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Direktor: Herr Prof. Dr. med. Dr. h.c. Thomas Zahnert

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# Advancing Olfactory Training:
# Perspective from patients, neural mechanism, and efficacy

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Zetian Li, MSc

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## List of Abbreviations

| | |
|---|---|
| **CRS** | Chronic Rhinosinusitis |
| **COVID-19** | Coronavirus Disease 2019 |
| **ENT** | Ear, Nose and Throat |
| **EOG** | Electro-Olfactogram |
| **EPI** | Echo-Planar Imaging |
| **FOV** | Field of View |
| **GMV** | Gray Matter Volume |
| **$H_2S$** | Hydrogen Sulfide |
| **MATLAB** | Matrix Laboratory |
| **MRI** | Magnetic Resonance Imaging |
| **OB** | Olfactory Bulbs |
| **OD** | Olfactory Dysfunction |
| **OFC** | Orbitofrontal Cortex |
| **OT** | Olfactory Training |
| **ORNS** | Olfactory Receptor Neurons |
| **PEA** | Phenyl Ethyl Alcohol |
| **RM-ANCOVA** | Repeated Measures Analysis of Covariance |
| **ROI** | Region of Interest |
| **SARS-Cov-2** | Severe Acute Respiratory Syndrome Coronavirus 2 |
| **SST** | Sniffin' Sticks Test |
| **SPM** | Statistical Parametric Mapping |
| **SPSS** | Statistical Package for The Social Sciences |
| **TE** | Echo Time |
| **TDI** | Threshold-Discrimination-Identification |
| **TR** | Repetition Time |
| **VBM** | Voxel-Based Morphometry |

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**Li, Z.,** Pellegrino, R., Kelly, C., & Hummel, T. (2024). Olfactory training: perspective from people who were disturbed by their smell problems. *European Archives of Oto-Rhino-Laryngology*, *281*(12), 6423-6430. doi:10.1007/s00405-024-08911-7

**Li, Z.,** Gebler, J., Joshi, A., Xu, X., Thaploo, D., Hähner, A., ... & Hummel, T. (2025). Functional but Not Structural Brain Changes After Olfactory Training in Women With COVID-19-Associated Olfactory Dysfunction. *The Laryngoscope,* doi: 10.1002/lary.32128

**Li, Z.,** Anne, A., & Hummel, T. (2023). Olfactory training: effects of multisensory integration, attention towards odors and physical activity. Chemical Senses, 48, bjad037. doi: 10.1093/chemse/bjad037

# Introduction

The sense of smell, or olfaction, plays a fundamental role in human life, influencing survival, nutrition, social interactions, and emotions (Boesveldt & de Graaf, 2017; Boesveldt & Parma, 2021; Croy et al., 2014; Kontaris et al., 2020; Lee et al., 2024; Schubert et al., 2011). Olfactory dysfunction (OD) affects around 20% of the population, which significantly impacts quality of life (Desiato et al., 2021). Olfactory training (OT) has emerged as a simple and also effective method to improve OD. Based on repeated exposure to odorants, OT engages the olfactory system's neuroplasticity to improve olfactory function (Patel, 2017; Pieniak et al., 2022; Sorokowska, 2017). Abundant research has reported the effectiveness of improving olfactory function in the clinical context, albeit the perspective from patients with OD regarding OT remains unclear, for instance the reasons for not participating in OT. Its mechanisms might involve peripheral regeneration of olfactory receptor neurons (ORNs) and central neural plasticity such as the olfactory bulbs (OB) and related brain areas (Gellrich et al., 2018; Gürbüz et al., 2022; Kim et al., 2020; Mahmut et al., 2020; Negoias et al., 2017; Rezaeyan et al., 2022). While classical OT protocols have demonstrated efficacy and are recommended for OD patients, modified training regimes may further enhance outcomes, even in healthy population.

This thesis explores the perspective regarding OT from patients with OD, underlying neural mechanisms of OT, and modification in training protocols to optimize olfactory recovery.

**Overview of the sense of smell**

The process of odor detection begins when air currents carry odor molecules into the nostrils, guiding them to the olfactory cleft (Firestein, 2001). There, the molecules dissolve into the mucus layer covering the olfactory epithelium and bind to olfactory receptors on the ciliated dendrites of ORNs. This binding activates olfactory-specific G-protein coupled receptors and adenylate cyclase, which generate cyclic adenosine monophosphate. The cyclic adenosine monophosphate opens ion channels in the cell membrane, allowing sodium and calcium ions to flow into the cell, depolarizing the membrane and triggering an action potential (Schwob, 2002).The action potential travels along the axons of the ORNs through the cribriform plate to the glomeruli in the OB, where the axons form synapses with the dendrites of mitral and tufted cells (Lundstrom et al., 2011). These cells then transmit the signal through the lateral olfactory tract, which is composed of bundled axons from mitral and tufted cells, to the primary olfactory cortex, including regions such as the anterior olfactory nucleus, piriform cortex, amygdala, and entorhinal cortex (Dikecligil &

Gottfried, 2024; Wilson et al., 2006). From there, the primary olfactory cortex relays the information to the secondary olfactory cortex, including the hippocampus, orbitofrontal cortex (OFC), and insular cortex. The secondary cortex integrates this input with systems involved in emotion, learning, and memory.

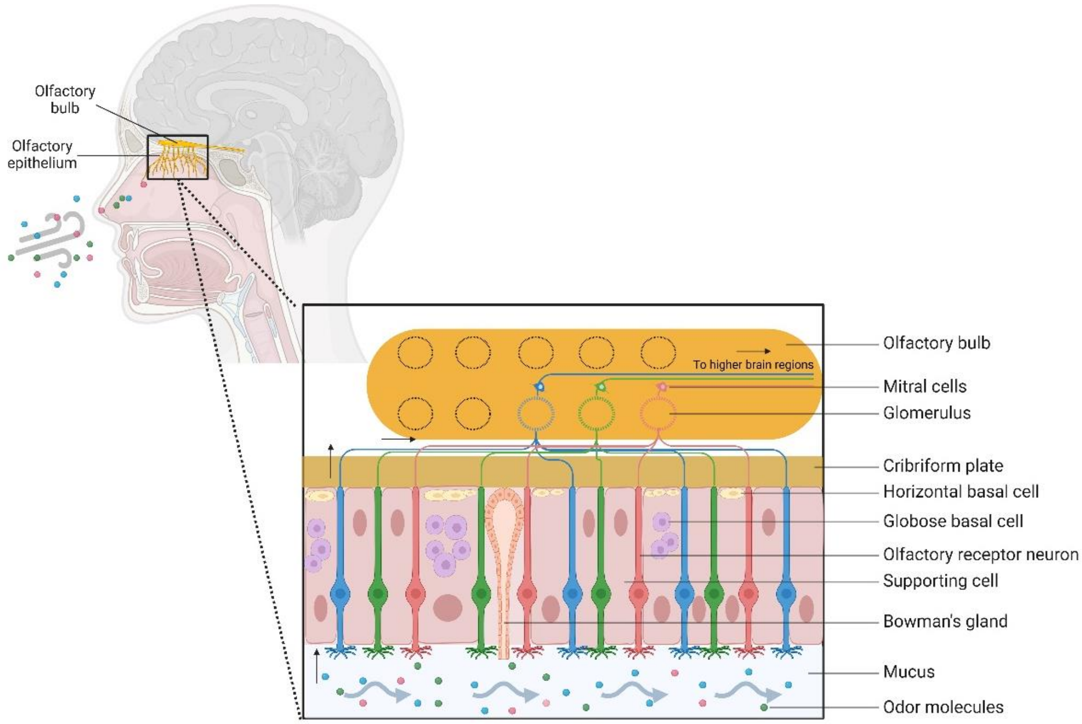


***Figure 1*** *The process of odor detection (Created in https://BioRender.com)*

These complicated and sophisticated processes enable human to perceive the sense of smell, or olfaction, which is an essential part of human life, influencing survival, nutrition, social interactions, emotions, and importantly, quality of life (Boesveldt & de Graaf, 2017; Boesveldt & Parma, 2021; Croy et al., 2014; Kontaris et al., 2020; Lee et al., 2024; Schubert et al., 2011). As one of the most ancient sensory systems (Rowe et al., 2011), it plays a key role in detecting environmental dangers, such as fire or toxic substances, providing an early warning system that ensures safety (Iravani et al., 2021). Beyond this protective role, smell is central to dietary behavior, allowing people to identify food quality and freshness while enhancing the overall experience of eating through flavor perception (Boesveldt & de Graaf, 2017; Shanahan et al., 2021). Without smell, the enjoyment of food is significantly reduced, which can impact nutrition and overall satisfaction (Kershaw & Mattes, 2018).

Olfaction is critical in social interactions (Blomkvist & Hofer, 2021). Humans are able to detect fear or happiness through body odor of other individuals, influencing interactive attraction and intimacy (Roberts et al., 2022). Impairments in olfaction can disrupt these processes, leading to social insecurity, loneliness, and challenges in forming and maintaining close social bond. Olfaction has a close link to emotions as well (Leschak & Eisenberger, 2018). For instance, exposure to body odor collected from individuals in a happy state elicited facial expressions and perceptual-processing styles associated with happiness in those who received the signals (de Groot et al., 2015). On the other hand, olfaction also serves as a marker for depression (Croy, Symmank, et al., 2014; Croy & Hummel, 2017; Li et al., 2021; Taalman et al., 2017). Losing the ability to smell can lead to feelings of isolation, anxiety, and depression, further highlighting the importance of olfaction in quality of life (Sivam et al., 2016).

## Olfactory dysfunction

Despite its importance, the prevalence of overall OD is around 22% worldwide (Desiato et al., 2021), with about 5% experiencing severe OD (Schlosser et al., 2020). It is particularly common among older adults and strongly predicts five-year mortality in this population (Pinto et al., 2014). Symptoms like anosmia (no usable olfactory function assessed by olfactory measurement) or hyposmia (a quantitatively reduced ability to detect and identify the presence of certain odors), parosmia (a symptom of qualitative OD where distorted odor perception occurs in the presence of an odor), and phantosmia (the perception of an odor, often unpleasant in the absence of an odor stimulus) not only disrupt basic daily functions but also reduce quality of life (Hernandez et al., 2023). In recent years, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has brought unprecedented attention to the sense of smell, as millions of individuals experienced sudden OD due to Coronavirus disease 2019 (COVID-19) (Walker et al., 2020), highlighting the profound impact of OD not only on quality of life but also its critical role in health and safety. Consequently, understanding and addressing OD has become a priority in both clinical and research domains.

Managing OD is complicated by its varied causes, which include viral infections, sinus diseases, head injuries, congenital and idiopathic causes, and neurodegenerative conditions like Alzheimer’s or Parkinson’s disease (Whitcroft et al., 2023). However, many people remain unaware of their smell loss until it noticeably impacts their daily lives (Oleszkiewicz et al., 2020). Diagnosing OD typically involves a combination of self-reports and standardized tests like the Sniffin’ Sticks test (SST, Hummel et al., 1997). Advanced diagnostic tools, such as imaging scans, can provide additional insights into the underlying causes of OD, but these are not always accessible.

Various treatments are available for OD (Jafari & Holbrook, 2022). Medications, such as systemic and intranasal corticosteroids, are commonly prescribed for cases linked to chronic rhinosinusitis (CRS) or inflammatory conditions, helping to reduce inflammation and restore nasal patency (Gudis & Soler, 2016). Surgical interventions may be beneficial for CRS-related OD but are less effective for other etiologies (Ye et al., 2022). Novel approaches such as vitamin A therapy, stem cell treatments, and platelet-rich plasma are under research, offering potential for regeneration of olfactory neurons, though their clinical usefulness is still limited (Hummel et al., 2017; Kurtenbach et al., 2019; Yan et al., 2020).

Among these treatments, OT has garnered significant attention as an effective and non-invasive therapy (Patel, 2017; Pieniak et al., 2022; Sorokowska, 2017). Unlike medications or surgical methods, OT harnesses the neuroplasticity of the olfactory system. This intervention involves repeated, structured exposure to specific odors over time, which is supposed to stimulate ORNs and enhance functional improvement in central olfactory systems. Its simplicity, cost-effectiveness, and minimal side effects position it as an essential treatment option for OD.

## Olfactory Training: A Simple but Effective Method

OT, the systematic exposure to odors, has been validated to enhance olfactory function as an effective, affordable and easy-to-conduct intervention (Pieniak et al., 2022; Sorokowska, 2017). OT was initially presented as a treatment for patients with various causes for OD, with exposure to four odors twice daily: phenyl ethyl alcohol (PEA, rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves) (Hummel et al., 2009). These odors were selected based on Henning's “odor prism” concept, which categorizes primary odors into flowery (e.g., rose), fruity (e.g., lemon), resinous (e.g., eucalyptus), aromatic (e.g., cloves), foul, and burnt (Hans Henning, 1916). After being exposed to the selected four odors for 12 weeks, the experimental group showed improved olfactory performance in the Sniffin’ Sticks test (Hummel et al., 1997), suggesting a better olfactory function.

OT’s appeal lies in its simplicity and accessibility. Patients can perform training at home with minimal equipment, making it an affordable option for individuals with limited access to specialized care. It is also a safe method, free from the side effects associated with medications or surgery (Patel, 2017). Importantly, OT may align with principles of neuroplasticity of the ORNs and also associate with central olfactory systems processing (Kim et al., 2019; Reichert & Schöpf, 2018).

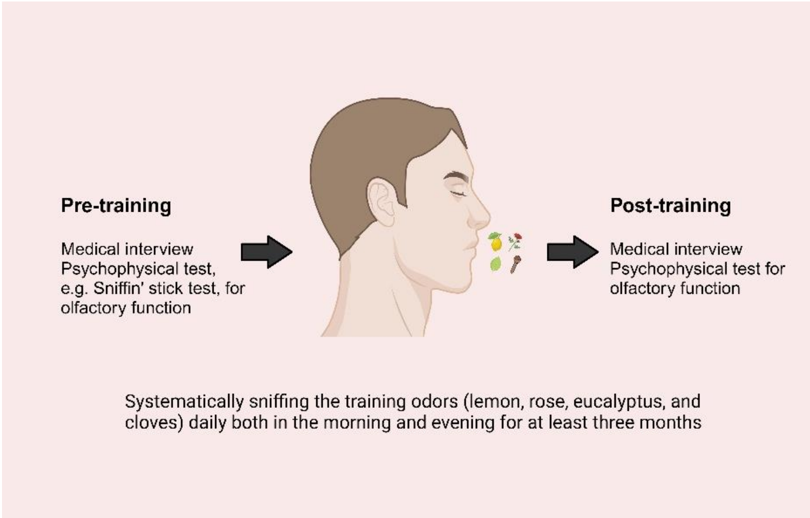


***Figure 2*** *The classical protocol of olfactory training (Created in https://BioRender.com)*

**Potential mechanism of OT**

Approximately fifteen years after the first experimental OT study in humans was published (Hummel et al., 2009), evidence suggests that OT enhances olfactory function through a combination of peripheral changes in the olfactory epithelium and central changes in the OB, primary olfactory cortex, and secondary olfactory cortex.

At the peripheral level, OT potentially accelerates the regeneration of ORNs, employing the unique regenerative capability of olfactory system (Schwob et al., 2017). Unlike many other sensory systems, the olfactory system possesses a remarkable ability to regenerate throughout life, supported by basal cells located in the olfactory epithelium (Schwob, 2002). During OT, repeated and systematic exposure to odorants activate these basal cells, promoting their differentiation into mature ORNs (Avaro et al., 2022). These neurons replace damaged or degenerated ORNs, ensuring the continued ability to detect and process odorant signals. It is hypothesized that OT may upregulate olfactory-specific genes that enhance receptor function and signal transduction (Croy et al., 2015). Studies on mouse model have provided more evidence that OT boosts the activity of key molecular components involved in olfactory signal transduction (Kim et al., 2020). Increased messenger ribonucleic acid levels of olfactory marker protein, which is highly expressed in mature ORNs, support the hypothesis that OT accelerates the turnover and maturation of ORNs (Kim et al., 2020). OT also increases the expression of neurotrophic factors, which are critical for neuronal survival, growth, and plasticity and may drive the differentiation and survival of ORNs (Kim et al., 2019, 2020).

In addition, an early study by Youngentob & Kent (1995) demonstrated that rats repeatedly exposed to odors showed enhanced response magnitudes in the olfactory mucosa, suggesting that OT can modify sensory processing at the peripheral level. In humans, peripheral odor-evoked potentials can be recorded using electro-olfactogram (EOG), a method that directly measures the activity of the olfactory epithelium. Evidence indicates that OT increases EOG responses. For example, Wang and colleagues reported that repetitive exposure to androstenone in specific-anosmic individuals led to increased EOG amplitudes, alongside improvements in olfactory perception (Wang et al., 2004). This study provided direct evidence of peripheral plasticity, linking enhanced receptor activity in the olfactory epithelium to improved olfactory sensitivity. Similarly, Hummel et al. (2018) observed increased EOG responses to odorants such as PEA and hydrogen sulfide (H2S) in patients undergoing OT for 4–6 months, further supporting the role of peripheral mechanisms in OT-induced recovery (Hummel et al., 2018). These findings suggest that OT promotes stimulus-induced plasticity in ORNs, potentially through mechanisms such as increased receptor expression, improved receptor affinity, or the regeneration of ORNs. Together, these processes appear to enhance the responsiveness of ORNs to odorant stimuli, forming the foundation for olfactory recovery.

OT not only involves peripheral changes but also induces structural and functional improvement in the central olfactory pathways, particularly in the OB and higher brain regions. The OB, which serves as the first relay station for olfactory signals, is found to be enlarged in most of the studies after OT (Gürbüz et al., 2022; Mahmut et al., 2020; Negoias et al., 2017; Rezaeyan et al., 2022); both in healthy and patients with OD populations, suggesting OT modified the OB structure. However, some research also reported no improvement of OB volume after training (Gellrich et al., 2018; Haehner et al., 2022; Pellegrino et al., 2019). The literature regarding gray matter volume (GMV) of olfactory-related brain regions also yields inconclusive results. Increase in the olfactory cortex such as entorhinal cortex and OFC was reported (Al Aïn et al., 2019; Haehner et al., 2022; Han et al., 2021), while the thickness of cerebellum which is not classically close related to olfaction is also mentioned (Gellrich et al., 2018; Rezaeyan et al., 2022), or no improvement was found (Chen et al., 2022).

As for functional changes, increased activation in the frontal gyrus was reported after training (Pellegrino et al., 2019). OT led reorganization in the function networks. For instance, a decline in non-olfactory networks was induced, with a stronger connection within the piriform cortex, which is an essential region of primary olfactory cortex (Kollndorfer et al., 2015). Similarly, Jiramongkolchai et al. (2021) found an increased functional connectivity in olfactory regions, accompanied with a decreased connectivity in visual areas. In a resting-state functional MRI study, OT strengthened the connection from cingulate cortex to the insula, as well as the self-inhibitory connectivity of the OFC (Hosseini et al., 2020).

Despite the exact mechanism are understudied, the evidence from previous studies supports this plausible theory: OT improves olfactory function by influencing both peripheral regeneration and central neuroplasticity. At the peripheral level, the exposure to repeated odors may support the renewal of ORNs and improve odor detection, while centrally OT could enhance the function in the olfactory cortex to process and interpret olfactory signals. These combined effects might help individuals recover some aspects of their sense of smell and potentially improve quality of life, such as nutrition, social interactions, and emotional well-being. Yet, the major drawback of these research is the lack of a control group (Chen et al., 2022; Gürbüz et al., 2022; Hosseini et al., 2020; Mahmut et al., 2020; Negoias et al., 2017; Pellegrino et al., 2019), as well as a small sample size (Al Aïn et al., 2019; Gürbüz et al., 2022; Jiramongkolchai et al., 2021; Kollndorfer et al., 2014, 2015; Rezaeyan et al., 2022). These drawbacks may restrict the statistic power and lead to a biased conclusion.

**Training efficacy**

OT has been validated and has been recommended for treating OD over the last years (Patel, 2017; Pieniak et al., 2022a; Whitcroft et al., 2023; Whitcroft & Hummel, 2020). In the clinical context, patients with post-viral OD demonstrated notable improvements in olfactory function, reaching a clinically significant level (Kattar et al., 2021). Studies show that consistent training significantly enhances odor threshold, discrimination, and identification in this population (Pekala et al., 2016). The effectiveness is most pronounced in individuals with a shorter duration of OD (less than one year), highlighting the importance of early intervention (Kattar et al., 2021).

The overall effectiveness of OT in post-traumatic OD remains unclear due to the heterogeneous nature of this patient group and the limited sample sizes in clinical studies. Factors such as the severity of head trauma, cognitive impairments, and brain lesions contribute to variability in outcomes (de Freitas Cardoso et al., 2019; Gudziol et al., 2014; Han et al., 2018). A meta-analysis has reported that 36% patients with post-traumatic OD achieved clinically significant results responses to OT (Huang et al., 2021). These findings highlight the potential of OT and emphasize the need for further research to explore how trauma-related variables influence its effectiveness.

For patients with OD related to CRS or nasal polyps, the effects of OT tend to be less pronounced (Fleiner et al., 2012; Mahmut et al., 2020). While beneficial outcomes from OT have been reported, these findings are not etiology-specific. The chronic inflammation characteristic of sinonasal conditions often hinders recovery at the mucosal level, limiting the overall improvement. However, studies suggest that OT following sinonasal surgery can result in better olfactory improvement compared to non-training groups (Park et al., 2022; Zhang et al., 2022). This indicates that adjunctive therapies, such as OT, hold promise in supporting olfactory recovery in this population.

Although OT was primarily designed for patients with OD, studies have also demonstrated its efficacy in enhancing olfactory abilities among healthy individuals. Children demonstrated significant improvements in olfactory performance compared to controls, mostly in odor sensitivity (Mori et al., 2015) and identification (Mahmut et al., 2021). Moreover, a recent study suggests an improvement of emotional facial expression following OT compared to the placebo group which trained with odorless pens (Pieniak et al., 2024). Studies in healthy young adults report that OT enhances olfactory function, but also increases cortical thickness in key olfactory processing areas, such as OB volume, (Negoias et al., 2017) the OFC, and entorhinal cortex (Al Aïn et al., 2019). OT is particularly relevant for healthy older adults, who often experience age-related decline in olfactory function. Regular exposure to odorants through OT has been shown to mitigate these declines, improving both olfactory performance and quality of life (Lamira et al., 2019; Schriever et al., 2014). Additionally, studies indicate that OT in older adults may enhance related cognitive functions, such as verbal memory, and reduce depressive symptoms (Wegener et al., 2018). On the other hand, OT had limited effect on improving olfaction and cognition, but enhanced functional response to odors in frontal area in older adults with mild cognitive impairment, an early stage of Alzheimer's Disease (Chen et al., 2022).

Numerous evidences shown above support the idea that OT fosters neuroplasticity in OD patients with different etiologies and also in individuals with normal olfactory function. So far, the majority of research focused on the improvement of olfactory function after OT in the clinic, yet there is still a lack of studies investigating OT from the patients' point of view. It is highly important to obtain the patient's perspective and investigate the characteristics of people who do or do not participate in OT and to learn about possible reasons for such different behaviors related to OT.

**Modified training regimes**

To enhance the effectiveness and applicability of OT, several studies have introduced modifications to the classical protocol. Extended training durations—ranging from 12 to 36 weeks—have been shown to yield better outcomes (Altundag et al., 2015; Damm et al., 2014; Geißler et al., 2014). Adjustments to exposure times, such as increasing the duration of inhaling each odor from 10 seconds to 40 seconds per odor have also been investigated (Geißler et al., 2014; Jiang et al., 2019; Jiramongkolchai et al., 2021). In addition, alternative materials, such as Sniffin' Sticks, have replaced brown jars in some studies for greater convenience (Geißler et al., 2014). Training odors were also modified in various studies. For instance, in studies involving children, researchers used carefully selected odors to ensure safety and engagement (Mori et al., 2015). A recent study using Chinese herbal medicine for the training odors revealed the enhancement of odor identification and discrimination, with improvement of anxiety and sleep quality after OT (Qiao et al., 2024). Other researchers have expanded the range of training scents to include menthol, thyme, orange, jasmine, and green tea, stimulating a broader spectrum of olfactory receptors and potentially enhancing results (Altundag et al., 2015).

Beyond these modifications, novel OT methods have emerged. Olofsson et al. (2020) developed an olfactory memory game involving 24 scent-filled tins containing 12 distinct odors, such as vanilla, strawberry, cinnamon, and mint. Participants matched paired scents on a 6×4 grid, with fewer attempts indicating better performance. The game significantly improved odor discrimination, with participants reaching levels comparable to professional wine tasters. Al Aïn et al. (2019) designed a more complex OT protocol comprising three tasks: (1) ranking 16 scented sticks by odor intensity, (2) sorting 11 target odor samples by concentration, and (3) detecting target odors among 14 samples. This protocol resulted in significant improvement in odor identification and increased cortical thickness in olfactory-related brain regions, reflecting neuroplastic changes.

A study involving multisensory training that pairs odors with visual and auditory stimuli was employed in patients with Parkinson's disease (Knudsen et al., 2015). In this study, patients undergoing OT were exposed to the smells in an odor identification test accompanied by visual images, resulting in better odor identification ability. Behavioral and neuroimaging studies highlight that olfaction functions in concert with other senses (Schaal & Durand, 2012; Thesen et al., 2004). For instance, colors can change the perception of odors' intensity, pleasantness, and identity (Zellner, 2013). Similarly, sounds modulate the hedonic tone of odors, where, for example, congruent sounds increase the pleasantness ratings of odors (Seo et al., 2014; Seo & Hummel, 2011). On the other way around, odors influence the perception of sounds and visual impressions. Odor-cued stimuli facilitate sound localization (La Buissonnière-Ariza et al., 2012), as well as the visual identification of an object (Seigneuric et al., 2010). Together with multiple sensory inputs, for instance, conducting OT along with congruent visual (images of training odor: lemon, rose, cloves, and eucalyptus) and auditory stimulation for different odors, the efficacy of OT might be enhanced compared with performing OT alone.

## Objectives

Regarding the context mentioned above, this thesis aims to optimize OT by understanding the perspective from patients, investigating its neurological mechanism, and testing additional approaches to enhance its effectiveness and try to answer following questions:

- Which factors influence patients' adherence to the OT? What are the potential barriers for conducting OT?
- What are the changes in the brain regions both structurally and functionally after OT utilizing functional MRI approach?
- Are there any ancillary methods to induce improvement on OT outcomes?

# Methodology and Results

## Study 1: Olfactory Training: Perspective from People Who Were Disturbed by Their Smell Problems

### *Methodology: Online Questionnaire in Individuals with Olfactory Complaints*

#### Study Design and Participants

Between January 2021 and January 2023, a dataset including 450 people with OD was obtained via an anonymous online questionnaire, which was launched on an informational website about OD. They were divided into OT (n = 161), and No OT (n = 289) groups based on their OT participation. All participants took part in the study voluntarily and agreed with the consent.

#### Online Questionnaire

The Sense of Smell Questionnaire was mainly targeted to obtain perspectives from people who were disturbed by their smell problems. It consisted of several parts, for example, the demographic information (e.g. age range and sex) and general questions such as the causes and onset of their smell loss based on their opinion. Questions were also included regarding parosmia, phantosmia, OT, and quality of life. For instance, "When was the onset of your smell problem", "How often are you aware of your smell problem?", or "Do you think smell loss has led to a loss in your quality of life?". The list of questions included in the analyses can be found in Table 1. The present study focused on the OT part of the survey and divided patients into two groups: OT (n = 161), and No OT (n = 289) groups, according to their responses to the question "Are you doing smell training?" According to previous research suggesting that parosmia and phantosmia exhibit unique demographic profiles, medical backgrounds, and impacts on quality of life (Pellegrino et al., 2021), we removed individuals reporting both parosmia and phantosmia, retaining those who had either parosmia or phantosmia or neither of these conditions in the analysis. In addition, the question "How has your problem changed since it started" was considered a change in impairment (or olfactory condition) and its response (worsened, unchanged, improved) was recoded to be continuous as "-1, 0, and 1" respectively. Symptoms were calculated by counting the number of symptoms including "Stuffy nose, sneezing, facial pain, allergies, polyps, and others".

**Table 1** Items in the Sense of Smell Questionnaire

| Variable | Question | Levels |
|---|---|---|
| **Age** | Your Age | 21-30, 31-40, 41-50, 51-60, 61-70, 71 and over |
| **Gender** | Your Gender | Female, Male, Other, Prefer not to say |
| **Onset** | When was the onset of your smell/taste problem? | Less than 3 months ago, 3-12 months ago, 1-2 years ago, more than 2 years ago, as long as I can remember, I don't know |
| **Olfactory condition** | How has your problem changed since it started? | The situation has worsened, the situation is unchanged, there has been improvement |
| **Cause** | In your opinion, what might have been the cause? | Accident, cold infection, dry mouth, medication, nasal polyps CRS, other, surgery |
| **Symptoms** | Have any of these symptoms? | Catagory: Stuffy nose, Sneezing, Allergies, Polyps, Facial pain, Other |
| **Doctor visit** | Have you seen a doctor for your condition? | No, Yes |
| **Specialist visit** | Have you seen a specialist, such as an Ear, Nose and Throat (ENT) doctor or neurologist, for your condition? | No, Yes |
| **Parosmia** | Do you have parosmia (distorted sense of smell)? | No, Yes |
| **Phantosmia** | Do you experience smells that are not present (phantosmia)? | No, Yes |
| **Olfactory Training** | Are you doing smell training? | Yes; No, I have tried smell training in the past but stopped; No, I have never tried smell training |
| **Olfactory Training never** | If you have not tried smell training, what is the reason? | I do not think it would help me, I am afraid to start, because I might be disappointed if it doesn't work, I don't understand it, I don't have time, Other |
| **Awareness** | How often are you aware of your smell problem? | Constantly, daily, weekly, monthly, it doesn't bother me |
| **Quality of life** | Do you think smell loss has led to a loss in your quality of life? | Greatly, considerably, moderately, slightly, not at all |

### Statistical Analysis

Statistical Package for the Social Sciences (SPSS, Armonk, NY, USA; version 29.0) was used for data analysis. A series of Chi-square analyses or independent t-tests were utilized to investigate the difference between groups (No OT * OT) and demographic and medical information, namely age range, gender, etiology (accident/infection/CRS), onset, symptom count, the change of olfactory condition, parosmia and phantosmia, awareness (less frequent than daily, daily, constantly) and the degree of decline in quality of life for their smell problems. Numeric coding was given based on the description where the higher number indicated older age, later onset, better change of olfactory condition, greater quality of life loss, and more frequent awareness of their OD, respectively. Furthermore, logistic regression analysis was utilized to determine OT participation. For those in the OT groups, we built a regression model to investigate the relationship between the duration of OT (< 4 weeks * 4-8 weeks * 8-12 weeks * 12-16 weeks * > 16 weeks, coded numeric from 1 to 5) and age, gender and the degree of decline in quality of life. For those in the No OT group, we ran Chi-square analyses to investigate the reasons for not performing OT age and gender. A two-tailed p-value below 0.05 denoted significance. Adjusted standardized residuals were used for chi-square post hoc analysis where an absolute residual greater than 2 indicates significance (Agresti, 2002).

***Results***

A total of 450 people with OD was divided into OT (n = 161), and No OT (n = 289) groups based on their OT participation. Women predominated in the sample (78%). Participants were distributed in the older age range (>50 years old). However, neither age nor gender ratio differed in whether people participated in OT or not (both $p > 0.7$).

**Factors predicting OT participation (see Figure 1 in study 1)**

Binary regression analysis revealed that the degree of decline in quality of life and olfactory condition contributed significantly to predicting OT participation (Omnibus $\chi^2 = 46.36$, $p < 0.001$). Patients with greater loss of quality of life caused by their smell problems ($p < 0.001$) and who considered their olfactory condition improved since the OD started were more likely to participate in OT ($p < 0.001$).

Chi-square analysis showed that the causes of smell problems differed between groups (No OT vs. OT; $\chi^2 = 9.61$, $p = 0.008$). Post hoc analysis showed that participants with post-viral OD tended to conduct OT (89%, adjusted residuals = 3.1), while patients with CRS were not engaged in OT participation (adjusted residuals = 2.3). Patients with CRS are often congested via mucus or polyps and tend to have more stuffy or blocked nose, leading to a barrier to participate in a smelling activity. We further checked this result by conducting a one-way ANOVA (accident, infection, CRS) and found that patients with CRS had higher symptom counts than both other groups (both $p < 0.001$). Parosmia was a common complaint in the present study (45%), but did not differ between groups (No OT vs. OT, $\chi^2$=5.38, $p$=0.068), yet post hoc analysis suggested patients with solely parosmia were more likely to participate in OT (adjusted residuals = 2.2). Patients who participated in OT had a later onset of OD ($t = 3.13$, $p = 0.002$), greater impairment in quality of life ($t = 5.08$, $p < 0.001$), improved olfactory condition ($t = 2.05$, $p = 0.041$), and more awareness of their condition ($t = 3.31$, $p = 0.001$).

**OT duration (see Figure 2 in study 1)**

The majority of participants performed OT for less than four weeks (76.4%). Regression analyses showed that gender was associated with OT duration ($F = 4.38$, $p = 0.006$), whereas men were more likely to have a longer OT duration ($p = 0.002$). No other significant results were found (all $p > 0.05$).

**Reasons for not performing OT (see Figure 3 in study 1)**

In the No OT group, the most common reason for not conducting OT was not knowing about OT (37%). To explore the reasons behind the lack of awareness about OT, we conducted further analysis by examining the proportion of patients who sought medical advice from doctors or ENT specialists. A third of the NO OT patients (37.7%, n=109) sought consultation from a doctor regarding their condition. In comparison, a larger percentage of patients who did participate in OT consulted their doctor (54%, N=87), but no differences were seen between NO OT and OT groups who consulted an ENT specialist (65.1% and 65.5%, respectively). However, regardless of seeing a general practitioner or ENT specialist, half of NO OT patients chose "did not know" about OT as a leading reason for that they did not participate [51% (N = 45)]. This indicates that a significant portion of patients who sought medical advice, including specialized care, remained uninformed about OT. Gender had no association with the reason for not performing OT ($p = 0.95$). Interestingly, people over 50 years were more likely to be unaware of the method of OT compared with the younger population aged below 30 years ($\chi^2 = 43.86$, $p < 0.001$; adjusted residuals = 4.5), whereas a higher proportion (26%) of those aged below 30 were more afraid to be disappointed by OT (adjusted residuals = 3.9).

## Study 2: Functional but Not Structural Brain Changes After Olfactory Training in Women With COVID-19-Associated Olfactory Dysfunction

***Methodology: Objective Olfactory Tests, Structural and Functional MRI Before and After Three Months of Classical Olfactory Training in Patients with Post-viral Olfactory Dysfunction***

### Participants

Twenty female patients (mean age ± sd = 52 ± 7) years with COVID-19 related OD (mean duration ± sd = 22.4 ± 13.4 months, range 5-48) were recruited from August 2023 to July 2024. Twenty healthy participants were enrolled; however, one healthy participant was excluded due to technical problems. In the end, 19 healthy participants (mean age ± sd = 45 ± 9) were included in the analyses.

Inclusion criteria were: (1). Female gender (in order to avoid a possible effect of gender (Yousem et al., 1999)); (2). Age: ≥ 18 years; (3). Patients should have COVID-related OD; (4). Healthy individuals should not have had COVID-related OD at any time. Exclusion criteria were (1). Lack of capacity to consent; (2). Pregnancy and breastfeeding; (3). Significant health impairments (e.g. uncontrolled diabetes mellitus, Parkinson's disease, significant renal insufficiency), which can be associated with disorders of olfactory function; (4). Acute or chronic inflammation of the nasal cavity; (5). MRI-specific exclusion criteria (e.g. metallic implants, pacemakers, intrauterine spiral).

All participants received detailed written and oral information, and provided written informed consent. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty Carl Gustav Carus at the Technical University Dresden (BO-EK-318072022).

### Measures

#### *Sniffin' Sticks test*

Olfactory function was evaluated using the Sniffin' Sticks Test (SST), a validated assessment composed of three subtests: odor threshold, discrimination, and identification (Hummel et al., 1997).

The odor threshold test uses 48 pens in a triple-forced-choice paradigm, where each set of three pens includes two containing odorless propylene glycol and one with diluted PEA.

The examiner uncaps each pen and holds the tip approximately 2 cm below the participant's nose, allowing the odor to release. Participants must identify the pen with PEA using a single staircase procedure: two correct detections or one incorrect choice trigger a staircase reversal. The mean of the last four reversals (out of seven) determines the threshold score, ranged from 1 to 16.

Similarly, in the odor discrimination test, 48 pens with suprathreshold odors are presented in sets of three, with two pens containing the same odor and the third a different one. Participants are required to discriminate the distinct pen in a 3-alternative forced-choice task. Each correct answer is scored 1 point, with a maximum score of 16.

The odor identification test involves 16 common odors. Participants need to identify the odor based on 4 verbal options. Correct identifications are scored as 1 point each, with a maximum score of 16.

The TDI (Threshold-Discrimination-Identification) score, summing the subtest scores, ranged from 1 to 48, with higher scores indicating better olfactory function (Oleszkiewicz et al., 2019).

***Figure 3*** *Overview of the Sniffin' Sticks Test (SST). SST is a standardized, reusable olfactory assessment tool comprising three subtests: odor threshold, odor discrimination, and odor identification. The odor threshold test uses 48 pens, 16 of which contain PEA at varying concentrations while the remaining pens are odorless. The odor discrimination test similarly employs 48 pens that present suprathreshold odors. For the odor identification test, 16 pens with everyday odors are used, and participants choose the correct odor from a list of four descriptors. The scores from these three subtests are combined to produce a composite TDI score, with higher scores indicating better olfactory function.*

### *Olfactory training*

Figure 4 illustrates the utilized set of the current study. Both patients and controls were given four brown glass jars, each containing 3 ml of one of four different odors (PEA for rose, product number: 77861; eucalyptol for eucalyptus, C80601; citronellal for lemon, 814575; eugenol for cloves, W246719; Sigma, Taufkirchen), soaked in cotton pads (Fuhrmann, Much; reference number: 40709). They were instructed to sniff each odor for approximately 20 s, both in the morning and evening for 3 months. Adherence to the training was asked in visit 2 using an adherence scale with 4 questions.

***Figure 4*** *The olfactory training set. The cotton pads were soaked with odorants (red: rose; yellow: lemon; blue: clove; green: eucalyptus) in brown glasses.*

### *MRI protocol*

A 3-Tesla MRI scanner (Siemens MAGNETOM Prisma, Forchheim) with a 32-channel head coil was used for image acquisition. T1 images were acquired using a 3D magnetization prepared gradient rapid acquisition gradient echo sequence with repetition time (TR) = 2300 ms, echo time (TE) = 3.43 ms, field of view (FOV) = 256*256 $mm^2$, and voxel size 1*1*1 $mm^3$. Images of OB were collected using a coronal T2 single-shot echo-planar imaging (EPI) sequence with the following parameters: TR = 1000 ms, TE = 127 ms, flip angle = 100°, voxel size = 0.5*0.5*0.5 $mm^3$, slice thickness = 0.5mm; FOV = 160*160 $mm^2$.

Each individual had 300 functional images collected with parameters below: TR = 1000 ms, TE = 37 ms, flip angle = 52°, voxel size = 2*2*2 $mm^3$, slice thickness = 2 mm; FOV = 208*208 $mm^2$, with multiband factor = 8.

### *Block design in functional MRI*

N-butanol (Sigma, order number: 101543207; 5 ml) soaked in a cotton pad was selected for functional MRI scanning. This was delivered birhinaly using Teflon™ tubing connected to a portable computer-controlled olfactometer (Sniff-O, Cynexo, Udine, Italy, http://www.cynexo.com (Albayay et al., 2019)). Odorous stimuli were embedded in a 2l/min constant airflow. Stimuli were presented in a block design format, alternating between 8-second “ON” (odor) and 12-second “OFF” (odorless air) blocks. Following each odor presentation, participants rated the perceived intensity, pleasantness, and familiarity of the odor through an intercom system.

***Image preprocessing***

MRI images were pre-processed and analyzed using SPM12 (Statistical Parametric Mapping, UCL, London, UK) implemented in MATLAB (Matrix laboratory, Version 2024a for Windows; The Mathworks Inc., Natick, MA, USA). The pre-processing steps were oriented by the default settings in SPM12 and included realignment and unwarping, slice timing, co-registration of functional with anatomical T1 images, segment based on the Tissue Probability Maps, normalization to the Montreal Neurological Institute space, and smoothing of functional images with a Gaussian kernel of $8 \times 8 \times 8$ $mm^3$ full width at half maximum.

***Functional MRI data analyses***

Functional data analysis employed a two-level restricted maximum likelihood approach. To better capture olfactory blood-oxygen-level-dependent signal, the initial 2 seconds of ON and OFF sessions were excluded, yielding 6 seconds of ON and 10 seconds of OFF data for analysis. Paired t-tests examined pre- and post-training differences, while repeated measures analysis of covariance (rm-ANCOVA) assessed the time effect, and group and time interactions, with age as a covariate. Region of interest (ROI) analyses were conducted in Marsbar (https://marsbar-toolbox.github.io/) and analyzed using rm-ANCOVA in IBM SPSS version 29.0 (Chicago, IL, USA), and activations were reported in Montreal Neurological Institute coordinates. Results reported at uncorrected $p < 0.001$.

***OB volume measurement***

The segmentation of the OB was performed using ITK-SNAP (http://www. itksnap.org) to process T2-weighted images. Two observers manually outlined the OB on each slice to obtain bilateral volumes, which were then summed and multiplied by the slice thickness to calculate the total volume. Measurements were averaged if the volume discrepancy was less than 10%; otherwise, the third observer performed an additional measurement. Final

OB volumes were computed by averaging the two most concordant measurements (Rombaux et al., 2009).

### ***Voxel-based morphometry***

Voxel-based morphometry (VBM) analyses were performed using the CAT12 toolbox (https://neuro-jena.github.io/cat//) implemented through SPM12 in MATLAB (Gaser et al., 2024). T1 images segmented into gray matter, white matter, and cerebrospinal fluid. Images were smoothed with a Gaussian kernel (full width at half-maximum 6*6*6 $mm^3$). The following analyses were conducted: (1) t-test (pre- vs. post-training) in both control and patient groups; (2) F-test in flexible factorial model to analyze the interaction effect of group*time. All results are reported at uncorrected $p < 0.001$.

### ***Statistical analyses***

Statistical analyses were performed using IBM SPSS version 29.0 (Chicago, IL, USA). Independent t-tests were applied to examine age differences in patient and control groups. The effect of OT on changes in olfactory function was analyzed with rm-ANCOVA, with “group” (patients vs. control) and “time” (pre- vs. post-training) as factors, controlling for age. For OB volume analysis, the right and left OB volumes were calculated separately using similar rm-ANCOVA with age included as a covariate. Pearson correlation analysis was conducted to explore the relationship between the duration of OD, changes (post-pre) in olfactory scores, and selected ROI values. Two tailed $p < 0.05$ denoted significance.

## ***Results***

### ***Behavioral results (see Figure 2 in study 2)***

Patients were significantly older than controls ($t = 2.85$, $p = 0.007$) and had significantly reduced olfactory function based on TDI total and subtest scores. During scans they rated butanol as less intense compared with controls (all $p < 0.001$).

Results from rm-ANCOVA controlling age suggested a significant interaction effect of TDI total score between time and group ($F = 4.46$, $p = 0.041$, Figure 2 in study 2). Bonferroni corrected post-hoc analysis indicated that this improvement was only significant for patients’ group (post-training > pre-training, $p < 0.001$). Regarding olfactory subtests this interaction effect was mainly seen in odor thresholds ($F = 5.09$, $p = 0.03$), but not for discrimination and identification (both $p > 0.05$). Following OT both groups tended to rate butanol more intense in the scan (Time main effect: $F = 3.72$, $p = 0.062$), with no difference for pleasantness ratings ($p > 0.05$).

### *Functional MRI results from whole brain analyses (see Figure 3 in study 2)*

For the interaction effect between group and time (contrast: [patient post - patient pre] - [control post – control pre]), the activations of right medial OFC were increased in patients (peak: [12, 62, -14, k = 10], Figure 3 in study 2). Moreover, for the time effect, the activation of left and right parahippocampal cortex (peak: left: [-22, -20, -20, k = 10]; right: [20, -14, -22, k = 20]), and bilateral middle temporal gyrus were significantly higher after training (peak: left: [-56, -44, -4, k = 22]; right: [66, -46, 1, k = 22]) in both groups.

Paired t-tests with the contrast of post > pre-training in patient group suggested that n-butanol activation was enhanced in the regions of left inferior temporal gyrus (peak: [-38, -8, -34, k = 20]) and right fusiform (peak: [40, -6, -30, k = 21]). For controls, the activation of right middle temporal gyrus (peak: [50, -24, -10, k = 123]), right superior frontal gyrus (peak: [24, 50, 16, k = 50]), left superior motor area (peak: [-10, 16, 56, k = 37]) and OFC (peak: [16, 66, -44, k = 17]) were higher after training.

### *ROIs results*

The OFC, both left and right parahippocampal gyrus, and bilateral middle temporal gyrus, were chosen based on whole brain analysis. Significant time effect ($F = 5.39$, $p = 0.026$) and trend-significant interaction effect between group and time were found in the right parahippocampus ($F = 3.68$, $p = 0.063$). Post hoc analysis suggested only patients were improved after OT compared to baseline activation (post-training > pre-training, $p = 0.006$). There was a trend towards significance for an effect of time in the left parahippocampus ($F = 3.61$, $p = 0.065$). The post hoc analysis suggested that more activation was present post-training compared to pre-training ($p = 0.015$). When looking into the post hoc analysis even without a significant interaction effect, the higher activation in response to n-butanol only existed in patients (post-training > pre-training, $p = 0.012$). No other significant results were found (all $p > 0.05$).

Pearson's correlation results (see Table 2 in study 2) showed that the change of OFC activation negatively correlated with the change in pleasantness ($r = -0.33$, $p = 0.046$). Duration of OD positively correlated with change in discrimination ($r = 0.52$, $p = 0.024$) and TDI scores ($r = 0.52$, $p = 0.022$). The change in intensity of butanol positively correlated with the change in threshold ($r = 0.44$, $p = 0.006$) and TDI scores ($r = 0.47$, $p = 0.003$). The change in pleasantness negatively correlated with the change in discrimination scores ($r = -0.51$, $p = 0.001$)

***VBM results***

Paired t-tests with the contrast of post more than pre-training in patient group suggested that OT enlarged the GMV in the regions of right cerebellum (peak: [10, -54, -12, k = 23]). Similarly, for controls, the GMV of right cerebellum (peak: [8, -30, 33, k = 10]) was increased after training. There were no significant main effects or interaction effect in the F test.

***OB measurement***

Both left and right OB volumes of patients were lower compared to healthy controls before OT (left: $t = 2.29$, $p = 0.014$; right: $t = 2.62$, $p = 0.006$). The rm-ANCOVA suggested a main effect of time on the left OB ($F = 5.22$, $p = 0.028$), while the post hoc analysis suggested no difference ($p = 0.83$). There was a trend-level significance of group main effect on the right OB ($F = 3.89$, $p = 0.056$), with the post hoc analysis suggesting controls had a larger right OB volume than patients regardless of the time. There were no relationships between the change in OB volume and measured olfactory function or duration of OD. No other results were found (all $p > 0.05$).

## Study 3: Olfactory Training: Effects of Multisensory Integration, Attention Towards Odors and Physical Activity

### *Methodology: Objective Olfactory Tests Before and After Three Months of Modified and Classical Olfactory Training in Healthy Individuals*

#### Participants

One hundred and twenty-eight participants were initially recruited via flyers and word of mouth. They were allocated to one of four groups randomly: (i) Video group (involving multisensory integration, n = 33); (ii) Counter group (involving attention, n = 30); (iii) Training only group (only performing OT, n = 35) and (iv) Control group (n = 30). Twenty-eight participants dropped out due to several reasons (e.g., contact loss, house moving), with 100 participants remaining for the final analysis (Video: n = 26; Counter: n = 24; Training only: n = 24 and Control: n = 26). With regard to age or olfactory function there was no significant difference between the remaining participants and those who had dropped out (all $p > 0.2$) indicating that the reasons for leaving the study did not follow a pattern for these parameters. Utilizing G*Power software (Faul et al., 2007) within the repeated measures design with between-within group interactions, our sample size was able to obtain the power of 0.99 with α level set to 0.05 to detect moderate effects of f = 0.25 (Sorokowska, 2017).

Inclusion criteria were: (i) age between 18-35 or 50-85 years; (ii) subjective normal olfactory function; (iii) voluntary participation. To be included in the Video group participants had to own a smartphone, a tablet, or a laptop to be able to display the videos at their homes. Exclusion criteria were: (i) neurodegenerative diseases, such as Alzheimer's disease, metabolic diseases like severe diabetes mellitus and renal disease; (ii) pregnancy or breastfeeding; (iii) massive head trauma that affects olfactory-related brain regions; (iv) smoking (more than 5 cigarettes per week); (v) after data collection, external factors during the training period which may cause significant change of olfactory function, e.g. SARS-CoV2 infection (n = 3).

The present study was approved by the Ethics committee at the Medical Faculty Carl Gustav Carus of the Technische Universität Dresden (application number EK 21012018). All participants gave written informed consent and received a moderate financial compensation for their participation.

**Sniffin' Sticks test**

As described in study 2, SST is based on pen-like odor dispensing devices. They comprise three subtests: odor thresholds, discrimination, and identification (Hummel et al., 1997). Results are summated in the TDI total score. The higher TDI total score indicates better olfactory function.

**Olfactory training and physical activity**

Except for one control group who were not required to conduct OT, three training groups were set up in the present study. Those in the Video group received the video file to be displayed on phones, pads, or laptops owned by the participants. The video guiding them through the whole process was used twice daily, in the morning and evening. While sniffing an odor from a vial, a superimposed clock runs through the training time of 20 seconds backward, with the instruction of watching the video and listening to the sounds while sniffing. Those in the Counter group received an additional device that could be worn on a finger (a "finger counter", which is often used, for example, for counting the number of hits when golfing, for knitting, or for praying), allowing participants to count odors that had been detected. For example, a rose odor in one room would count once, another odor in a different room would count again, and re-smelling the rose odor again in the first room would also count. Participants were also instructed that they should not count while they were cooking or eating/drinking. They should wear this device one day a week and record the olfactory impression at the end of the day. Those with "OT only" should conduct OT by smelling the vials four times a day.

Participants sniffed the smells from 4 vials (brown glass, 50 ml volume, diameter of opening 45 mm), containing a cotton pad soaked in 2 ml odors (single molecule odorants: eugenol (Cosmo International Fragrances, Paris, France 53041369), d-limonene (lemon smell, Cosmo 53041800), eucalyptol (Cosmo 53040616), and 2-Phenylethanol (rose smell, Sigma Aldrich, Steinheim, 102331609); complex odors: lemon (Cosmo 53046670), clove (Cosmo 53046350), eucalyptus (Cosmo 53044350), and rose (Accords and Parfums, Spéracèdes. France FSASH00172)) in each vial. Notably, participants in each of the three OT groups were randomly allocated to receive either single odorants or complex odors. A training step included (i) opening a vial, (ii) 20 seconds sniffing the odor and (iii) closing the vial, which was performed with each vial. This procedure was repeated once more both in the morning and evening so that a complete training session included smelling each odor four times a day for 3 months at home. During the training period, participants were contacted to check their compliance and the four questions was used as a proxy for compliance in the post-training assessment. In addition, they were asked to fill in a “smell diary” each week to note down the intensity of the odors in each vial and how often they adhered to the OT procedure or some other remarks about the training during the week.

The physical activity was estimated once a week using the Global Physical Activity Questionnaire (Armstrong & Bull, 2006; Wanner et al., 2017) and adapted four questions (time of vigorous-intensity, moderate-intensity activity, walking, and sitting) referring to the day they did the most vigorous-intensity physical activity in the past week were also recorded. The degree of physical activity was calculated using Metabolic Equivalents per week based on the responses from Global Physical Activity Questionnaire and adapted 4 questions (WHO, 2012).

**Procedure**

Participants visited the Smell & Taste Clinic, Department of Otorhinolaryngology, of the University Hospital of Dresden, Germany, and completed the pre-training tests. After that, all participants in the three groups with OT received the odors (“single molecule odorants” or “complex odors”) for OT, the smell diary, and scales of physical activity. Participants in the control group received the scales of physical activity alone. After 3 months, the smell tests were repeated for all participants in Session 2.

**Data analysis**

SPSS v28.0 (IBM, Armonk, NY, USA) was utilized to analyze the data. Age and gender ratios were assessed using ANOVA and Chi-square analysis. RM-ANOVA was conducted to investigate the training efficacy. Our interest was the interaction effect between the within-subjects variable of Session (pre-training vs. post-training) and the between-subject variable of Group (Video vs. Counter vs. Training only vs. Control), following the Post hoc analysis with a Bonferroni correction. Similar models of rm-ANOVA treating Training odor (single molecule odorants (n = 38) vs. complex odors (n = 36), excluding the control group), Age (young (n = 68) vs. old (n = 32)) as between-subject variables were built separately. We also examined the relationship among changes (performance of the post-test minus pre-test) in olfactory function and averaged physical activity using Spearman’s correlation analysis. Two-tailed $p < 0.05$ denoted significance.

## ***Results***

**Age, gender, baseline olfactory function, compliance with OT**

Age was comparable between groups (mean age ± SD: Video: 39 ± 19; Counter: 38 ± 17; Training only: 38 ± 20; Control: 36 ± 15; $p = 0.93$), as well as the gender ratio ($p = 0.71$). There were no differences for all measured olfactory performances among the four groups at baseline (all $p > 0.05$). Compliance with OT was mostly high (n = 52) and medium (n = 19), with only 3 participants showing low compliance.

**OT in relation to manipulated groups (see Figure 1 in study 3)**

Repeated measures ANOVA analysis showed that the main effects of Session on odor threshold, identification, TDI total scores were significant (Threshold: $F = 6.58$, $p = 0.012$; Identification: $F = 6.23$, $p = 0.014$; TDI total: $F[1, 96] = 14.78$, $p < 0.001$, table 2 in study 3) indicating that, in general, olfactory function improved from Session 1 to Session 2. There was no significant main effect for the factor "Group" (all $p > 0.05$). The interaction between Session and Group was significant in TDI total scores ($F = 2.87$, $p = 0.04$), as well as in odor threshold score ($F = 2.99$, $p = 0.034$) suggesting that effects of the manipulation differed for the various groups. The Counter group yielded the largest increase of odor threshold, discrimination, and TDI scores in session 2 than session 1. The Bonferroni corrected pairwise comparisons suggested that after training, the TDI total score of participants in the Counter group ($p < 0.001$) improved significantly, specifically in odor threshold ($p = 0.003$) and discrimination ($p = 0.02$) scores. The TDI total score also improved in the Video group ($p = 0.041$), especially in odor threshold score ($p = 0.02$). Interestingly, even though the baseline performance was similar, the odor discrimination scores were better in Video and Counter groups than in the Control group in the post-training test (Video vs. Control: $p = 0.042$; Counter vs. Control: $p = 0.046$), without any significant differences in OT alone or control groups.

**OT in relation to training odor molecule**

Regarding the variable of Training odor molecule, the main effects of Session in odor threshold, discrimination, and TDI total scores were significant (odor threshold: $F = 7.81$, $p = 0.007$, discrimination: $F = 7.86$, $p = 0.006$, TDI total: $F = 17.58$, $p < 0.001$), which suggested odor threshold, discrimination, and TDI total scores were performed better in Session 2 than Session 1 regardless of training odor. Moreover, a group difference was found in the odor discrimination score ($F = 5.35$, $p = 0.024$), with pairwise comparisons suggesting that participants using single molecule odorants performed better than those who used complex odors for training. However, we did not find any interaction between Training odor and Session ($p > 0.05$).

**OT in relation to age and other factors**

In terms of Age, the main effects of Session were significant in TDI total scores (TDI total: $F = 8.87$, $p = 0.004$), which suggested TDI total scores was better in Session 2 than Session 1 regardless of age, without significant interaction between Age and Session. There were group differences showing that young participants had better odor threshold, discrimination, and TDI total scores (odor threshold: $F = 3.98$, $p = 0.049$; discrimination: $F = 10.12$, $p = 0.002$; TDI total: $F = 5.28$, $p = 0.024$) than older people.

**Correlation analysis**

Across all participants performing the OT, the change of olfactory function had no relationship with the degree of physical activity ($p > 0.05$).

# Publication 1: Olfactory Training: Perspective from People Who Were Disturbed by Their Smell Problems

**Li, Z., Pellegrino, R., Kelly, C., & Hummel, T. (2024).**
**Olfactory training: perspective from people who were disturbed by their smell problems. *European Archives of Oto-Rhino-Laryngology*, *281*(12), 6423-6430.**
**doi:10.1007/s00405-024-08911-7**

**Abstract**

**Background:** Olfactory training (OT) is an effective and affordable option in the treatment of OD. Despite significant progress in the field in recent years, some factors influencing OT participation remain unclear.

**Methodology:** Based on an anonymous online survey orchestrated by AbScent.org the present study enrolled 450 participants and divided them into OT (n=161) and No OT (n=289) groups based on their OT participation. Participants also provided information on demographics, medical history, quality of life, OT duration for those who engaged in OT, and the reasons for non-participation in OT among those who did not.

**Results:** Patients who had greater loss of quality of life participated in more OT. Similarly, more participation was observed in patients who noticed an improvement in their ability to smell. Notably, most of the sample engaged in OT trained less than four weeks (73%). In the No OT group, the primary barrier to OT participation was the unawareness of OT treatment (37%) and these barriers differed by age, where older people expressed interest but were unaware of OT treatment, while younger individuals exhibited more cautiousness about its effectiveness.

**Conclusion:** Lower quality of life drives active OT participation. Limited training periods and unawareness of OT serve as potential barriers to olfactory recovery. Clinicians should actively promote the background of OT and underscore the significance of adhering to the "prescribed" training regimen.

*Keywords: adherence, olfactory training, quality of life, smell*

Publication Discussion

This study explored patients' perspectives on OT, addressing three key questions:

1. What factors influence patients' decisions to participate in OT?
2. For those who participated in OT, what is the typical training duration, and how is it associated with demographic factors such as gender and age?
3. For those who did not participate in OT, what are the barriers, and are these obstacles related to demographic factors?

**Factors Influencing OT Participation**

Both demographic and clinical factors were analyzed to understand their role in OT participation. Initial comparative analyses, including t-tests and $\chi^2$ tests, revealed significant differences between patients who participated in OT and those who did not, including the etiology, onset of OD, parosmia symptoms, olfactory condition since OD started (worsened, unchanged, or improved), awareness of OD, and the degree of quality of life impairment. Results indicated that patients who engaged in OT were more likely to have post-viral OD, a shorter onset, an improved olfactory condition, greater awareness of their loss, and more severe quality of life impairment. Further analysis using binary logistic regression identified two significant predictors of OT participation: the degree of quality of life impairment and olfactory condition. Patients with greater loss of quality of life and an improved olfactory function since OD started were more likely to engage in OT.

Lower quality of life due to OD emerged as a vital motivator for patients to pursue OT. OD impacts multiple aspects of daily life, including food enjoyment, social interactions, associates closely to emotions such as depression (Coelho et al., 2021; Croy et al., 2014). Individuals who experience a significant decline in their quality of life are more likely to seek assistance, such as OT. Olfactory condition was another significant factor influencing OT participation in this study. Patients who reported improvement in their olfactory function were more actively involved in OT. Previous findings suggest that OT can enhance olfactory performance (Choi et al., 2021; Huang et al., 2021; Pieniak et al., 2022; Sorokowska, 2017). Those who participated in OT may have perceived improvement in their olfactory function, which in turn motivated them to continue the training and maintain active engagement.

Etiology also played a role, with variations in OT efficacy linked to different causes of OD (Pieniak et al., 2022). Subgroup analyses suggested that patients with post-viral etiologies were more involved in OT, while patients with CRS were less likely to engage in OT. These patients might focus more on alleviating symptoms like nasal congestion, potentially lowered their engagement in OT for smell recovery. The duration of OD also influenced participation, with patients experiencing shorter durations being more likely to engage in OT. Those with longer-term OD might have adjusted to their condition, reducing their motivation to seek treatment. Additionally, parosmia, a common and distressing symptom characterized by unpleasant olfactory distortions (Pellegrino et al., 2019; Reden et al., 2007), was associated with a greater likelihood of pursuing OT. This distress of distorted olfaction likely amplifies the perceived need for treatment, motivating individuals to seek solutions (Altundag, 2023; Pellegrino et al., 2021). This observation may also extend to those who exhibited more awareness and the improvement of their smell problems, subsequently motivating their active engagement in OT.

**Adherence of OT**

The present study revealed that patients who were engaging in OT mostly lasted for less than a month, despite recommendations suggesting a minimum training duration of three months or longer. Evidence indicates that extended OT durations yield greater improvements in olfactory function (Konstantinidis et al., 2016; Sorokowska, 2017). In the clinical context, one month of training may not be sufficient to produce significant improvement (Qiao et al., 2019), whereas prolonged OT relates to a higher chance of improvement (Damm et al., 2014; Geißler et al., 2014; Lamira et al., 2019).

Interestingly, a gender difference emerged among those participating in OT. Women were more likely to engage in OT for less than four weeks, while men were more prone to participate in OT over 16 weeks. This finding is inconsistent with previous research suggesting that gender has no significant association with olfactory recovery following OT (Chao et al., 2022; Konstantinidis et al., 2013). However, this distribution implies that women may be more inclined to initiate OT for short-term periods, whereas men are more likely to commit to prolonged training. These observations underscore the importance of clinicians to emphasize the need for patients, regardless of gender, to adhere to the recommended duration of OT to maximize its effectiveness.

**Reasons for non-participation in OT**

One major reason for not engaging in OT was the widespread lack of awareness about OT, with over one-third of patients reporting that they had never heard of it, despite many having consulted general practitioners or ENT specialists for their OD. This lack of awareness was particularly pronounced among older patients.

Post hoc analyses using adjusted residuals from the Chi-square test revealed that older individuals generally viewed OT positively. They considered it helpful, not overly time-consuming, and were less concerned about potential disappointment. In contrast, younger participants appeared more skeptical about the effectiveness of OT. Anecdotal observations suggest that younger individuals, who are often active on social media, may be influenced by negative comments from those who only underwent short-term OT. These narratives can create an incorrect impression that OT is ineffective, as such users may not have completed the recommended duration of training to fully realize its benefits.

These findings highlight the need for caregivers and healthcare providers to raise awareness about OT. Educating patients on how and why OT works, along with emphasizing the importance of adhering to the recommended three-month training period or longer, is essential to address misconceptions and encourage broader participation.

In summary, the question mentioned above could be answered as:

1. *What factors influence patients' decisions to participate in OT?*

Patients' participation in OT was significantly influenced by the degree of quality of life loss caused by OD, the change of their olfactory condition since OD started, and their awareness of OD. Those with greater quality of life impairment and improved olfactory conditions were more likely to engage in OT. Additionally, factors such as etiology played a role, with post-viral cases showing higher participation rates, while patients with CRS were less engaged, possibly due to concurrent symptoms like nasal congestion which might require additional treatment.

2. *For those who participate in OT, what is the typical training duration, and how is it associated with demographic factors such as gender and age?*

Most patients engaged in OT for less than a month, despite evidence suggesting that longer training durations yield better outcomes. Gender differences were observed in training duration: women were more likely to initiate short-term OT (<4 weeks), while men were more likely to complete longer-term OT (>16 weeks). Age was not associated with the training duration.

3. *For those who do not participate in OT, what are the barriers, and are these obstacles related to demographic factors?*

Lack of awareness emerged as a primary barrier to OT participation, especially among older patients. Younger individuals, despite being more aware of OT, often held misconceptions about its effectiveness possibly due to insufficient short-term OT duration shared online.

These findings underscore the importance of educating patients across demographics, and clinicians as they do not recommend OT to patients about OT’s benefits and the necessity of adhering to the recommended duration to maximize effectiveness.

# Publication 2: Functional but Not Structural Brain Changes After Olfactory Training in Women With COVID‑19‑Associated Olfactory Dysfunction

**Li, Z., Gebler, J., Joshi, A., Xu, X., Thaploo, D., Hähner, A., Avaro, V., Calegari, F. & Hummel, T. (2025).**
**Functional but Not Structural Brain Changes After Olfactory Training in Women With COVID‑19‑Associated Olfactory Dysfunction. *The Laryngoscope*. doi: 10.1002/lary.32128**

**Abstract**

**Background:** Olfactory training (OT) is a recommended treatment for olfactory loss and has proven effective in clinical contexts, yet its effects on the central-nervous system remain unclear. This study aimed to investigate the functional and structural brain changes in patients with post-viral olfactory loss undergoing OT.

**Methods:** Twenty patients with post-viral olfactory loss and 19 healthy controls underwent OT for 3 months. All participants were assessed using the Sniffin' Sticks test and magnetic resonance imaging (MRI). Voxel-based morphometry and OB volumetry were performed on structural images. Presenting an unpleasant odor, n-butanol, in a canonical block design, functional MRI was performed using whole-brain and region of interest analyses.

**Results:** Patients with post-viral olfactory loss showed significant improvement following OT. Enhanced functional activations were observed in the OFC and parahippocampus, while OT had little or no effects on brain structures.

**Conclusion:** The present findings suggest that OT provides early perceptual and functional benefits, with structural changes potentially emerging later with extended training duration.

*Keywords: COVID, MRI, olfactory loss, olfactory training, smell*

## Publication Discussion

Study 2 using MRI technique and focusing on the olfactory cortex, has advanced the potential neuroimaging evidence of OT that the functional activation of OFC and parahippocampus has increased after OT. These results suggest that OT contributes to the functional improvement in brain regions which are crucial to the olfactory processing. On the other hand, limited structural changes have been observed, such as enlargement only in the GMV of cerebellum and no increase of OB volume.

OFC, a crucial structure of secondary olfactory cortex, mainly involving in high order olfactory processing, such as odor identity, odor valence, and olfactory multimodal stimuli (Rolls, 2004). Increased activation in the OFC after OT indicates improved integration and interpretation of sensory input, potentially reflecting enhanced cognitive and emotional processing of smells. Parahippocampal cortex plays a significant role in memory formation (Aminoff et al., 2013). In the context of olfaction, it is associated with the emotional and memory-related aspects of odors. Greater activation in this region suggests that OT may strengthen the connection between olfactory processing and memory or emotional learning, enhancing the ability to associate smells with specific memories or contexts.

However, limited structural changes were observed in the current sample, only the GMV of cerebellum in both groups increased. Cerebellum is involved in olfactory processing and has been shown to be increased in previous research following OT (Gellrich et al., 2018; Han et al., 2021). This increase might be associated with the increased frequency of sniffing the olfactory environment which is organized to some degree in the cerebellum (Sobel et al., 1998). Clinically, the delayed appearance of structural changes following functional changes can be seen as positive in terms of recovery. In cases of short-term OD, the brain appears capable of relatively easy repair without the possible consequences of lasting structural alterations, which might be more challenging to compensate in cases with a longer duration of OD.

Previous OT studies on patients with post-viral OD have reported reorganized functional networks (Kollndorfer et al., 2015) or increased functional connectivity within olfactory-related networks (Jiramongkolchai et al., 2021). However, these often involve small sample sizes and lack healthy control groups that undergo scanning after OT. Ideally, we would have manipulated three groups: patients with OT, patients without OT, and controls with OT, to allow for comparisons across different domains. Nevertheless, contrary to most previous studies (Gellrich et al., 2018; Kollndorfer et al., 2015; Pellegrino et al., 2019), the present investigation included two scans for the controls, performed before and after OT. This allowed the present study to investigate the isolated effect of OT in individuals with and without OD. One plausible explanation for the absence of structural changes could be that both patients and controls experienced structural improvements (in line with behavioral improvement), but these changes were too subtle to be detected within the relatively short training duration at the structural level. Future studies should consider extending the OT duration and ideally include another patient group without training to distinguish the effects of spontaneous olfactory recovery from those induced by OT.

This study provides further evidence that OT enhances olfactory processing at the neural level, particularly in patients with post-viral OD. Increased activation in the OFC and parahippocampus suggest that OT facilitates functional changes in important olfactory-related brain regions. However, structural changes, such as OB volume had limited increases, indicating that functional improvement may occur before detectable anatomical alteration. By including a control group that also underwent OT and was scanned pre- and post-training, this study employed a more rigorous design to strengthen the reliability of its findings.

## Publication 3: Olfactory training: Effects of multisensory integration, attention towards odors and physical activity

**Li, Z., Anne, A., & Hummel, T. (2023).**

**Olfactory training: effects of multisensory integration, attention towards odors and physical activity. *Chemical Senses*, *48*, bjad037.** [doi: 10.1093/chemse/bjad037](https://doi.org/10.1093/chemse/bjad037)

**Abstract**

**Background:** Olfactory training (OT) has been shown to be of value in the treatment of OD. The present study aimed to investigate whether the efficacy of OT could be modulated with multisensory integration, attention towards odors, odor complexity, or physical activity assessed with a questionnaire.

**Methodology:** One hundred healthy participants were recruited and divided into four groups. Except for controls (n=26, mean age±sd = 36±15 years) all participants performed OT four times a day. In the “Video” group (n=26, age 39±19 years) OT was performed while watching specific and congruent video sequences. In the “Counter” group (n=24, 38±17 years) participants additionally counted the number of odors one day per week, and in the “Training only” group no additional measures were taken in addition to OT (n=24, 38±20 years). “Single-molecule” odorants or “complex mixtures” were distributed randomly for training stimulation. Sniffin’ Sticks tests (odor identification, odor discrimination and odor threshold), cognitive tests, and a series of scales were measured at both baseline and after 3 months of OT. The degree of physical activity was recorded with a questionnaire.

**Results:** Olfactory function improved in the Video and Counter groups after OT, especially for odor threshold and discrimination. Yet, odor complexity and the degree of physical activity had limited effects on olfactory improvement after OT.

**Conclusion:** Both multisensory interaction and attention towards odors plus OT appeared to facilitate improvement of olfactory function in healthy individuals compared with OT alone and controls, which could provide new promising treatments for clinical applications.

*Keywords: attention, multisensory, odor complexity, olfactory training, physical activity*

## Publication Discussion

This study aimed to explore ancillary approaches to enhance the efficacy of OT, focusing on factors such as multisensory integration, attention to surrounding odors, the molecule complexity of training odors, and the degree of physical activity in healthy individuals.

### Multisensory integration

Participants who performed OT combined with congruent multisensory integration over a 3-month period demonstrated significant improvements in odor thresholds and discrimination. In contrast, participants who engaged in OT alone or received no training showed no such enhancements. This effect may be attributed to the overlap of brain regions involved in processing multiple sensory modalities, such as audition, vision, and olfaction. For instance, the OFC, a key area for olfactory processing, also plays an essential role in associating olfactory and visual stimuli (Thesen et al., 2004). While OT primarily stimulates peripheral olfactory systems, such as ORNs (Kim et al., 2019), the addition of multisensory inputs likely activates a broader network of brain regions involved in olfactory processing, potentially amplifying the benefits of OT.

Moreover, congruent multisensory stimuli, such as pairing smells with matching sounds, have been shown to enhance odor pleasantness (Seo & Hummel, 2011). This added pleasantness may improve participants' compliance with the training regimen, further contributing to its efficacy.

### Attention to surrounding odors

Counting surrounding smells contributes to the awareness and attention towards them. A previous study reported a subtle improvement in olfactory performance after participants engaged in odor counting for two weeks (Oleszkiewicz et al., 2021). The authors proposed that this improvement stimulates the olfactory system through both top-down and bottom-up processes, ultimately enhancing olfactory function. Our findings support these attentional effects, demonstrating that combining odor counting with OT effectively improves olfactory function in healthy participants, while OT alone or control conditions showed no such benefits. However, the underlying mechanisms behind these associations remain unclear and warrant further investigation.

### Molecule complexity of training odors

In the present study the complexity of OT stimuli seemed not to affect the training effect. We observed higher improvements in odor identification, discrimination, and TDI scores in

Session 2 as a general training effect regardless of molecule complexity. Participants training with single molecule odorants improved in odor discrimination more than those using complex mixtures. Nevertheless, there was no interaction effect between “Training odor” and “Session”, suggesting that odor complexity has little or no effect on olfactory enhancement after OT. While evidence on the impact of odor molecule complexity on OT effectiveness remains scarce and inconsistent, the present findings align with previous research suggesting that odor complexity does not significantly affect training outcomes. (Oleszkiewicz et al., 2018). Yet, it does not confirm the observation that the complexity of olfactory stimuli increases OT efficacy in patients with OD (Altundag et al., 2015). Further considering the inconsistency of additional previous results (Oleszkiewicz et al., 2021), it seems that this issue requires more research.

**The degree of physical activity**

In terms of physical activity, our finding suggests that it is not associated with the olfactory improvement after OT, which does not confirm prior research suggesting that the more time dedicated to exercising, the better the olfactory function or the lower the risk of olfactory impairment (Schubert et al., 2011; Sollai & Crnjar, 2021). Similar non-significant results were also reported by a small study focused on exercising to improve olfactory function in Alzheimer’s disease (Bhalla et al., 2018). With a much bigger sample size, the present study failed to reveal the association between physical activity and olfactory improvement after OT. One possible reason for this could be the bias introduced by the recording of the degree of physical activity with a questionnaire. Future studies are needed where physical activity is directly recorded, possibly using accelerometers. In such an experimental context it would be highly interesting to re-examine the combination of OT and exercise.

The lack of a significant training effect in the OT-only group in this study is likely due to a ceiling effect commonly observed in healthy individuals. Previous research targeting this population has employed more complex training protocols to elicit measurable improvements (Al Aïn et al., 2019; Olofsson et al., 2020).

Among these additional approaches, multisensory integration and heightened awareness of odors appear to enhance olfactory function, even in healthy individuals, offering valuable insights for refining OT protocols in clinical settings. While odor molecule complexity and the degree of physical activity contributed limited benefits to OT in this context, these factors remain worth exploring in clinical populations. Future studies with more refined designs may uncover their potential to augment OT outcomes.

## Discussion and Outlook

This thesis aimed at advancing OT knowledge, exploring the participation, mechanisms, efficacy, and modification of OT in both clinical and healthy populations. The main findings from the three studies highlight the following insights:

1) **Factors Influencing OT Participation from the Patient Perspective:**
   Significant quality-of-life loss drives patients to pursue OT. However, OT is not sufficiently promoted among patients with OD, particularly in older individuals, many of whom remained unaware of its benefits. Among those who initiated OT, most withdrawn within a month, with a higher proportion of early withdrawal observed in female individuals.

2) **Potential Central Mechanisms of OT:**
   Functional MRI analyses revealed that OT increases functional activation in olfactory-related brain regions. In patients with post-viral OD, the OFC exhibited greater activation following OT. Both patient and control groups showed higher activation in the bilateral parahippocampal cortex and middle temporal gyrus after training. However, no substantial changes were observed in OB or GMV in olfactory-related regions, indicating that structural changes may require longer durations.

3) **Efficacy of OT in Clinical and Healthy Populations:**
   OT effectively improved olfactory function in patients with post-viral OD. In healthy individuals, OT also demonstrated potential benefits, particularly when combined with more complex training protocols such as multisensory integration or heightened awareness of surrounding odors. These approaches provide additional benefits beyond standard OT, offering insights for further improvement of training regimes in both clinical and non-clinical contexts.

**What do patients think about OT? Factors influencing OT participation**

Advancing knowledge about OT requires a deeper understanding of how patients with OD perceive this method. Important questions include: What factors contribute to OT participation? What is the common training duration among those who engage in OT? And what barriers prevent others from participating?

Several factors influence OT participation, including the etiology and onset of OD, impaired quality of life, olfactory condition changes, and patients' awareness of their condition. Among these, the most significant drivers are a greater impairment in quality of life and improved olfactory condition since the OD started, which motivate patients to pursue OT. The close association between quality of life and the sense of smell has been well-documented (Croy et al., 2014). A significant proportion of individuals are unaware of their OD until it begins to impair quality of life, prompting them to seek medical assistance (Oleszkiewicz et al., 2020). Previous research has highlighted the impact of OD on various aspects of life, including diminished food enjoyment, impaired social interactions, and emotional distress, all of which contribute to reduced quality of life. In turn, this quality of life impairment drives individuals to seek interventions, such as OT, to restore or improve their olfactory function.

The change of olfactory condition plays an important role in OT participation. In Study 1, patients who experienced improvement in their olfactory condition after the onset of OD were more likely to engage in OT. This improvement may stem from various factors, such as spontaneous recovery. Additionally, some patients may have previously initiated OT, and the early benefits they experienced could have motivated them to continue training. Numerous studies have demonstrated the efficacy of OT in enhancing olfactory function, with additional evidence suggesting potential cognitive and emotional benefits (Vance et al., 2024; Wegener et al., 2018). However, it is also common for patients to discontinue OT once they perceive their condition as improving (Haas et al., 2024; Pieniak & Hummel, 2023). This pattern of discontinuation may be partially explained by the gender differences observed in Study 1. Female patients had a higher initial participation rate in OT during the first four weeks but showed a steep drop-off in subsequent sessions. This trend suggests that while women may be more motivated to start OT, they are also more likely to stop or adopt spontaneous training.

One major finding highlighted in Study 1 is the insufficient training duration reported by participants. Most patients engaged in OT for less than four weeks (76.4%), a duration which has been proved to be insufficient to achieve meaningful olfactory recovery in clinical contexts (Qiao et al., 2019). Another striking observation is the widespread lack of awareness about OT, even among patients who have consulted ENT specialists for their olfactory issues. This is particularly pronounced in older adults. Although OT is recommended as an effective treatment for conditions such as post-traumatic and post-viral OD, it appears that ENT specialists are not consistently promoting this simple and beneficial intervention. As a result, many patients, especially older individuals, remain unaware of OT and miss the opportunity to benefit from it. Bridging this gap requires collaboration between general practitioners and ENT specialists to actively advocate for OT. Efforts should focus on educating patients about its mechanisms and potential to significantly enhance their quality of life. To improve awareness, compliance and maximize the efficacy of OT, several strategies can be proposed:

- Awareness and Education: Specialists should actively promote knowledge about OT, including its mechanisms and benefits. Pricing OT kits at a moderate cost may also underscore its value and encourage adherence.
- Convenience: OT tools should be designed for portability and easy to use, such as incorporating training odors into carriers like Sniffin' Sticks, making them suitable for use during travel.
- Renewal of Training Odors: Offering multiple sets of training odors that can be renewed after several months. This could maintain patient engagement and allow for regular follow-ups to monitor adherence and progress.

Overall, the findings from Study 1 suggest that quality of life plays an important role in motivating OT participation, as well as improvements in olfactory condition. To enhance compliance, strategies such as more promotion about OT, accessible training tools, and measures to encourage sustained engagement are recommended. Addressing barriers, including insufficient training durations and the lack of awareness, will be critical to optimize OT protocols and to achieve improved olfactory outcomes for patients with OD.

**How does OT work: Potential OT Mechanisms?**

The next question is: What knowledge should be promoted? First and foremost, raising awareness about the importance of olfaction is essential. Reduced olfactory function can increase exposure to environmental hazards, decrease enjoyment of food, strain social connections, and negatively impact emotional well-being. Additionally, while OT has proven effective across various populations, public education about its mechanisms—how it works and why it is effective—is equally important. Research over the past decades has demonstrated that OT induces both peripheral and central changes through repeated exposure to odors.

At the peripheral level, OT involves in olfactory system's unique regenerative capacity (Schwob, 2002). Systematic exposure to odorants during OT activates basal cells in the olfactory epithelium, facilitating their differentiation into mature ORNs (Avaro et al., 2022). In mouse models, OT has been shown to boost the activity of important molecular components involved in olfactory signal transduction (Kim et al., 2019, 2020). In humans, OT heightened neuroactivities at the mucosal level (Hummel et al., 2018; Wang et al., 2004). Collectively, these peripheral adaptations might form the foundation for the recovery of olfactory function, demonstrating OT’s potential to improve olfactory function.

OT induces both structural and functional changes in central olfactory pathways. The OB, the primary relay station for olfactory signals, has been shown to enlarge following OT in both healthy individuals and patients with OD, suggesting structural plasticity driven by repeated odor exposure (Gellrich et al., 2018; Gürbüz et al., 2022; Mahmut et al., 2020; Negoias et al., 2017; Rezaeyan et al., 2022), while some studies also reported no significant OB volume changes after OT (Haehner et al., 2022; Pellegrino et al., 2019). Findings on GMV in olfactory-related regions remain inconclusive. While increases in the entorhinal cortex and OFC have been reported (Al Aïn et al., 2019; Haehner et al., 2022; Han et al., 2021), changes in other regions, such as the cerebellum, were also noted (Gellrich et al., 2018; Rezaeyan et al., 2022). Conversely, some studies found no structural improvements (Chen et al., 2022), highlighting the variability in these effects. Study 2 employed a more rigorous study design compared to previous research, providing additional evidence of limited structural improvements following OT. Considering that structural changes may require longer training durations to manifest, future studies should aim to include larger sample sizes to further investigate these effects, given the limited existing literature on structural changes induced by OT.

Functionally, OT enhances brain activation and connectivity within olfactory networks. Increased activity in the frontal gyrus and stronger functional connections within the piriform cortex have been observed, accompanied by a reduction in non-olfactory network activity (Kollndorfer et al., 2015; Pellegrino et al., 2019). OT also strengthens connectivity between the cingulate cortex and insula and enhances self-inhibitory connectivity within the OFC (Hosseini et al., 2020). Additionally, increased functional connectivity in olfactory regions alongside reduced connectivity in visual areas has been reported (Jiramongkolchai et al., 2021). These findings suggest that OT promotes reorganization and neuroplasticity in both olfactory-specific and broader sensory networks. Study 2 revealed that OFC activation was increased specifically in patients with post-viral OD following OT, while heightened parahippocampal activation was observed in both patients and controls. These findings provide evidence that OT enhances central nervous system activity in olfactory-related brain regions, particularly benefiting patients and consistent with improvements in behavioral olfactory function.

One notable observation is that OT's effects on the central nervous system appear modest, with inconsistent findings regarding the magnitude and specific localization of brain changes. To enhance statistical power, many previous OT-related MRI studies have compared only training patients before and after OT. Despite these modest central effects, when combined with peripheral improvements, OT seems sufficient to promote overall olfactory recovery. In Study 2, the evidence suggests that OT primarily induces functional changes rather than structural modifications—a distinction that may explain differences in outcomes across various etiologies. For example, patients with olfactory-related brain damage due to trauma may experience limited structural benefits from short-term OT.

In summary, OT enhances olfactory function through peripheral mechanisms, such as the regeneration and maturation of ORNs, and central mechanisms, including neuroplastic changes in olfactory-related brain regions. Study 2 reinforced these findings by demonstrating that OT improves olfactory performance in patients with post-viral OD, with significant functional enhancements observed in crucial brain regions like the OFC and parahippocampus. However, structural changes, such as in the OB or GMV in olfactory-related regions, were limited, suggesting that structural changes may require longer training durations.

**What can be refined for improving OT efficacy**

After gaining a deeper understanding of the potential mechanisms underlying OT, it is crucial to investigate the effectiveness of this method in practice. Additionally, exploring ways to enhance its efficacy through the integration of ancillary approaches is equally important. Study 2 demonstrated that OT is effective in improving olfactory function in patients with post-viral OD, particularly those with COVID-related OD. Similarly, Study 3 highlighted that OT, when combined with more complex tasks such as multisensory integration and enhanced awareness of surrounding odors, can improve olfactory performance even in healthy populations.

The findings from Study 2 align with previous research suggesting that OT is most beneficial for patients with viral-related OD and is recommended as a therapeutic approach for COVID-19 patients (Patel, 2017; Pieniak et al., 2022; Whitcroft et al., 2023; Whitcroft & Hummel, 2020). Specifically, OT led to significant improvements in the threshold subtest, while other subtests showed slight increases that did not reach statistical significance. Among healthy controls who followed the OT protocol, a subtle increase in mean TDI scores was observed (pre- vs. post-TDI total scores: 36.00 vs. 37.42), though this improvement did not reach statistical significance. This result partially aligns with a prior study that reported improvements in olfactory thresholds in both participants with olfactory impairment and healthy participants (Oleszkiewicz et al., 2022).

However, it is essential to consider the ceiling effect in healthy populations when interpreting these findings, where individuals with normosmia, who already score near the upper limits of olfactory tests may experience subtle changes that are less easily captured. This narrow range leaves limited room for further improvements and presents a risk of the ceiling effect. Despite its limitations, Study 3 highlights that healthy individuals can benefit from OT, particularly when more complex training protocols are applied, which aligns with previous research utilizing more complex training tasks inducing olfactory improvements (Al Aïn et al., 2019; Olofsson et al., 2020).

Compliance remains a critical challenge in OT studies, as highlighted in Study 1. In Study 3, trained participants exhibited mostly high or moderate compliance (96%), with a higher proportion of high compliance in the counting group (43%) compared to the training-only group (33%), though this difference did not reach statistical significance. Furthermore, a recent study in patient populations showed that only 60% of patients completed an average of 10 out of the prescribed 14 weekly sessions, which was still considered adherence to a 4-month OT regimen. Notably, those who adhered to the protocol achieved clinically meaningful improvements in both orthonasal and retronasal olfactory functions compared to non-adherents (Boscolo-Rizzo et al., 2024). These results highlight the importance of following the prescribed OT regimen, even with the classical OT protocol. In efforts to improve compliance, one study introduced the olfactory training balls—a baseball-sized device with four odor-containing tubes—have shown promise in enhancing compliance and yielding greater improvements in patients with post-viral OD (Saatci et al., 2020). These findings underscore that the effectiveness of OT relies on consistent participation. Moving forward, compliance may be the key factor in optimizing olfactory recovery through OT. Ancillary approaches of OT should focus on increasing engagement and enjoyment to sustain adherence. Strategies such as developing personalized training regimens, integrating digital reminders, and improving accessibility to OT materials could help enhance adherence and maximize benefits.

Another critical challenge in OT research is to distinguish the improvements is attributed to OT or to spontaneous recovery, especially within patient populations. The neuroplasticity of the human olfactory epithelium, driven by basal cell regeneration into ORNs, facilitates natural recovery over time. Therefore, even significant improvements in olfactory function may not necessarily be the direct result of OT. To address this, control groups are essential for ruling out the effects of spontaneous recovery. Study 3 included four groups: two with ancillary approaches, one training-only control group, and a pure control group. This design enabled multiple comparisons, including assessing whether ancillary approaches enhance OT effectiveness or if OT alone is sufficient. In contrast, Study 2 included only two groups (patients and controls) both participating in OT, enabling the comparison of training effects across populations but limiting the ability to rule out spontaneous recovery. Nevertheless, among existing OT studies using MRI techniques, Study 2 included a control group that also underwent OT and was scanned both before and after training, providing a more rigorous study design to enhance statistical power to detect the effect of OT at the central level. Future studies should consider an even larger sample size and include an additional control group to isolate the effects of OT from spontaneous recovery.

Existing literature and Study 2 and 3 suggest that classical OT methods are effective for most patients with OD, also for healthy populations with additional task accompanied. While increasing the number of training odors offers limited additional benefits (Genetzaki et al., 2024), extending the training duration consistently improves outcomes (Altundag et al., 2015; Damm et al., 2014; Geißler et al., 2014). Personalized OT protocols may provide promising insights toward better efficacy. Incorporating patient preferences, such as selecting preferred training odors, could enhance engagement and effectiveness (Kim et al., 2019). Furthermore, tools like smartphone applications with reminders and instructional videos integrating multimodal stimulation could be developed to potentially improve adherence and enhance engagement in the training process.

**Limitations**

The findings of this thesis should be interpreted considering several limitations across the three studies:

First, the modest effect size of OT may hinder the detection of significant changes of olfactory improvements, particularly in central brain regions or within certain patient populations, such as patients with mild cognitive impairment. Increasing the sample size in future research could improve statistical power, wihle the inclusion of two scans for both control and patient groups provided valuable longitudinal insights in study 2.

Second, selective bias poses a limitation in olfactory research. Participation is often self-selected, as only individuals with a strong interest in olfaction tend to enroll, potentially reducing ecological validity and limiting the generalizability of the findings to the broader population.

Third, a relatively high dropout rate is a crucial challenge in OT studies, underscoring the importance of improving adherence. While Study 2 maintained a robust sample with all participants completing two scans, Study 3 experienced an approximate 22% dropout rate, although no significant differences regarding demographic data and baseline olfactory function were found between completers and dropouts in Study 3.

**Outlook for Future Research**

The findings from this thesis highlight the factors influencing participation, underlying neural mechanisms, and efficacy of OT in both clinical and healthy populations. However, several important questions remain, providing directions for future research:

**Addressing the Challenge of Awareness and Compliance:** Despite strong evidence supporting OT's effectiveness, awareness of this method remains low, particularly among older adults. Integrating OT into standard clinical practice could improve accessibility to this method.

One of the main obstacles in OT is patient adherence, as seen in Study 1. Future research should explore strategies to improve engagement, such as mobile applications, reminder systems, and more engaging training methods.

**Expanding Neuroimaging Research:** Study 2 demonstrated functional changes in olfactory-related brain regions, but structural modifications were less evident. Future studies should employ additional control groups, longer training periods and larger sample sizes to determine whether structural neuroplasticity occurs with extended OT. Similarly, other techniques such as electroencephalogram-graph or event-related potentials measured before and after OT in both healthy and patient population should shed light on the potential mechanism of OT.

**Optimizing OT Protocols:** While classical OT methods have been shown to be effective, enhanced protocols incorporating multisensory integration and attentional strategies may yield greater benefits. Future studies should employ OT with these additional approaches in the clinical context, to investigate its efficacy in patients with OD. In addition, future research could investigate whether combining OT with other interventions—such as, cognitive training, or physical exercise—can enhance its efficacy. The role of training duration remains a crucial factor, with evidence suggesting that prolonged OT provides continued improvement. Further research should try to determine if there is an optimal training length or conducting lifelong OT.

## Conclusion

This thesis explored OT from three perspectives: patient participation, its neural mechanisms, and its efficacy in different populations and different protocols. By examining both the subjective experiences of individuals undergoing OT and objective measures of its effects on the brain, this work provides a comprehensive understanding of how OT can be optimized for improved adherence and effectiveness.

Study 1 investigated what motivates or hinders individuals from engaging in OT. The results showed that greater impairment in quality of life and perceived olfactory improvement since OD started were strong motivators for participation. Additionally, adherence remained a major challenge, with most participants discontinuing training within a month. Gender differences were also observed, with women more likely to initiate OT but also more likely to discontinue early. For those who did not participate in OT, the major barrier is the unawareness of OT, especially in older population. These findings highlight the need for promoting the method of OT and strategies to enhance long-term engagement in OT.

Study 2 examined the neural mechanisms underlying OT using MRI technique. The findings showed increased activation in olfactory-related brain regions, particularly the OFC in patients with post-viral OD. However, structural changes, such as OB volume had no enlargement, while GMV only increased in cerebellum. This suggests that OT primarily enhances functional activation rather than inducing immediate structural changes. These results provide important evidence that OT enhances central olfactory processing, reinforcing its role as an effective method.

Study 3 evaluated the effectiveness of OT in healthy individuals, incorporating modified training approaches such as multisensory integration and odor awareness. While OT was effective in improving olfactory function in patients with post-viral OD in the previous studies and also in study 2, the study 3 also demonstrated that healthy individuals could benefit when more complex training protocols are used.

This thesis advances the understanding of OT by addressing three key aspects: patient perspectives, neuroimaging evidence, and training adaptations to enhance efficacy. Study 1 highlighted the need for better instructions and strategies to improve adherence, providing valuable insights for clinical practice. Study 2 demonstrated OT-induced neuroplasticity, offering evidence of its impact on brain function. Study 3 explored ways to optimize OT through modified protocols, paving the way for future research. By tackling these critical issues, this work contributes to the advancement of OT, provides clinically relevant information, and opens new avenues for further investigation.

## Zusammenfassung

### Einführung

Der Geruchssinn spielt eine wesentliche Rolle im täglichen Leben, mit Einfluss auf Gefahrerkennung, Ernährung, soziale Interaktionen und Emotionen. Etwa 20 % der Bevölkerung leiden an einer Riechstörung (OD), was zu einem deutlichen Rückgang der Lebensqualität führen kann. Riechtraining (OT) hat sich als effektive Methode zur Verbesserung von OD erwiesen. Dabei schnüffeln Betroffene wiederholt an bestimmten Gerüchen. Obwohl zahlreiche Studien den Erfolg von OT in klinischen Zusammenhängen belegen, ist die Patientenperspektive, insbesondere Gründe für eine Nichtteilnahme, bislang kaum untersucht. Die zugrunde liegenden Mechanismen von OT umfassen vermutlich sowohl die periphere Regeneration der Riechrezeptorneurone (ORNs) als auch zentrale neuroplastische Veränderungen im Riechkolben (OB) und assoziierten Gehirnregionen. Obwohl etablierte OT-Standardprotokolle wirksam sind, könnten angepasste Trainingsmethoden zusätzliche Vorteile bieten.

### Hypothesen

- Die Teilnahme an OT wird durch Faktoren wie Lebensqualitätsbeeinträchtigung, Parosmie-Symptome und wahrgenommene Verbesserungen des Riechvermögens beeinflusst; mangelndes Wissen und unzureichende Durchführung des OT stellen dabei wesentliche Probleme dar.
- OT induziert strukturelle und funktionelle Verbesserungen in riechbezogenen Hirnregionen.
- OT verbessert die olfaktorische Funktion, wobei komplexe Trainingsansätze, die multisensorische Integration und erhöhte Geruchswahrnehmung beinhalten, bei gesunden Individuen zu größeren Verbesserungen führen als Standard-OT oder keine Teilnahme.

### Methodologie

Studie 1: Eine Querschnittsuntersuchung mit 450 Teilnehmern, bei der demografische Daten, Ursachen und Beginn der Riechstörung sowie Informationen zu Parosmie, Phantosmie, OT und Lebensqualität erfasst wurden. Die Teilnehmer wurden in zwei Gruppen unterteilt (OT: n = 161; kein OT: n = 289), und die Daten wurden mittels Chi-Quadrat-Tests, unabhängiger t-Tests und logistischer Regression analysiert.

Studie 2: 20 weibliche Patienten mit COVID-19-bedingter OD und 19 gesunde Kontrollpersonen wurden rekrutiert und absolvierten ein klassisches OT über drei Monate. Vor und nach dem OT wurden olfaktorische Tests (Sniffin' Sticks) und funktionelle sowie

strukturelle MRT-Untersuchungen durchgeführt, um Veränderungen in der Hirnaktivierung und -struktur zu ermitteln.

Studie 3: 100 Teilnehmer wurden zufällig in vier Gruppen (Video, Zähler, OT allein, Kontrollgruppe) eingeteilt. Vor und nach dem OT wurde das Riechvermögen gemessen. Die Trainingsgruppen erhielten unterschiedliche OT-Protokolle, wobei multisensorische Integration und ein Fingerzähler zur Verstärkung der Geruchswahrnehmung eingesetzt wurden. Zusätzlich wurde das Ausmaß der körperlichen Aktivität wöchentlich mittels des Global Physical Activity Questionnaire erfasst.

**Ergebnisse**

**Studie 1:** Eine starke Beeinträchtigung der Lebensqualität und wahrgenommene Verbesserungen des Riechvermögens motivierten die Teilnahme am OT. Allerdings war das Wissen um OT, insbesondere bei älteren Personen, gering, und viele Teilnehmer brachen das Training innerhalb eines Monats ab. Geschlechtsunterschiede in der Adhärenz wurden ebenfalls beobachtet.

**Studie 2:** OT verbesserte das Riechvermögen was anhand der Sniffin' Sticks Tests nachgewiesen wurde. Insbesondere wurde eine erhöhte funktionelle Aktivierung im orbitofrontalen Cortex (OFC) bei Patientinnen mit post-viraler OD und im Parahippocampus bei beiden Gruppen festgestellt. Strukturelle Veränderungen, etwa im OB, waren jedoch begrenzt, was möglicherweise auf eine zu kurze Trainingsdauer hindeutet.

**Studie 3:** OT, ergänzt durch multisensorische Integration und gesteigerte Aufmerksamkeit für Alltagsgerüche, verbesserte insbesondere die Schwellenwerte und Diskriminierungsfähigkeit. Die Komplexität der Trainingsgerüche und das Ausmaß der körperlichen Aktivität hatten nur begrenzte Effekte auf die Verbesserung des Riechvermögens.

**Schlussfolgerungen**

Diese Arbeit erweitert das Verständnis von OT, indem sie Patientenperspektiven, neuroimaging-basierte Belege und angepasste Trainingsansätze integriert. Studie 1 zeigte, dass Patienten mit starker Lebensqualitätsbeeinträchtigung und wahrgenommenen Verbesserungen des Riechvermögens eher an OT teilnehmen, wobei jedoch ein Wissensmangel und eine geringe Adhärenz bestehen, insbesondere bei älteren und jüngeren Personen. Studie 2 legt nahe, dass OT zu funktionellen Verbesserungen in olfaktorisch relevanten Hirnregionen führt, während strukturelle Veränderungen möglicherweise längere Trainingszeiten erfordern. Studie 3 verdeutlicht, dass OT, besonders in Kombination mit multisensorischen Ansätzen, die olfaktorische Funktion sowohl bei Patienten als auch bei gesunden Personen verbessern kann. Zukünftige Forschungen sollten personalisierte OT-Protokolle, langfristige Effekte und ergänzende Interventionen untersuchen, um die Effektivität von OT weiter zu optimieren und die Patientenadhärenz zu verbessern.

## Summary

### Introduction

The sense of smell plays a vital role in our daily lives, influencing survival, nutrition, social interactions, and emotions. Despite its significance, Olfactory dysfunction (OD) affects approximately 20% of the population, leading to a notable decline in quality of life. Olfactory training (OT) has emerged as an effective approach to improve OD by repeatedly exposing individuals to specific odors. While numerous studies have demonstrated OT's effectiveness in clinical settings, less is known about patients' perspectives, particularly the reasons for non-participation. The underlying mechanisms of OT involve both peripheral regeneration of olfactory receptor neurons (ORNs) and central neuroplasticity in the olfactory bulbs (OB) and olfaction-related brain regions. Although standard OT protocols have shown success, adapted training methods may offer even greater benefits. This thesis tries to answer the following questions: (1) What factors influence patients to engage in OT? (2) What are the neural mechanisms underlying OT? (3) How effective is OT in patients and healthy individuals?

### Hypotheses

Study 1: OT participation is driven by factors such as quality of life impairment, parosmia symptoms, and perceived olfactory improvement.

Study 2: OT induces both structural and functional improvements in olfactory-related brain regions.

Study 3: OT is effective in improving olfactory function. In healthy individuals, more complex approaches will yield greater improvements.

### Methodology

Study 1: A cross-sectional survey was conducted to assess factors influencing OT participation. Four hundred fifty participants completed questionnaires about the demographic information (e.g. age range and sex) and general questions such as the causes and onset of their smell loss based on their opinion. Questions were also included regarding parosmia, phantosmia, OT, and quality of life. Patients were divided into two groups: OT (n = 161), and No OT (n = 289) groups, according to their responses to the question “Are you doing smell training?”. Data analyses were performed using Chi-square analyses, independent t-tests, and logistic regression analysis.

Study 2: Twenty female patients with COVID-19 related OD and 19 healthy controls were recruited. They all underwent classical OT for three months. Before and after OT, Sniffin' Sticks test was applied for measuring olfactory function; MRI techniques were measured to determine the functional and structural brain changes. N-butanol was selected for functional MRI scanning, delivered birhinally using Teflon™ tubing connected to a portable computer-controlled olfactometer. Stimuli were presented in a block design format, alternating between 8-second "ON" (odor) and 12-second "OFF" (odorless air) blocks. MRI images were pre-processed and analyzed using SPM12 implemented in MATLAB. Functional data analysis employed a two-level restricted maximum likelihood approach. ROI analyses were conducted in Marsbar toolbox. The segmentation of the OB volume was performed using ITK-SNAP to process T2-weighted images. Voxel-based morphometry analyses were performed using the CAT12 toolbox. Independent t-test, repeated measures ANCOVA controlling for age, and Pearson correlation analysis were employed in the analyses.

Study 3: One hundred participants were divided into four groups (Video: n = 26; Counter: n = 24; Training only: n = 24, and Control: n = 26). Before and after OT, Sniffin' Sticks test was applied for measuring olfactory function. Except for control group, three training groups were set up: participants in the Video group followed a guiding video during each session, which included visual and auditory stimuli designed to enhance multisensory integration. Participants in the Counter group received a wearable finger counter to track the number of odors they detected throughout the day, reinforcing odor awareness. In OT-only group, participants performed classical OT without additional modifications. Data were analyzed using one-way ANOVA, Chi-square tests, repeated-measures ANOVA and Spearman's correlation analysis.

**Results**

Study 1: Quality of life impairment and perceived olfactory improvement since OD started were the strongest motivators for OT participation. Awareness of OT was low, especially in older adults, and most participants discontinued training within a month. Gender differences in adherence were observed.

Study 2: OT improved olfactory function in patients. Importantly, OT increased functional activation in the OFC in patients, and increased activation of parahippocampus in both patients and controls. However, structural changes in the OB and other regions were minimal, with only increased GMV in cerebellum.

Study 3: OT together with multisensory integration and the attention to daily odors enhanced olfactory function, especially in odor thresholds and discrimination.

**Conclusions**

This thesis advances the understanding of OT by integrating patient perspectives, neuroimaging evidence, and training adaptations. Study 1 indicates that patients who experienced a significant decline in quality of life due to OD and those who perceived olfactory improvements since OD started were more likely to engage in OT. However, many patients did not adhere to the training for a sufficient duration. Main barriers for participation included low awareness of OT among older individuals and skepticism about its effectiveness among younger individuals. Given the growing evidence supporting OT's benefits, clinicians should actively promote OT to patients while emphasizing the importance of long-term adherence for optimal outcomes.

Study 2 suggests that OT is linked to improved olfactory function and increased activation in the OFC in female patients with post-viral OD and in parahippocampus for both groups. The absence of significant structural changes may be due to the relatively short training duration, suggesting that while functional improvements can occur relatively quickly, structural adaptations may require a longer period of training.

Study 3 reveals that OT incorporating ancillary approaches, such as multisensory integration and enhanced attention, can improve olfactory function in individuals with subjectively normal olfactory function. These modified training methods hold potential for clinical applications.

## Publication Data

(according to Journal Citation Reports, as of March 2025, https://jcr.clarivate.com/jcr/home)

**European Archives of Oto-Rhino-Laryngology**

“European Archives of Oto-Rhino-Laryngology is an international scientific journal covering the broad variety of head and neck diseases with an inherent focus on clinical and translational research in all specialties of Oto-Rhino-Laryngology and Head & Neck.”

2023 Journal Metrics

Journal Impact Factor: 1.9

5-year Impact Factor: 2.2

Immediacy Index: 0.4

Eigenfactor Score: 0.01270

Normalized Eigenfactor: 2.79201

Article Influence Score: 0.569

Rank (by Journal Citation Indicator Otorhinolaryngology): 10/66

**Laryngoscope**

“The Laryngoscope has been the leading source of information on advances in the diagnosis and treatment of head and neck disorders since 1896. The Laryngoscope is the first choice among otolaryngologists for publication of their important findings and techniques.”

2023 Journal Metrics

Journal Impact Factor: 2.2

5-year Impact Factor: 2.6

Immediacy Index: 0.3

Eigenfactor Score: 0.01931

Normalized Eigenfactor: 4.24419

Article Influence Score: 0.732

Rank (by Journal Citation Indicator Otorhinolaryngology): 25/66

**Chemical Senses**

“Chemical Senses publishes original research and review papers on all aspects of chemoreception in both humans and animals. An important part of the journal's coverage is devoted to techniques and the development and application of new methods for investigating chemoreception and chemosensory structures.”

2023 Journal Metrics

Journal Impact Factor: 2.8

5-year Impact Factor: 3.2

Immediacy Index: 0.5

Eigenfactor Score: 0.00220

Normalized Eigenfactor: 0.48530

Article Influence Score: 0.940

Rank (by Journal Citation Indicator Behavioral Sciences): 17/55

## Other Publications

### Journal Articles

**Li, Z.**, Richter, L., Krueger, T., Eichwald, H., Hähner, A., & Hummel, T. (2024). Patients with parosmia respond faster to unpleasant odors than patients with hyposmia: Insights from olfactory event-related potentials. International Forum of Allergy & Rhinology, March, 1–9. https://doi.org/10.1002/alr.23350

**Li, Z.**, Abdul Manan, H., Heitmann, H., Witte, V., Wirkner, K., Riedel-Heller, S., Villringer, A., & Hummel, T. (2023). The Association Between Depth of the Olfactory Sulcus, Age, Gender and Olfactory Function: An MRI-based Investigation in More Than 1000 Participants. Neuroscience, 519, 31–37. https://doi.org/10.1016/j.neuroscience.2023.03.017

**Li, Z.**, Salloum, R., & Hummel, T. (2023). Patients with olfactory loss exhibit pronounced adaptation to chemosensory stimuli: an electrophysiological study. *Rhinology Journal*, *61*(5), 449–455. https://doi.org/10.4193/Rhin23.049

**Li, Z.**, Mignot, C., Sinding, C., & Hummel, T. (2023). Effects of desensitization on odors varying in concentration and pleasantness. Journal of Sensory Studies, August. https://doi.org/10.1111/joss.12877

**Li, Z.**, Gottschall, T., Antje, H., & Hummel, T. (2022). Retronasal olfaction is relatively less affected in older individuals with subjectively normal olfactory function. Food Quality and Preference, 101(2022), 104632. https://doi.org/10.1016/j.foodqual.2022.104632

**Li, Z.**, Stolper, S., Draf, J., Haehner, A., & Hummel, T. (2022). Smell, taste and trigeminal function: similarities and differences between results from home tests and examinations in the clinic. *Rhinology*, *19*(14), 293–308. https://doi.org/https://doi.org/10.4193/Rhin21.430

## Conferences and Presentations

Part of the presented work was introduced at the following international meetings:

| | |
|---|---|
| October 12, 2023 | "Olfactory training: perspective from patients with smell problems"<br>Chemosensory lab meeting<br>Zoom meeting between Dresden, Germany and Chongqing, China |
| September 20, 2023 | "Olfactory training: effects of multisensory integration, attention towards odors and physical activity"<br>European Chemoreception Research Organization XXXIII Conference<br>Nijmegen, Netherlands |

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