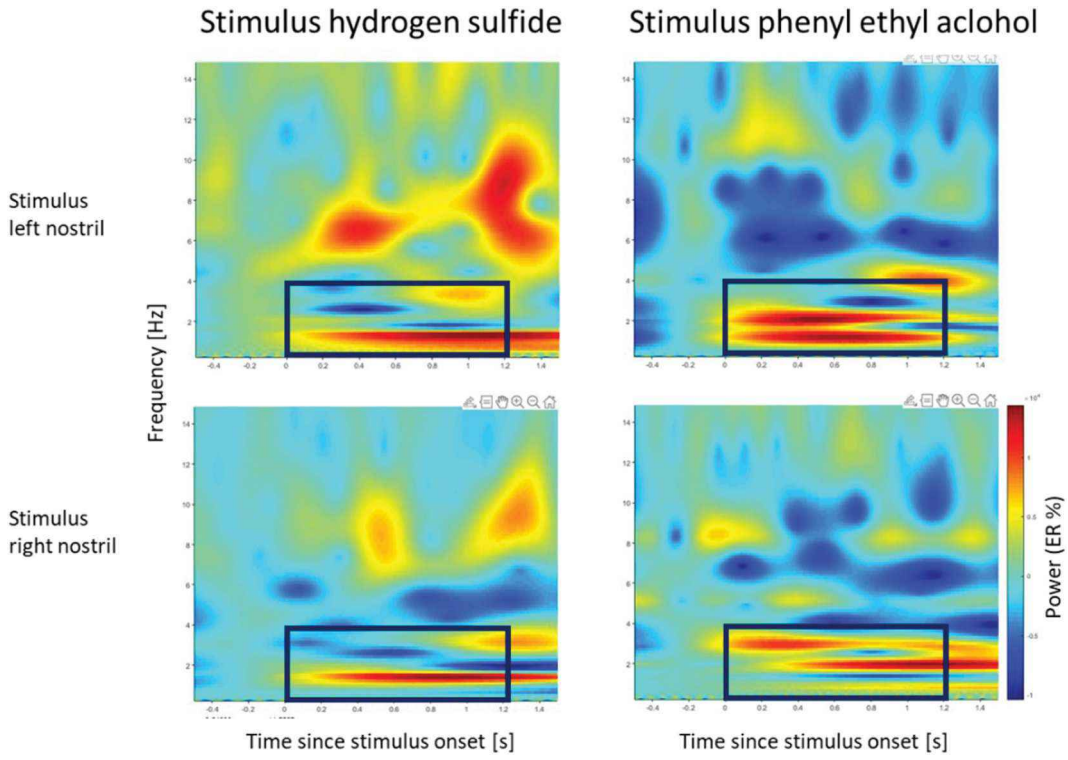

Figure 2. Time–frequency representation of the non-phase locked EEG responses to trigeminal and olfactory chemosensory stimulation (CWT-SINGLE). Non-phase locked EEG responses were identified by performing across-trial averaging in the time-frequency domain, a procedure which enhances time-locked EEG responses regardless of whether they are phase-locked to the onset of the stimulus. The panels show the time-frequency maps of oscillation amplitude (electrode Pz vs. A1A2). Note that olfactory stimulation elicits a long-lasting non-phase-locked increase of signal amplitude centered around 2–4 Hz. The scale displays EEG-power change in percent compared to the pre-stimulus interval.

was diagnosed in her early teenage years, most likely after it was brought to her attention that others smell (Abolmaali et al., 2002). However, in her mid-20s, she started to perceive odors. From then on, she also perceived an occasional odor phantom, i.e., phantosmia, following an odorous sensation, elicited by an odorous stimulus, which could not be switched off. Hence, she experiences an olfactory percept, and then the sensation lingers from that previous exposure even with no airflow. To our knowledge, this is the first report on a patient recovering from lifelong anosmia. Our results clearly show an electrophysiological signal to two unimodal odorants which clearly indicates the presence of an (at least partially) intact sense of smell (Lötsch & Hummel, 2006; Schriever et al., 2017). In addition, the patient had a retronasal score in the hyposmic range and self-reported the ability to smell some non-trigeminal odors (e.g., lavender, lilac) (Hummel & Frasnelli, 2019).

Recovery of smell after several years of loss has been reported, but typically after loss from traumatic brain injury (Mueller & Hummel, 2009; Sumner, 1964; Zusho, 1982). The MRI scans point to a more developed sulcus in the right hemisphere while the electrophysiological results demonstrate activity regardless of the stimulated side. To this end, recent work shows that a subset of individuals, and in particular females, may have olfactory experience without definitive olfactory bulbs (Rombaux et al., 2007; Weiss et al., 2020). Morphological changes outside of the primary olfactory cortex have been shown for congenital anosmia (Frasnelli et al., 2013; Peter et al., 2020) while preserving the functional connectivity of the olfactory cortex (Peter et al., 2021). Thus, it may be speculated that neurogenesis during recovery for this patient may have taken alternative routes. To this degree, the authors hypothesize that hormonal status may have delayed the initial neurogenesis to the olfactory bulb or parts of olfactory cortex (for alternative function) such as the anterior olfactory nucleus. Interestingly, several of the odors perceived by the patient have a slightly trigeminal component which has been shown to boost odor intensity, even at subthreshold levels (Pellegrino, Walliczek-Dworschak, et al., 2017).

This appearance of olfactory function after lifelong absence appears to have some negative aspects. The patient reported being disturbed by the presence of the new sense, and also by the co-occurrence of phantosmia. Some smells, as they appear, are pleasant, but most new smells are perceived to be unpleasant and annoying. One explanation could be the lack of memory and emotional associations with each odor, which may be comparable to patients with severe hearing impairment receiving cochlear implants some of whom also cannot tolerate some of the newly acquired sounds (Brodie et al., 2018). Most odor evaluations by humans are perceptually learned over years of exposure; however, trigeminal feelings like pain are innately avoided. Many of the odors rated as unpleasant by the patient (such as spices) carry a trigeminal signal, which may warrant unpleasantness until learned to not be dangerous. However, peppermint and mint both give off a “cooling” sensation while presenting similar odor qualities (Pellegrino & Luckett, 2019).

This may describe a discrepancy in odor experience in which appetitive odor conditioning through exposure has been made with one bimodal odor, but not the other (Martin-Soelch et al., 2007).

As for phantom smells, the odors were unpleasant and lingered within the nose for minutes to hours. Phantosmia is implicated in many neurological and psychiatric diseases (e.g., mental illness, migraines) (Hong et al., 2012; Leopold, 2002) and is higher in younger individuals and women (Bainbridge et al., 2018; Sjölund et al., 2017). It has been related to dysfunctions at the level of the olfactory mucosa, the olfactory bulb or the primary/secondary olfactory cortex; however, points of origin are less clear when direct damage (e.g., head trauma) is not observed such as in cases of neurological disease. It appears unclear why the patient developed these phantoms, but upon further investigation appears to be lingering odors from prior exposure. These lingering odors may represent disinhibition of olfactory excitations that are part of the process of developing olfactory function.

More obvious questions are how it should be possible that (1) somebody without olfactory bulbs should have olfactory percepts, and that (2) a person without a sense of smell from birth should develop olfactory function. At least the former question has been discussed in depth previously (Weiss et al., 2020). Among the major ideas were (1) that, although unlikely given the resolution of present MR scans, OBs might have been too small to be detected, (2) that the olfactory sensations are mediated by the trigeminal nerve, which would be astonishing given the many subtle, unimodal odors the patient was able to detect and the electrophysiological response to pure unimodal odorants. In addition, a hypothesis could be that portions of the coding of olfactory information are different from that in other mammals so that some olfactory sensations are possible even without an olfactory bulb. In any case, the current case gives room to a discussion whether congenital anosmia is a permanent condition and whether it may be possible to develop a therapeutic regimen to enable these individuals to peak into the olfactory realm, possibly through the use of structured olfactory exposure (Sorokowska et al., 2017). Hence, the current case study represents a rare incidence of olfactory recovery after lifelong anosmia.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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