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Sensory, emotional, and cognitive effects of olfactory training in children and adolescents

Wpływ treningu węchowego na funkcjonowanie sensoryczne, emocjonalne i poznawcze dzieci i adolescentów

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Ph.D. Dissertation

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Abstract in English

Human sense of smell (olfaction) exhibits remarkable plasticity. The olfactory system subjects to damage and regenerates cyclically throughout life. Regeneration of the olfactory system can be induced by exposure to odors. In animals, olfactory stimulation supports the survival of the neurons and increases olfactory abilities. In humans, exposure to odors changes brain structure and functionality, which is reflected in enhanced olfactory performance. Plasticity of the olfactory system is used for treating olfactory dysfunction – a regular, structured stimulation of the sense of smell (olfactory training, OT) promotes olfactory rehabilitation and leads to structural and functional reorganization of the olfactory brain network.

Among the sensory systems, the olfactory system has a unique neuroanatomical architecture. Odors directly activate the limbic system without a complete thalamic relay. Thus, olfactory input may modulate certain emotional and cognitive processes. Additionally, structures comprising primary and secondary olfactory cortices are functionally engaged in emotional and cognitive functions. For this reason, OT has been hypothesized to have effects not only in the olfactory domain but also benefit emotional functioning and cognition. Preliminary empirical evidence supports this hypothesis. Thus far, no studies on the cognitive and emotional effects of OT in children have been reported.

Olfactory development in childhood is intertwined with the maturation of cognitive and emotional functions. However, OT effects in children are understudied, with only preliminary verification of OT effects on olfactory abilities being available. This dissertation aimed to investigate how OT might influence children's olfactory, emotional, and cognitive functions. To this end, three experimental studies were conducted.

Study 1 verified if OT conducted in a school setting (i.e., with maximized compliance) may benefit 8-year-old children's olfactory sensitivity and odor identification ability. Control group performed an odorless training. Whereas OT did not change children's olfactory sensitivity, it increased odor identification ability and this increase continued after OT offset. The latter finding suggests that OT in children may induce changes in olfactory knowledge (e.g., increase odor awareness) that lead to better odor identification also after OT completion.

Study 2 investigated whether OT might benefit the olfactory and cognitive (executive functions, fluid intelligence) abilities of children and adolescents aged 6 to 16 years who sustained mild traumatic brain injury and their healthy counterparts. In this study OT effects were investigated in two variants – OT was conducted with either high- or low-concentrated

odors. OT with low-concentrated odors improved olfactory sensitivity in children after mTBI, and increased fluid intelligence in both injured and healthy children, for the first time demonstrating potential cognitive effects of OT in children.

Study 3 verified if OT might improve working memory across three sensory domains (olfaction, vision, audition) and enhance the ability to match emotional facial expressions in children aged 6 to 9 years. The control group performed an odorless training. Whereas working memory scores did not change after OT, children performing OT improved in matching emotional facial expressions. The gathered evidence demonstrates that OT effects might exceed to the emotional domain.

Altogether, this dissertation deepened the knowledge about OT effects in children and demonstrated that certain psychological effects of OT may be observed in olfactory, cognitive, and emotional domains. Further research, including neuroimaging studies, is required to explore what other domains of children's functioning might benefit from OT, and what mechanisms lead to the observed effects.

Keywords: olfactory training, olfaction, cognitive abilities, emotional functioning, children, adolescents

Streszczenie w języku polskim

Zmysł węchu cechuje wysoki poziom plastyczności. Mimo podatności na uszkodzenia, układ węchowy posiada niezwykłą zdolność regeneracji, a zdolność ta jest wzmacniana ekspozycją na zapachy. Badania na zwierzętach wykazały, że stymulacja układu węchowego za pomocą zapachów zwiększa przeżywalność neuronów i usprawnia funkcje węchowe. U ludzi ekspozycja na zapachy prowadzi do zmian strukturalnych i funkcjonalnych w obrębie części układu nerwowego aktywowanych bodźcami węchowymi oraz zwiększa zdolności węchowe. Plastyczność zmysłu węchu jest wykorzystywana w leczeniu jego dysfunkcji – regularna, ustrukturyzowana ekspozycja na zapachy, czyli trening węchowy, wspiera rehabilitację węchu i prowadzi do strukturalnej i funkcjonalnej reorganizacji kory węchowej mózgu.

W porównaniu do innych zmysłów, węch ma unikalną budowę neuroanatomiczną. Bodźce zapachowe aktywują układ limbiczny, bez konieczności ich integracji we wzgórzu, wpływając tym samym na procesy emocjonalne i poznawcze. Struktury pierwszo- i drugorzędowej kory węchowej są również funkcjonalnie zaangażowane w procesy emocjonalne i poznawcze. Na tej podstawie sformułowano hipotezę, że trening węchowy wpływa pozytywnie na zdolności węchowe oraz na funkcjonowanie emocjonalne i poznawcze człowieka. Pierwsze badania prowadzone w grupie osób dorosłych potwierdziły tę hipotezę. Dotychczas nie analizowano, czy trening węchowy korzystnie wpływa na procesy poznawcze i emocjonalne u dzieci.

Rozwój węchu w dzieciństwie jest powiązany z rozwojem funkcji poznawczych i emocjonalnych. Efekty treningu węchowego u dzieci pozostają jednak niedostatecznie zbadane, a jedyne dostępne badania dotyczą wpływu treningu węchowego na zdolności węchowe. Celem niniejszej rozprawy doktorskiej było zbadanie, w jaki sposób trening węchowy może wpływać na funkcje węchowe, emocjonalne i poznawcze dzieci. W tym celu przeprowadzono trzy badania eksperymentalne.

Badanie 1 weryfikowało, czy trening węchowy prowadzony w szkole (tj. przy maksymalnej regularności treningu) zwiększa wrażliwość węchową i zdolność identyfikacji zapachów u 8-letnich dzieci. Grupa kontrolna trenowała z bezwonnymi substancjami. Choć trening węchowy nie zmienił wrażliwości węchowej dzieci, zwiększył on zdolność identyfikacji zapachów, a pozytywny efekt utrzymywał się po zakończeniu treningu. Poprawa zdolności identyfikacji zapachów postępująca po zakończeniu treningu sugeruje, że

potencjalnym mechanizmem może być zwiększenie świadomości zapachów w otoczeniu, które przekłada się na zwiększenie zdolności ich identyfikacji.

Badanie 2 weryfikowało, czy trening węchowy może korzystnie wpływać na zdolności węchowe i poznawcze (funkcje wykonawcze, inteligencja płynna) dzieci i młodzieży (6-16 lat), które doznały łagodnego urazowego uszkodzenia mózgu, i ich zdrowych rówieśników. Efekty treningu węchowego badano w dwóch grupach, które trenowały z zapachami o wysokim lub niskim stężeniu. Trening z zapachami o niskim stężeniu doprowadził do poprawy wrażliwości węchowej u dzieci po urazie mózgu i zwiększył inteligencję płynną zarówno u dzieci po urazie, jak i zdrowych, wykazując poznawcze efekty treningu węchowego u dzieci.

Badanie 3 weryfikowało, czy trening węchowy może wspierać pamięć roboczą w trzech modalnościach (węch, wzrok, słuch) i zwiększyć zdolność dopasowywania emocjonalnych wyrazów twarzy u dzieci (6-9 lat). Grupa kontrolna trenowała z bezwonnymi substancjami. Choć poziom pamięci roboczej nie zmienił się po treningu, dzieci wykonujące trening poprawiły zdolność dopasowywania emocjonalnych wyrazów twarzy, wykazując, że efekty treningu węchowego obejmują sferę emocjonalną.

Podsumowując, niniejsza rozprawa dostarczyła dowody na skuteczność treningu węchowego u dzieci i wykazała wybrane psychologiczne efekty treningu w sferach węchowej, poznawczej i emocjonalnej. Dalsze badania, w tym badania neuroobrazowe, pozwolą ustalić, jakie inne domeny funkcjonowania dzieci mogą być wspierane przez trening węchowy i określić mechanizmy jego działania.

Słowa kluczowe: trening węchowy, węch, zdolności poznawcze, funkcjonowanie emocjonalne, dzieci, adolescenci

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List of publications

This cumulative PhD dissertation consists of the following five papers published in peer-reviewed scientific journals:

1. **Pieniak, M.**, Oleszkiewicz, A., Avaro, V., Calegari, F., & Hummel, T. (2022). Olfactory training – Thirteen years of research reviewed. *Neuroscience & Biobehavioral Reviews*, *141*, 104853. https://doi.org/10.1016/J.NEUBIOREV.2022.104853 [IF: 9.052/2021, MNiSW: 200]

   Contribution: Literature review, Writing – original draft (human research), Writing – review & editing, Response to reviews

2. Mahmut, M. K., **Pieniak, M.**, Resler, K., Schriever, V. A., Haehner, A., & Oleszkiewicz, A. (2021). Olfactory training in 8-year-old increases odour identification ability: a preliminary study. *European Journal of Pediatrics*, *180*(7), 2049–2053. https://doi.org/10.1007/s00431-021-03970-y [IF: 3.860/2021, MNiSW: 70]

   Contribution: Conceptualization, Methodology, Investigation, Writing – review & editing

3. **Pieniak, M.**, Seidel, K., Oleszkiewicz, A., Gellrich, J., Karpinski, C., Fitze, G., & Schriever, V. A. (2023). Olfactory training effects in children after mild traumatic brain injury. *Brain Injury*, *37*(11), 1272–1284. https://doi.org/10.1080/02699052.2023.2237889 [IF: 1.9/2022, MNiSW: 100]

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4. **Pieniak, M.**, Rokosz, M., Nawrocka, P., Reichert, A., Żyżelewicz, B., Mahmut, M. K., & Oleszkiewicz, A. (2024). Null cross-modal effects of olfactory training on visual, auditory or olfactory working memory in 6-9 years old children. *Neuropsychological Rehabilitation,* 1-22. https://doi.org/10.1080/09602011.2024.2343484 [IF: 2.7/2023, MNiSW: 70]

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5. **Pieniak, M.**, Rokosz, M., Ivcevic, Z., Reichert, A., Żyżelewicz, B., Nawrocka, P., Lebuda, I., Oleszkiewicz, A. (2024). Olfactory training improves emotion matching ability in 6–9 years old children — preliminary evidence. *Journal of Sensory Studies*, *39*(2), e12912. https://doi.org/https://doi.org/10.1111/joss.12912 [IF: 2/2023, MNiSW: 100]

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Introduction

Human brain exhibits remarkable plasticity. The structure and functionality of neural networks change with age and are shaped by learning, environmental inputs, and brain injuries (Kolb et al., 2017; Kossut, 2019). Brain plasticity inspired researchers to focus on how various interventions, including sensory or motor stimulation, cognitive training, or transcranial magnetic/electric stimulation, might benefit human sensory processing, cognitive functions, and emotional well-being (Nejati et al., 2020; Sala & Gobet, 2020; Whiteman et al., 2016).

The premise to explore the effectiveness of various interventions on human sensory, cognitive, and emotional functions relies on a body of neuroimaging evidence linking psychological functions to single brain structures or complex neural circuits (Suárez et al., 2020). Most interventions leveraging the neuroplasticity of the human brain assume that regular stimulation of specific brain structures will positively affect the functions rooted in these structures (Dinse & Tegenthoff, 2015; Suthana & Fried, 2014).

Various sensory modalities are used in interventions aiming to improve emotional well-being and cognitive function, including visual, auditory, olfactory, gustatory, and motor stimulation (Canbeyli, 2010; Olmstead, 2005). Of these, olfaction is the sensory modality of particular interest. Among sensory systems, the olfactory system exhibits a unique neuroanatomical architecture. The olfactory perception starts when volatile odorous molecules bind to olfactory receptor neurons (ORNs) located in the olfactory epithelium, from where the signal is projected to the olfactory bulb (Dikeçligil & Gottfried, 2024). The olfactory bulb has synaptic connections to the olfactory cortex, i.e., the entorhinal cortex, piriform cortex, and amygdala (Witt, 2020), thus accessing the limbic areas. The signal is transmitted to multiple brain regions relevant to cognitive and emotional processing, such as the orbitofrontal cortex, hippocampus, and insula (Fjaeldstad et al., 2017; Freiherr, 2017). Unlike other sensory systems, projections from the peripheral olfactory system are only partly mediated by the thalamus before reaching the limbic system (Gottfried, 2010; Witt, 2020). It makes the olfactory cues potent modulators of amygdala activity (Costafreda et al., 2008) and elicitors of emotions and autobiographical memories (Larsson et al., 2014; Willander & Larsson, 2007).

The olfactory system is plastic and regenerates throughout its lifetime (Manzini et al., 2022). The high regenerative capacities of the olfactory system are partially counterbalancing its vulnerability. Being separated from the external environment by a thin layer of mucus, ORNs are a gateway to the central nervous system. This exposes the olfactory system (and further nervous system) to penetration by viruses, prions, and other hazardous agents, e.g., airborne metals or toxins; leading to neural infection, local inflammation, and neurodegeneration (Doty, 2008; Rey et al., 2018). The olfactory system has several features minimizing threats arising from exposure to external threats, including (1) the complex local immune system of the olfactory mucosa (Wellford & Moseman, 2024), (2) viral infection induced apoptosis of ORNs (I. Mori et al., 2002), and (3) ongoing neurogenesis of ORNs. Mature neurons are integrated into the olfactory system at the peripheral and central levels – the novel ORNs in the olfactory epithelium mature from their progenitors, i.e., horizontal and globose basal cells. In contrast, mature neurons in the olfactory bulb migrate from the sub-ventricular zone through the rostral migratory stream (Avaro et al., 2022; Schwob et al., 2017; Witt, 2020). These findings demonstrate that the olfactory system exhibits unique ways of regeneration and plasticity that are not observed in other sensory modalities.

One way to induce neuroplasticity of the olfactory system in animals is through olfactory stimulation. For instance, in rodents, regular exposure to odors (1) enhances the expression of the anti-apoptotic gene Bcl-2 promoting the survival of ORNs (Watt et al., 2004), (2) supports the survival of neurons in the olfactory bulb and piriform cortex (Shapiro et al., 2007; Veyrac et al., 2009), and (3) increases the density of inhibitory interneurons in the olfactory bulb (Mandairon et al., 2008). These changes are reflected in the animal’s behavior as an increased ability to discriminate odors and localize food based on olfactory cues (Kim et al., 2020; Mandairon et al., 2006).

Similar conclusions have been reached in humans. Professionals with increased odor exposure in their work like sommeliers, perfumers, and herbalists exhibit enhanced olfactory sensitivity and increased abilities to discriminate, identify, and name odors than their control counterparts (Casillas et al., 2019; Hummel et al., 2004; Mariño-Sanchez et al., 2010; Tempere et al., 2012). The behavioral findings are congruent with neuroimaging studies reporting the increased volume of the olfactory bulb and thickness of the entorhinal cortex in sommeliers and sommelier students (Filiz et al., 2022). Additionally, functional activity of the piriform cortex, hippocampus, and orbitofrontal cortex during olfactory imagery tasks is correlated with sommeliers’ professional experience, suggesting functional adjustment of the olfactory system to everyday olfactory tasks (Plailly et al., 2012). Contrary to professionals working in odorous environments, people working in odorless conditions (such as a microchip factory) show reduced olfactory sensitivity and odor discrimination ability, and these deficits positively correlate to the number of years worked in an odorless setting (Chen et al., 2024). Finally, odor detection thresholds change as a function of geographical location (Oleszkiewicz et al., 2020; Sorokowska, Sorokowski, et al., 2015), and these differences might be at least partially driven by environmental factors such as air pollution (Bratman et al., 2024; Calderón-Garcidueñas et al., 2010; Ekström et al., 2022), which once again demonstrates the plasticity of the human olfactory system in response to the odorous sensory input.

To date, regular, structured exposure to odors, known as olfactory training, has mainly been considered a therapeutic intervention for individuals suffering from olfactory dysfunction (Hummel et al., 2009; Sorokowska et al., 2017). However, the above-mentioned features of the olfactory system, specifically: (1) the shared engagement of brain structures in olfactory, cognitive, and emotional processes; (2) the high regenerative capacity of the olfactory system in the periphery and at the central level; (3) the ability of odors to trigger regenerative processes and potently activate the limbic system; make olfaction a promising sensory modality for interventions aimed at improving sensory sensitivity, cognitive abilities, and emotional function.

Olfactory training as an intervention improving sensory, emotional, and cognitive functions

This chapter summarizes key findings and conclusions presented in the following publication:

Pieniak, M., Oleszkiewicz, A., Avaro, V., Calegari, F., & Hummel, T. (2022). Olfactory training – Thirteen years of research reviewed. *Neuroscience & Biobehavioral Reviews*, 141, 104853. https://doi.org/10.1016/J.NEUBIOREV.2022.104853

Human olfaction serves three major purposes: (1) to localize food and assess its quality, (2) to detect airborne molecules signaling potential threats (e.g., smoke), and (3) to navigate social relationships through body odor perception (Stevenson, 2010). Impairment of these functions is reflected in complaints of patients with olfactory dysfunction (dysosmia[1]) who report decreased food enjoyment and weight fluctuations (Aschenbrenner et al., 2008), higher frequency of hazardous events (e.g., failure to notice a gas leakage; Santos et al., 2004), increased anxiety (Speth et al., 2020), and issues with intimacy in close relationships (Schäfer, Mehler, et al., 2019), which all significantly diminish the quality of life (Croy et al., 2014).

The negative impact of olfactory dysfunction on life quality motivated research on dysosmia treatment. However, the heterogeneity of olfactory dysfunction etiologies (e.g., sinonasal disease, head injuries, neurodegenerative diseases, upper-respiratory-tract infections, aging) poses a challenge to find a universal treatment method. For instance, pharmacological treatment with corticosteroids and monoclonal antibodies is effective against olfactory dysfunction in chronic rhinosinusitis but it has limited efficacy in other etiologies of dysosmia (Whitcroft et al., 2023).

A compelling body of evidence coming from rodent research demonstrated that olfactory functions might be enhanced by regular, structured exposure to odors. This line of research showed that systematic stimulation of the olfactory system in animals with induced anosmia (complete olfactory loss) prompts expression of olfactory receptors (Kim et al., 2020), increases neural activity of the olfactory mucosa (Youngentob & Kent, 1995) and promotes expression of anti-apoptotic genes (Watt et al., 2004) as well as genes mediating neuronal

[1] In the presented dissertation terms 'olfactory dysfunction' and 'dysosmia' are used interchangeably, as terms for any type of quantitative or qualitative olfactory impairment, according to a recently published consensus statement (Hernandez et al., 2023).

survival and synaptic plasticity (Tepe et al., 2018). All these changes are reflected in behavior, for example in the increased performance in food-finding tasks relying on olfactory functions (Kim et al., 2019, 2020).

Based on the findings from animal research, systematic exposure to odors has been hypothesized to benefit olfactory function in patients with dysosmia. In 2009, Hummel et al. (2009) tested the effectiveness of 12-week bi-daily stimulation of the olfactory system with four odorous molecules (phenyl ethyl alcohol – rose odor; eugenol – cloves odor; citronellal – lemon odor; eucalyptol – eucalyptus odor) in patients with olfactory dysfunction of different etiologies (post-infectious, post-traumatic, idiopathic). This treatment protocol has been called 'olfactory training' (OT) and it proved to be more effective in restoring olfactory function than spontaneous recovery (28% vs 6% of clinically significant recovery, respectively). The original procedure of OT proposed by Hummel et al. is presented in Figure 1.

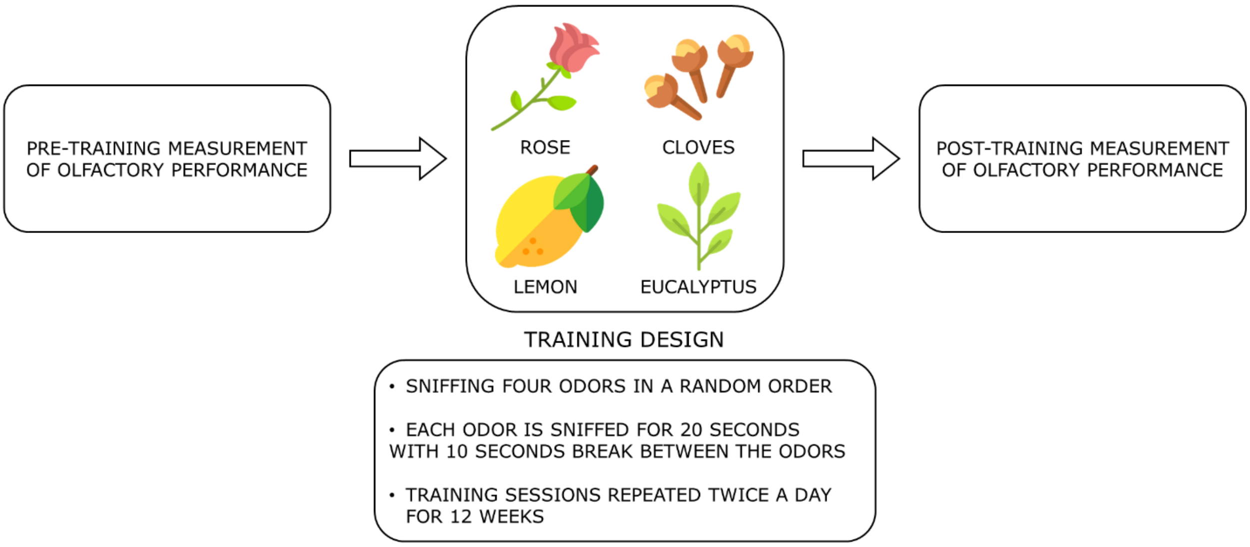

Figure 1. Olfactory training procedure described by Hummel et al. (2009).

Note: This figure is a slightly modified version of a figure previously published in *Neuroscience & Biobehavioral Reviews* (Pieniak et al., 2022).

The abundance of research on OT, especially in SARS-CoV-2 pandemic when olfactory dysfunction became an emblematic symptom of COVID-19 infection, urged providing a comprehensive synthesis of the available findings on treatment methods for dysosmia. While there are several meta-analyses focusing on OT effectiveness in patients with olfactory dysfunction, they either include relatively small number of studies that were available at the time (Pekala et al., 2016; Sorokowska et al., 2017) or focus solely on subgroup of patients, e.g., patients with post-infectious (Kattar et al., 2021) or post-traumatic dysosmia (Huang et al., 2021). The aim of the review published in the *Neuroscience & Biobehavioral Reviews* was to (1) provide a comprehensive overview of available clinical research on OT effectiveness in smell rehabilitation, (2) delineate potential mechanisms through which OT improves olfactory function, (3) present its potential psychological applications, and (4) discuss most common methodological challenges encountered in OT research. As such, the review aimed to introduce OT, a method primarily known to the otorhinolaryngologists, to the broader scientific public.

The review of the clinical research indicated that OT is most effective in patients with post-infectious olfactory dysfunction. In contrast, its effects are less pronounced in patients with post-traumatic olfactory dysfunction, and none-to-marginal in patients with idiopathic dysosmia (Konstantinidis et al., 2013; Oleszkiewicz et al., 2018; Poletti et al., 2016). The effectiveness of OT might be enhanced by increasing the duration of OT (Konstantinidis et al., 2016), and introducing novel odors throughout the OT period (Altundag et al., 2015), but not by employing specific types of odorants. OT with heavy-weight molecules (lesser vapor pressure) is equally effective as OT with light-weight molecules (higher vapor pressure; Poletti et al., 2016). OT with odor mixtures (potent to activate more receptors; resistant to specific anosmia) is just as effective as OT with single molecules (Z. Li et al., 2023; Oleszkiewicz et al., 2018).

Olfactory training may cause structural and functional changes in the central as well as peripheral olfactory system. Olfactory bulb volume has been shown to increase in patients with idiopathic olfactory dysfunction and healthy people after they completed OT (Mahmut et al., 2020; Negoias et al., 2017). In patients with olfactory dysfunction, an increased volume was also reported for other brain structures following OT – the anterior and medial orbitofrontal cortex, thalamus, and cerebellum (Gellrich et al., 2018; Han et al., 2021). Functional magnetic resonance imaging (fMRI) studies provided evidence that OT alters functional connectivity within olfaction-related regions, but also in brain areas relevant for cognition. Specifically, in patients with olfactory dysfunction, increased functional connectivity has been observed between the caudate nucleus and entorhinal cortex; between the insula, fusiform gyrus, and dorsolateral prefrontal cortex (Kollndorfer, Fischmeister, et al., 2015), and between the insula and cingulate cortex (Hosseini et al., 2020). Patients with post-traumatic dysosmia who underwent OT were shown to exhibit increased activity of the anterior cingulate cortex and

Broca's area during odor stimulation (Pellegrino et al., 2019). OT effects have also been observed in the peripheral nervous system. In patients with dysosmia, peripheral responses to odors (phenyl ethyl alcohol and hydrogen sulfide) evidenced by electroolfactogram were more frequently detected after OT than before the OT onset (Hummel et al., 2018).

OT affects brain regions that are involved in olfactory, cognitive, and emotional functioning. It can therefore be hypothesized that besides olfactory rehabilitation, OT might have psychological effects. Preliminary evidence coming from adults lends support to this hypothesis. OT benefits semantic verbal fluency (i.e., the ability to generate words in a given semantic category) in patients with olfactory dysfunction, as well as young and old healthy people (Oleszkiewicz, Bottesi, et al., 2022; Wegener et al., 2018; but see: Z. Li et al., 2023). Additionally, in aging people, OT increases well-being (Wegener et al., 2018) and slows down age-related cognitive decline (Oleszkiewicz, Abriat, et al., 2021). More complex design of OT, including regular exposure to odors during an olfactory short-term memory task, leads to increase in olfactory abilities, but also benefits visual short-term memory (Olofsson et al., 2020). OT has been shown to reduce depressive symptoms in older people with sub-clinical depression (Wegener et al., 2018), but not in patients diagnosed with major depressive disorder (Pabel et al., 2020).

Noteworthy, there are recurring challenges in OT research. Firstly, compared to clinical trials, where an indistinguishable placebo can be introduced (Gupta & Verma, 2013), there is no consensus on the most appropriate control group in OT studies. Clinical studies usually compare OT effectiveness with no treatment or pharmacological treatment (Haehner et al., 2013; Hernandez et al., 2022), whereas psychological research employs odorless or non-olfactory cognitive training in the control groups (Al Aïn et al., 2019; Wegener et al., 2018). Thus, different control groups limit comparability of the evidence. Another challenge in OT research is participants' adherence to the training procedure. For OT to be an effective training, study participants should perform the training bi-daily for 12 weeks. Being engaged for such a long time requires conscientiousness and consistency from the participants and a reliable measurement of training adherence from the experimenter. Participants may also quit the study due to a lack of desired effects or due to satisfaction with the obtained recovery. A non-random drop out fraction of the participants may bias the overall assessment of OT efficacy (Pieniak & Hummel, 2024). Another issue is a repeated testing within the three months. It is possible that some subjects may remember some of the test responses (e.g., in the odor identification test) what may result in the learning effect, i.e., better score obtained in the second measurement not because of the improvement of the olfactory function, but because of the memory of the correct answers (Lezak, 2012). The learning effect cannot be disentangled from the effects of OT unless parallel versions of the olfactory or cognitive tests are used. Alternatively, the magnitude of the learning effect may be estimated by including a control group that solves the tests the same number of times. Finally, many studies lack a follow-up measurement after OT completion which hinders the ability to assess the stability of OT effects long after OT has been completed.

Taken together, the review demonstrates that OT is an effective treatment for post-infectious dysosmia and might support olfactory recovery in other etiologies of olfactory dysfunction. OT is currently recommended as a primary treatment method for olfactory dysfunction of non-sinonasal etiologies (Whitcroft et al., 2023). OT has been demonstrated to trigger a range of structural and functional brain changes, also in the structures that are relevant for cognitive and emotional processes. The latter findings sparked question whether OT might benefit psychological functioning and the first studies in this area offer promising results. Yet, a systematic research program is needed to formulate more definitive conclusions about the usability of OT as a psychological intervention.

Although the above-mentioned conclusions are formulated based on a mosaic of neuroimaging and psychophysical studies in adults, the area of research on OT effects in children is strikingly overlooked. The scarcity of OT research in children is understandable from the clinical perspective as children constitute a minority of all patients in smell and taste clinics (Schriever & Hummel, 2020). Minors usually remain unaware of their olfactory dysfunction (Keller & Malaspina, 2013). However, clinicians report a post-pandemic increase in pediatric cases with post-infectious olfactory dysfunction (Deller et al., 2024), and this urges verification of OT utility for the pediatric population.

Until this dissertation, the evidence on OT effects in children was scarce. One study verified OT effects in 72 healthy children aged 9 to 15 years (E. Mori et al., 2015) and reported that OT increased olfactory sensitivity towards four odors and improved the ability to identify odors that were not included in the training. The study of Mori et al. also demonstrated that children are willing and able to train their sense of smell for 12 weeks.

Children’s olfaction is functional immediately after birth (or even in-utero; Schaal et al., 2000, 2020) but they acquire olfactory eloquence from infancy to adolescence (Oleszkiewicz et al., 2016; Schriever et al., 2020; Sorokowska, Schriever, et al., 2015). This fuels curiosity about potential sensory and psychological OT effects in the pediatric population. Thus far, this avenue of research remains largely unexplored.

Development of olfactory functions in children

The olfactory system begins to develop in the embryonic life. Morphologically mature ORNs are developed at the end of the first gestational trimester and olfaction is hypothesized to be functional in human fetus from the 29th gestational week (Schaal et al., 2004). A recent study of in-utero fetal facial expressions demonstrated that fetuses between 32nd and 36th gestational week exhibited differential responses to carrot and kale flavors. 4D ultrasound recordings of fetuses' facial movements revealed more laughter-like expressions in fetuses exposed to carrot flavor and more cry-like expressions in fetuses exposed to kale, demonstrating that (1) fetuses can discriminate flavors[2] and (2) they express flavor-dependent innate hedonic reactions (Ustun et al., 2022). Pregnancy is also the period when olfactory preferences are shaped – children born to mothers whose diet during pregnancy involved anise-flavored products demonstrated post-birth preference towards anise odor, whereas children born to mothers who did not consume anise reacted to the anise odor with aversion (Schaal et al., 2000).

Immediately after birth newborns begin to associate external odors with maternal body odor. They can discriminate the odors of the lactating mother's breast and milk formula, preferring the maternal odor (Schaal et al., 2020). The immediate functionality of the sense of smell is also confirmed by neuroimaging research demonstrating olfactory responses in pre-term and full-term infants (Gellrich et al., 2022; Schriever, Góis-Eanes, et al., 2014), with breast milk odors evoking distinct cortical responses from floral odors (Gellrich, Breuer, et al., 2021).

The development of olfaction in children in the post-infancy period is scarcely studied due to the limited availability of olfactory assessment methods in pre-verbal children and difficulties in sampling participants before they enter institutionalized education (i.e., the age of approximately 3-4 years). Odors activate the same olfaction-related brain structures in children as in adults (Kleinhans et al., 2019), but in children – contrary to adults – primary olfactory regions (i.e., piriform cortex, amygdala) are more responsive to odors than the frontal neocortical areas (Hummel et al., 2012), suggesting that although functional, olfaction in children is not fully developed. These differences are reflected at the behavioral level. Children identify and discriminate odors worse than adults and adolescents (Oleszkiewicz et al., 2016, 2019; Stevenson et al., 2007) which may be a result of limited verbal abilities or olfactory vocabulary in case of odor identification (Gellrich, Sparing-Paschke, et al., 2021; Monnery-

[2] Authors of the presented study acknowledge that when testing fetal responses to flavors, disentangling relative contributions of taste, olfaction and trigeminal chemesthesis is impossible (Ustun et al., 2022). However, these findings demonstrate that the chemical senses (including olfaction) are functional before birth.

Patris et al., 2009) or lack of experience with specific odors in case of odor discrimination (Oleszkiewicz, Behl, et al., 2022). Taken together, these results demonstrate that children are well prepared to sense odors, but their abilities to process these sensations develop as they grow.

Development of olfactory abilities is entangled in the increasing olfactory metacognition (i.e., the ability to assess and reflect on one's olfactory abilities, odor awareness, odor preferences etc.). The development of odor awareness in children is partially shaped by parental odor awareness (Martinec Nováková et al., 2018). Children become more aware of odors in the surrounding environment with age (Martinec Nováková & Havlíček, 2019) and the subjective significance of olfaction for their daily functioning increases during the childhood-to-adolescence transition (Oleszkiewicz et al., 2016).

Sex differences in olfactory abilities emerge in childhood. Girls exhibit greater ability to identify odors (with and without cues) than boys. This sex-related difference has been consistently demonstrated in children from France, Finland, Germany, Czech Republic, and Namibia (Ferdenzi, Mustonen, et al., 2008; Gellrich et al., 2019; Saxton et al., 2014). The same direction of sex differences has been reported in children's self-rated awareness of odors and the significance of the sense of smell for individual functioning (Ferdenzi, Mustonen, et al., 2008; Lohrer et al., 2022; Oleszkiewicz et al., 2016; Saxton et al., 2014). Interestingly, these sex differences are not accompanied by a difference in olfactory sensitivity (i.e., odor detection threshold) in children (Gellrich et al., 2019; Lohrer et al., 2022) that emerges later in life and is observed in adulthood (Sorokowski et al., 2019). Although the genesis of sex differences in olfactory abilities in childhood and adolescence is not fully understood, the available findings suggest the effects of superior verbal abilities of girls (Oleszkiewicz et al., 2016) or increased acquisition of olfactory knowledge and awareness during women-stereotyped activities, for example cooking, cosmetic care, or groceries (Ferdenzi, Coureaud, et al., 2008; Ferdenzi, Mustonen, et al., 2008).

Childhood is also the period when cognitive and emotional functions develop. Children expand their verbal abilities and increase the capacity of working memory and executive functions (Brocki & Bohlin, 2004; Gathercole et al., 2004; Hurks et al., 2010). They develop the lexicon of words describing the experienced emotions (Hoemann et al., 2019) and increase their ability to recognize the emotional states of other people (Mancini et al., 2013; Thomas et al., 2007). These developing cognitive and emotional abilities are partially dependent on the amygdala, hippocampus, and orbitofrontal cortex (Casey et al., 2005; Tottenham & Galván, 2016), i.e., the structures that are also part of the olfactory brain network (Fjaeldstad et al., 2017; Freiherr, 2017). Maturation of the nervous system, especially the prefrontal regions and their functional connections with the limbic system, guides the development of olfactory, cognitive, and emotional functions in childhood and adolescence (Cho et al., 2012; Herba & Phillips, 2004; Spencer-Smith & Anderson, 2009). The exact developmental trajectory of the acquisition of olfactory, cognitive, and emotional functions still calls for a precise characterization within the longitudinal paradigm. However, the already established links between the olfactory, cognitive, and emotional domains justify the hypothesis that olfactory stimulation in children might potentially benefit cognition and emotional functioning.

Aim of the research project

Despite robust evidence suggesting OT effectiveness in smell rehabilitation (Delgado-Lima et al., 2024; Sorokowska et al., 2017) and improvement of cognitive and emotional functioning in adults (Oleszkiewicz, Abriat, et al., 2021; Oleszkiewicz, Bottesi, et al., 2022; Wegener et al., 2018), the research on OT effects in children is still in its infancy. Olfaction is already functional at birth (Schaal et al., 2020) and the development of olfactory abilities is intertwined with the overall maturation of the nervous system and cognitive abilities (Casey et al., 2005; Gathercole et al., 2004; Gellrich, Sparing-Paschke, et al., 2021; Hummel et al., 2011). Brain plasticity is assumed to be highest before adulthood (Kolb & Gibb, 2011) and various cognitive trainings are more effective in children than adults (Wass et al., 2012). Considering the above arguments, it is justified to expect OT to affect children's sensory, cognitive, and emotional functions. This project aimed to address this assumption, and explore OT effects in children across sensory, cognitive, and emotional domains. Entering a research path that has been – thus far – empirically deserted, could provide twofold benefits. Firstly, it allows new insights into knowledge on the interplay between human olfaction, cognition, and emotional functioning. The dissertation leads to new theoretical advancements, by verifying OT effects in pediatric population. Apart from the theoretical gains, there are also potential practical implications of the project. OT is a highly accessible, low-cost, and enjoyable intervention that – upon proving its effectiveness – might be easily integrated into educational programs, cognitive trainings, or medical treatment protocols targeting children.

A sequence of three empirical studies aimed to thoroughly investigate OT effects in children by (1) applying OT in a school- and home-settings, (2) verifying OT effectiveness in children after mild traumatic brain injury (mTBI) who are at risk of olfactory dysfunction, and (3) including cognitive and emotional measures in the study design. The three studies were designed to address the most common methodological challenges encountered in OT research that have been previously identified and summarized in the review included in this dissertation (Pieniak et al., 2022), including: (1) odorless placebo as a control condition, (2) elimination of the learning effect by using equivalent versions of the tests when possible, (3) robust sample of homogenous age, (4) maximizing OT compliance by either conducting the teacher-supervised OT in schools or equipping participants with appealing and entertaining posters to track OT progress.

Sensory effects of olfactory training in healthy children

This chapter summarizes key findings and conclusions presented in the following publication:

Mahmut, M. K., Pieniak, M., Resler, K., Schriever, V. A., Haehner, A., & Oleszkiewicz, A. (2021). Olfactory training in 8-year-old increases odour identification ability: a preliminary study. *European Journal of Pediatrics*, *180*(7), 2049–2053. https://doi.org/10.1007/s00431-021-03970-y

The sensory effects of OT in healthy children have been studied by Mori et al. (2015) who demonstrated that 12 weeks of OT increased olfactory sensitivity and odor identification ability of odorants that were not involved in the training. Until now, no studies have been conducted to replicate and extend this finding. The first part of the project aimed to verify, whether a shorter OT (6 weeks) might lead to similar sensory effects when the training compliance is maximized. To this end, OT was conducted in schools and bi-daily training sessions were supervised by teachers. The study involved a homogeneous group of 8-year-old children. To further account for potential developmental changes occurring during the training period, half of the participants conducted OT with odorless propylene glycol.

OT did not influence children's olfactory sensitivity. This null effect of OT might either arise from a lack of the actual effect of OT on the olfactory threshold or might reflect measurement difficulties. The assessment of olfactory sensitivity includes multi-step, repetitive procedures lasting for approximately 15-20 minutes (Hummel et al., 1997). Although the Sniffin' Sticks threshold test can be used in children as young as 8 years of age (Oleszkiewicz et al., 2019), it may be bothersome at the same time (Gellrich et al., 2017).

We noted increased odor identification ability in children who completed OT. This effect was observed directly after the OT and extended to a follow-up period, 6 weeks after the OT offset. This finding demonstrates that the OT might be used to improve odor identification ability in children. Additionally, the increase in odor identification ability, ongoing even after the training was finished, suggests that OT might have psychological effects that benefit children's ability to identify odors. For instance, participation in OT may make children more interested in their sense of smell or initiate child-parent conversations about odors. These factors may potentially increase children's odor awareness and aid their odor identification ability in the post-training period, however, this assumption calls for further empirical verification.

In regard to the sensory effects of OT in children, the study has demonstrated that 6-weeks OT conducted in a school setting is feasible and might be an effective way of increasing odor identification ability, corroborating previous findings from a more heterogeneous group of children and adolescents (E. Mori et al., 2015). As this process is likely to be influenced by increased interest in odors and odor awareness arising from participation in a relatively interesting and unusual activity such as a scientific study on olfaction, OT might be a suitable candidate to be included in educational programs or interventions aimed at improving odor knowledge.

Sensory and cognitive effects of OT in children and adolescents after mild traumatic brain injury

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This chapter summarizes key findings and conclusions presented in the following publication:

Pieniak, M., Seidel, K., Oleszkiewicz, A., Gellrich, J., Karpinski, C., Fitze, G., & Schriever, V. A. (2023). Olfactory training effects in children after mild traumatic brain injury. *Brain Injury*, *37*(11), 1272–1284. https://doi.org/10.1080/02699052.2023.2237889

Before COVID-19 pandemic, traumatic brain injury (TBI) was the most common etiology of an acquired olfactory dysfunction in children (Deller et al., 2024; Schriever & Hummel, 2020), with the olfactory sensitivity being particularly vulnerable to impairment (Gellrich, Zickmüller, et al., 2024; Schriever, Studt, et al., 2014). TBI is also known to affect cognitive abilities (e.g., general intelligence, executive functions), with more severe injury leading to greater cognitive deficits (Babikian & Asarnow, 2009). In some children, even mild TBI (mTBI) may lead to lasting impairment of cognitive and olfactory functions (Lambregts et al., 2018; Schriever, Studt, et al., 2014).

Although OT has been demonstrated to be useful in the rehabilitation of olfactory function in adults with post-traumatic dysosmia (Konstantinidis et al., 2013; Pellegrino et al., 2019; meta-analysis: Huang et al., 2021), its effectiveness has never been verified in the pediatric TBI population. Similarly, beneficial cognitive effects of OT have been reported in elderly people (Oleszkiewicz, Abriat, et al., 2021; Wegener et al., 2018), but this line of research has not been pursued in children. Therefore, the second part of the project aimed to investigate the OT effects in children and adolescents after mTBI. The study focused on sensory (olfactory sensitivity, odor identification) and cognitive abilities (fluid intelligence, executive functions) as they are likely to be impaired in mTBI (Babikian & Asarnow, 2009; Bakker et al., 2016; Sandford et al., 2006). The available findings from the adults with post-traumatic olfactory dysfunction allowed prediction that OT will benefit olfactory functions (Huang et al., 2021; Konstantinidis et al., 2013; Pellegrino et al., 2019). The hypothesized effects of OT on fluid intelligence and executive functions were based on the premise of functional overlap between brain structures involved in olfactory perception and higher-order cognitive abilities (e.g., orbitofrontal cortex, anterior cingulate cortex; Challakere Ramaswamy & Schofield, 2022; Han et al., 2019; Salehinejad et al., 2021) and the OT's potential to induce changes in functional connectivity within olfactory and integrative networks (as demonstrated in adults with an olfactory dysfunction; Hosseini et al., 2020; Kollndorfer et al., 2015).

This part of the project was conducted in a hospital setting, where patients admitted with mTBI were recruited for the study. The clinical setting came with two methodological constraints – participants represented wide age range (6 to 16 years) resembling the demographic profile of pediatric departments' patients, and the study groups performed OT with either high- or low-concentrated odors as using OT with odorless substances was avoided[3]. Additionally, based on previous findings demonstrating that increased OT duration may boost its effectiveness in smell rehabilitation in adults (Konstantinidis et al., 2016; Sorokowska et al., 2017), the OT duration was extended to 6 months.

The participants' baseline scores indicated that (compared to their healthy counterparts) children after mTBI exhibited decreased olfactory sensitivity, but not odor identification ability or any of the cognitive abilities. The decreased olfactory sensitivity was successfully restored in children who performed OT with low-concentrated odors. A follow-up examination conducted 6 months after OT completion (i.e., 12 months after the brain injury) demonstrated that the olfactory sensitivity in children with mTBI a year after the injury reached the level observed in the healthy controls. Therefore, the study delivered evidence for recovery of olfactory sensitivity in children after mTBI that may be accelerated by OT with low-concentrated odors. Olfactory dysfunction undermines the quality of life (Croy et al., 2014) and increases the risk of hazardous events (Santos et al., 2004)[4]. Thus, olfactory rehabilitation obtained by OT with low-concentrated odors might limit the strain of dysosmia on the well-being of children who sustained mTBI.

Children performing OT with low-concentrated odor (both healthy and after mTBI) showed an increase in fluid intelligence, whereas such change was not observed in the high-concentration group. This study offers first, preliminary evidence for the cognitive effects of OT in children and constitutes a basis for further empirical endeavors investigating which other

[3] Based on author's experience and personal communication with other researchers, Ethical Review Boards often discourage using odorless OT as a control condition in the studies focusing on the clinical populations as OT is now the recommended treatment method for olfactory dysfunction of non-sinonasal etiology (Whitcroft et al., 2023). Therefore, the control groups in clinical studies usually receive a different variant of OT, e.g., differing in (1) the number of odorants used (Pires et al., 2022), (2) the number of daily training sessions (Oleszkiewicz, Bottesi, et al., 2022), (3) the molecular weight of odorants (Poletti et al., 2016), or (4) the odors concentration (Damm et al., 2014).

[4] The cited data on the impact of olfactory dysfunction on life quality and safety come from the adult population, therefore, may be not fully representative for children. However, the data on olfactory dysfunction consequences in children are lacking (Gellrich, Zickmüller, et al., 2024).

cognitive abilities may benefit from OT. Participants performing OT with high-concentrated odors showed improvement in executive functions. However, their performance at baseline was worse than the performance of the other experimental group and the observed improvement reflected stabilization of executive functions over time, suggesting either (1) OT's potential to improve executive functions but only when their baseline level is relatively low (what has been reported before in adults regarding olfactory sensitivity and verbal fluency; Oleszkiewicz, Bottesi, et al., 2022), or (2) a statistical artifact known as regression-to-mean when extreme scores stabilize over time without a necessary effect of a treatment (Morton & Torgerson, 2005).

The finding that OT with low-concentrated odors was more effective than OT with high-concentrated odors is somewhat surprising and intriguing, as the only study employing a similar design but focusing on adults with post-infectious olfactory dysfunction reported greater effectiveness of OT with high-concentrated odors (Damm et al., 2014). One plausible explanation for the enhanced effect of OT with low-concentrated odors is that weak olfactory perception leads to enhanced, more vigorous sniffing behavior during the training. Sniffing is an act of sensory sampling through which odorants in the ambient air may be detected (Wachowiak, 2011). When the perceived odor intensity is diminished due to a partial olfactory dysfunction, people try to maximize the amount of odorous molecules in the air by more vigorous scratching of cards containing microencapsulated odors (Doty et al., 1998) and enhanced sniffing. Sniffing (even in the absence of odorants) has been demonstrated to activate the primary olfactory cortex and its functional connections with higher-order olfactory structures (Kollndorfer, Jakab, et al., 2015; Mainland & Sobel, 2006). More vigorous sniffing behavior caused by low concentrations of odors used in this study might have led to a more pronounced activation of the olfactory brain network. Although the mechanism through which activation of the olfactory system leads to changes in olfactory abilities remains unclear, some OT effects are hypothesized to result from higher-order olfactory structure activation. For instance, lateralized OT conducted with only one nostril increases volume of both olfactory bulbs and this bilateral effect may result from the top-down processes initiated in the olfactory cortex (Negoias et al., 2017). Whether similar mechanism explains the changes in olfactory sensitivity in children with mTBI who conducted OT with low-concentrated odors remains unknown. This speculation requires two-stage verification – (1) a behavioral investigation of how participants' OT execution differs as a function of odor concentration and (2) a neuroimaging study verifying if (potential) enhanced sniffing induces different structural and functional changes in the brain.

Cognitive effects of olfactory training in healthy children

This chapter summarizes key findings and conclusions presented in the following publication:

Pieniak, M., Rokosz, M., Nawrocka, P., Reichert, A., Żyżelewicz, B., Mahmut, M. K., & Oleszkiewicz, A. (2024). Null cross-modal effects of olfactory training on visual, auditory or olfactory working memory in 6-9 years old children. *Neuropsychological Rehabilitation,* 1-22. https://doi.org/10.1080/09602011.2024.2343484

The study in children after mTBI provided evidence that in a certain setting, OT effects might exceed the olfactory domain and improve fluid intelligence. However, the OT effects on executive functions were inconclusive, likely due to the wide age range of participants. To get a better understanding of OT on cognitive abilities another study has been designed to address the hypothesis proposing OT to be an effective method to support working memory in a more age-coherent sample of children.

The study included a homogeneous group of healthy children aged 6-9 years who were conducting OT for 12 weeks with either a standard set of four odors (Hummel et al., 2009) or odorless propylene glycol as a placebo condition. As executive functions assessed in the study with children after mTBI rely on a few cognitive abilities simultaneously (e.g., planning, inhibition, working memory; Bull et al., 2004; Diamond, 2013), the focus has been narrowed down to working memory, i.e., the ability to store and manipulate information for a short time (Baddeley, 2012). Working memory was hypothesized to likely improve in children after OT because it has been successfully improved in odor-based cognitive training in adults (Olofsson et al., 2020). To verify if the potential improvement of working memory is cross-modal or sensory-specific, working memory has been measured in three sensory domains – olfactory, visual, and auditory. To limit the impact of the learning effect (Lezak, 2012), all working memory tests have been developed in parallel versions. All these methodological choices, together with the robust sample size, contributed to a solid study design that would allow reliable detection of the OT effects on working memory across the three sensory domains.

Performance in the olfactory, visual, and auditory working memory tests did not change after OT, neither in the experimental nor in the placebo group. This study suggests the limited potential of OT to improve working memory in children. It is plausible that the passive stimulation of the sense of smell without any additional cognitive engagement is not enough to cause substantial working memory improvement (Olofsson et al., 2021). Combining olfactory and memory training within one activity showed promising results in healthy adults whose visual and olfactory working memory (separately) improved following such intervention (Olofsson et al., 2020). However, such training combining olfactory and memory tasks in children has not been tested yet.

An explanation of OT's null effect on children's working memory would be more comprehensive with MRI data. Without gauging the neural processes and structural changes, it is difficult to verify whether the reported null effect arose from a lack of OT-induced changes in brain structure and functionality of the relevant regions, or the neuroanatomical changes that happened but were not reflected in behavior. Studies in adults delivered evidence for both these hypotheses (Han et al., 2021; Negoias et al., 2017), which underscores the need for further research.

Emotional effects of olfactory training in healthy children

This chapter summarizes key findings and conclusions presented in the following publication:

Pieniak, M., Rokosz, M., Ivcevic, Z., Reichert, A., Żyżelewicz, B., Nawrocka, P., Lebuda, I., & Oleszkiewicz, A. (2024). Olfactory training improves emotion matching ability in 6–9 years old children — preliminary evidence. *Journal of Sensory Studies*, 39(2), e12912. https://doi.org/https://doi.org/10.1111/joss.12912

In adults, OT effects have been verified in the emotional domain. OT has been found to improve well-being and reduce the severity of sub-clinical depressive symptoms (Pabel et al., 2020; Wegener et al., 2018). The premise to investigate the emotional effects of OT is based on behavioral data showing a bi-directional olfaction-depression link, i.e., increased depressive symptoms in individuals with olfactory dysfunction, and reduced olfactory sensitivity in individuals with depression (Croy & Hummel, 2017; Kohli et al., 2016; Pollatos et al., 2007; Sabiniewicz, Hoffmann, et al., 2022). These behavioral data were additionally supported by structural MRI findings reporting that patients with major depressive disorder have smaller olfactory bulbs than their healthy controls (Negoias et al., 2010).

However, the intimate relationship between olfaction and emotional functioning exceeds olfactory alterations in depression. The phylogenetic development of the olfactory and limbic systems is intertwined across species (Reep et al., 2007), with the limbic structures being hypothesized to evolve from the olfactory system (Northcutt, 2002; Soudry et al., 2011). In humans, multiple structures (e.g., the amygdala, insula, orbitofrontal cortex, anterior cingulate cortex) are engaged in processing both odors and emotional stimuli (Fjaeldstad et al., 2017; Lindquist et al., 2012; Menon & Uddin, 2010). These structures work in concert to detect potentially relevant information from the surrounding environment, e.g., inferring about food contamination from malodor or another person's disgusted facial expression. Consequently, dysfunction of any of these structures may be reflected in both the olfactory and emotional domains. For instance, compromised functioning of the orbitofrontal cortex may impair olfactory perception (W. Li et al., 2010) and is hypothesized to contribute to psychopathy which is characterized by inhibited emotional reactivity and reduced empathy (Blair, 2007). This neuroanatomical overlap is represented in behavioral studies that demonstrate a correlation between increased psychopathic traits, reduced empathy, and impaired odor discrimination and identification ability (Bettison et al., 2013; Mahmut & Stevenson, 2012, 2016). Interestingly, compensatory processes have been also reported between the olfactory and emotional domains. Specifically, individuals with congenital or prolonged acquired anosmia could more quickly recognize disgusted facial expressions than healthy controls. Faster recognition of facial disgust may compensate for the lack of olfactory perception to prevent from the exposure to chemical hazards.

The last part of the project aimed to explore whether the emotional functioning of children may be supported by OT. Given that OT in adults induces changes in the functional connectivity between brain structures that are partially involved in the perception of emotionally salient stimuli (Hosseini et al., 2020; Kollndorfer, Fischmeister, et al., 2015), it was hypothesized that the behavioral performance (which is related to the activity of the corresponding brain regions; Deuse et al., 2016; Nejati et al., 2020, 2022) in emotional facial expressions matching task will also increase after OT in children. Facial expressions are the primary source of information on the emotional states of other people (Izard, 1971). They are accessible even to preverbal infants who rely solely on perceptual cues (Ruba & Pollak, 2020; Ruba & Repacholi, 2020). Therefore, the study focused on the ability to match emotional facial expressions, i.e., the aspect of emotional perception that is least dependent on semantic knowledge (Morgan et al., 2010) and potentially most likely to improve through OT. To this end, healthy children aged 6 to 9 years completed 12 weeks of OT[5], either with a standard set of four odors (Hummel et al., 2009) or odorless propylene glycol. Their ability to match emotional facial expressions was assessed pre- and post-OT.

The study demonstrated an increase in the ability to match emotional facial expressions in children who performed OT, but not in children who conducted the training with odorless stimuli. Therefore, OT effects in the emotional domain might exceed the previously reported mitigation of subclinical depression (Wegener et al., 2018) and extend to facial emotion matching. Further research is required to verify if other aspects of emotional processing might benefit from OT. This finding might lay the fundament for further endeavors to include OT as a support method in psychological interventions aimed to enhance emotional processing in healthy children. This might be especially encouraging in children with emotional processing deficits, such as affective disorders or autism spectrum disorder (Collin et al., 2013; Schienle & Schlintl, 2019; Tonacci et al., 2017). The study also warrants more expensive and technically

[5] Findings described in this and the previous chapters have been obtained in the same sample of participants.

more demanding neuroimaging studies on the overlap of olfactory and emotional circuits in children, to understand the mechanism through which OT improves emotional facial expressions matching ability. Other emotion-processing tasks should be tested in the OT paradigm to gain a broader perspective on its emotional relevance.

General discussion

The presented dissertation aimed to explore the effectiveness of OT in sensory, cognitive, and emotional domains in healthy children and pediatric patients with mTBI. In three studies, this work has demonstrated that OT might be successfully employed in children as young as 6 years of age and its effects may exceed the olfactory function and extend to emotional (the ability to match emotional facial expressions) and cognitive domains (fluid intelligence, but not executive functions or working memory). This dissertation bridges the otorhinolaryngological practice and psychological interventions, relying on previously described neuroanatomical links between olfactory, cognitive, and emotional systems. The obtained results demonstrate that OT, a method primarily devoted to smell rehabilitation, has the potential to support psychological processes in children. Described studies suggest OT may have the potential to support selected sensory, cognitive, and emotional functions in healthy children and those that sustained mTBI, although the exact neural mechanism underpinning this effect awaits discovery.

The effects observed in the research project can be interpreted as small-to-moderate, which is in line with previous OT research in adults (Sorokowska et al., 2017). Nevertheless, even small effect sizes may remain of interest. Olfaction is important in various daily life situations including dietary behaviors, detecting environmental dangers, and social communication (Stevenson, 2010). Yet, experimental effects observed in this dissertation, and those reported by other research groups, remain small or moderate (e.g., fear chemosignaling: de Groot & Smeets, 2017; impact of partner's body odor on sleep quality: Hofer & Chen, 2020; association between olfactory abilities and declarative memory in older people: Jobin et al., 2023; sex differences in olfactory abilities: Sorokowski et al., 2019). It seems that the sum of these small effects adds up to the significance of the sense of smell in people's everyday lives. The importance of olfaction is reflected in the reduced quality of life of people deprived of the sense of smell (Croy et al., 2014; Frasnelli & Hummel, 2005), yet people with a functional sense of smell rarely appreciate it (Herz & Bajec, 2022). Whereas the small-to-moderate effects of OT are not surprising, they have practical implications – OT might be a suitable intervention to benefit selected sensory, cognitive, and emotional functions, but it is not a *panacea* and should be rather considered as a ‘first line’ treatment in otolaryngology and supportive technique in psychological interventions.

Estimation of OT efficiency is partially limited by the assessment method’s level of difficulty. As the OT effects are rather small, tasks that have a low score resolution might be not precise enough to capture the subtle changes following OT. Easy tasks may lead to a ceiling effect, i.e., all participants will be scoring high. The latter situation is possible when examining OT effects in a healthy population using olfactory tests designed for dysosmia diagnosis. For instance, the test of olfactory identification that is designed and validated for the pediatric population serves primarily to diagnose children with an olfactory dysfunction (Schriever, Agosin, et al., 2018). Therefore, healthy children are expected to score high on this test, but different levels of odor identification ability within the healthy range of olfactory function are not quantified by this screening test. Alternative tests possibly covering a wider range of olfactory abilities (i.e., more difficult) are needed to better monitor an increase in olfactory abilities in healthy children. However, it is potentially challenging to design such tests that would be appropriate for different age groups. An idea worth considering would be the development of an olfactory-related task that can have an incremental number of trials corresponding with children's age. Importantly, the test items need to exhibit incremental difficulty (Oleszkiewicz, Behl, et al., 2022), as a simple increase in the number of relatively easy trials will increase test's reliability (Sorokowska, Albrecht, et al., 2015), but also fatigue. Similarly to the odor identification test, the facial expressions matching task appeared easy for the children (even though it is not designed as a screening test; Morgan et al., 2010) who obtained scores in the upper limit of the task. Therefore, future research investigating the OT effects on the perception of emotional facial expressions may either use a morphed facial expressions paradigm instead of expressions matching task (Thomas et al., 2007) or include additional measures of response time (De Sonneville et al., 2002).

A certain limitation of this dissertation is the lack of neuroimaging data. With the available evidence, the studies could not verify what functional or structural changes occurred in the children's brains as a result of OT. Instead, the study design resembled a 'black box' model, where OT effects are observed at the behavioral level without insight into the neural mechanism and processes leading to the observed effects. Further studies in children, preferably utilizing structural and functional MRI or EEG-derived event-related potentials will shed new light on how OT affects sensory, cognitive, and emotional functions. Importantly, the mechanism through which OT improves sensory, cognitive, or emotional functioning may differ depending on the exact ability of interest, pinpointing the need for interdisciplinary examination of OT effects. For instance, the effect of OT on olfactory sensitivity might relate to increased expression of olfactory receptors or improved survival of sensory neurons (Avaro et al., 2022; Kim et al., 2019, 2020) whereas an increase in the odor identification ability may be a result of greater awareness of odors in one's environment (Oleszkiewicz, Heyne, et al., 2021) that supports better recognition of odors. Therefore, integration of multiple perspectives is required to fully understand how OT affects the brain and behavior, and allow for more accurate predictions regarding its utility (Craver & Darden, 2013).

The presented studies examined selected sensory, emotional and cognitive functions that may benefit from OT. This avenue of research is open for further exploration. Olfaction is interrelated with many different aspects of children's functioning, including (1) the interplay between semantic verbal fluency, odor identification and odor awareness (Martinec Nováková et al., 2018; Oleszkiewicz et al., 2016), (2) the presence of osmophobia (i.e., subjective aversion or hypersensitivity to odors) in children with migraine or tension-type headaches (Genizi et al., 2019, 2020; Pieniak et al., under review[6]), (3) the contribution of altered olfactory sensitivity and odor awareness to eating behaviors and food neophobia (Manesse et al., 2021; Sorokowska et al., 2022). All these areas and other intertwined with olfaction constitute potential targets of OT investigations. Two recent studies followed this exploratory path and reported OT effects on mitigating migraine severity in children and adolescents with headaches (Gossrau et al., 2023) and reducing the frequency of seizures in children with epilepsy (Yilmaz et al., 2022), corroborating that possible OT applications are numerous and exceed the rehabilitation of the sense of smell, and demonstrating increasing interest of the field of chemosensory research in OT effects in children.

The presented studies demonstrated that the OT's procedure is easy to administer by children from the age of 6 years. However, in selected groups, OT's administration might be hindered by age (e.g., in infants) or health status, e.g., by dementia (D'Andrea et al., 2022) or major depression (Pabel et al., 2020). In these populations, regular, structured stimulation of the olfactory system may be obtained with different approaches, for instance, overnight exposure via a nasal clip containing an odorant (Sabiniewicz, Zimmermann, et al., 2022; Schäfer, Schellong, et al., 2019), odor diffuser (Woo et al., 2023), or with an olfactory digital display (Niedenthal et al., 2021). Similarly, an adult person presenting odors in regular time intervals might administer olfactory stimulation in infants. The latter approach has been used in a seminal line of research investigating whether olfactory stimulation in newborns and premature infants benefits their nutrition and accelerates switching from gastric tube to oral

[6] Pieniak, M., Höfer, B., Knipping, J., Faria, V., Richter, M., Schriever, V.A., Haehner, A., Gossrau. G. (under review) Children and adolescents with primary headaches exhibit altered sensory profiles – a multi-modal investigation.

feeding (delivering some promising preliminary results; Gellrich, Messer, et al., 2024; Schriever, Gellrich, et al., 2018). These findings demonstrate that olfactory stimulation (either resembling OT or administered by other people or odors-releasing devices) may be used from infancy to old age, to benefit human functioning throughout a lifetime.

When the target population of an intervention is cognitively capable and motivated, more complex training designs may be used. For instance, working memory training involving odors have been shown to increase non-trained olfactory abilities and visual working memory in young healthy adults (Olofsson et al., 2020). In a similar sample, an intervention composed of three olfactory tasks (sorting odor intensities, sorting odor qualities, and detecting a target odor) improved free (uncued) odor identification and increased cortical thickness in the entorhinal cortex and fusiform gyrus (Al Aïn et al., 2019). More complex smell training is hypothesized to be more effective than standard OT in slowing down cognitive and olfactory decline in aging, as it imposes more cognitive demand on participants and leads to increased activation of cortical networks relevant to high-order cognitive functions (Olofsson et al., 2021). However, when designing interventions involving olfactory stimulation, multiple factors (task complexity, participants' cognitive capacities and motivation, easiness of administration, and costs) should be considered for choosing the optimal training design. Due to non-linear trajectories of olfactory and cognitive development that might be additionally affected by health status, designing a 'one-fits-all' smell training seems impossible.

Olfaction-based interventions aiming to improve one's functioning in sensory, cognitive, or emotional domain do not have to rely on the exact procedure of OT proposed originally by Hummel et al. (2009). The structured, regular OT is an appealing intervention as it is easily accessible, low-cost, easy to administer, enjoyable for participants varying in age, and well-studied, what makes it a perfect candidate for exploratory investigations of the benefits of olfactory stimulation in controlled conditions as well as for including it into medical treatments or psychological interventions. However, humans are functioning in odor-rich natural and urban environments (smellscapes) that also can positively or negatively (e.g., depending on the level of air pollution) influence human health, evoke emotional responses, and affect well-being (Bratman et al., 2024; Xiao et al., 2020). Therefore, creating unpolluted spaces where people are exposed to natural odors continuously stimulating their sense of smell may potentially benefit sensory, cognitive, and emotional functioning (Bratman et al., 2024). For the conceptual framework suggested by Bratman et al. to be viable and considered when designing public policies, knowledge about the effects of olfactory stimulation (including findings from the controlled studies, like the presented OT research) needs to be systematically expanded and shared with stakeholders and decision-makers.

Taken together, the presented dissertation aimed to explore the effectiveness of OT in children. The conducted studies delivered preliminary evidence that OT effects may exceed the olfactory domain and benefit selected cognitive and emotional functions. Therefore, this work lays the fundament for further investigations aiming to answer the question of how olfactory stimulation may be harnessed to improve children's sensory and cognitive abilities as well as benefit their emotional functioning. Considering that OT in children attracts the attention of experts representing various fields, including psychology, psychiatry, neurology, and otorhinolaryngology, we may expect more studies aimed at unraveling the full potential of olfactory stimulation in children.

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