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Olfactory Training Using Heavy and Light Weight Molecule Odors

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Abstract

Background: Repeated short-term exposure to odors is known to improve olfaction in patients with acquired olfactory dysfunction. The aim was to find out whether differences in molecular weight of odors used for olfactory training influences olfaction. We hypothesized a greater improvement following training with light weight molecule (LWM) odors.

Methods: A prospective study was performed in patients with posttraumatic (PTOL) and postviral olfactory loss (PVOL). Olfactory training was performed over a period of 5 months. One group ($n = 48$) used four odors containing heavy weight molecules (HWM; >150 g/mol) and another ($n = 48$) containing LWM (<150 g/mol). Olfaction was tested before and after the training using the Sniffin' Sticks test.

Results: Olfactory training was associated with olfactory improvement, with the improvement in PVOL patients being three times greater than that seen in the PTOL group. Compared with LWM training, HWM training was associated with a significantly greater improvement in Phenyl Ethyl Alcohol (PEA) threshold scores in PVOL patients; however, no such improvement could be shown for other subtests or in PTOL patients.

Conclusion: Overall, training was associated with olfactory improvement. With the exception of threshold scores in PVOL, there were no significant differences between LWM and HWM groups.

Keywords

olfaction, anosmia, dysosmia, smell, molecular weight, heavy weight molecule, light weight molecule, odor, olfactory training, upper respiratory tract infection

Introduction

Olfaction has several functions in humans and plays an important role in the quality of life. A general deterioration of quality of life could be shown in 67% of Swedish patients due to insecurity concerning personal hygiene, fear of not detecting fire or smoke, changes in eating and drinking habits and depression (Blomqvist, Brämerson, Stjärne, & Nordin, 2004).

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Similar findings could be shown in a recent study of the British population (Philpott & Boak, 2014).

The prevalence of olfactory disorders within the general population is still debated (Hoffman, Ishii, & MacTurk, 1998; Wysocki & Gilbert, 1989). More recent studies show frequencies around 18% for decreased olfactory function and 3% to 4% for functional anosmia (Vennemann, Hummel, & Berger, 2008). There are different reasons for smell impairment with the most important being aging where prevalence of olfactory dysfunction was found to be 25% above the age of 53 years (Murphy et al., 2002). Furthermore, an association between olfactory impairment and increased risk of mortality in elderly was shown recently suggesting that olfactory impairment might serve as a marker of pathologies leading to reduced survival (Schubert et al., 2016). Besides aging, the most common etiologies for smell disorders in decreasing order are sinunasal disease, post-upper respiratory tract infection, head trauma, and toxins or drugs where prevalence varies in literature mostly due to different inclusion criteria for patients (Nordin & Brämerson, 2008).

Improvement in olfaction after systematic olfactory training in the form of repeated short-term odor exposure has been shown for olfactory disorders due to upper respiratory tract infection, head trauma, and of idiopathic origin (Damm et al., 2014; Hummel, Reden, Hähner, Weidenbecher, & Hüttenbrink, 2009; Konstantinidis, Tsakiropoulou, Bekiaridou, Kazantzidou, & Constantinidis, 2013). Such improvement seems to result from stimulus-induced neuronal plasticity shown in animals (Wang, Wysocki, & Gold, 1993; Youngentob & Kent, 1995) as well as in humans (Wang, Chen, & Jacob, 2004; Wysocki, Dorries, & Beauchamp, 1989) suggesting changes at the level of olfactory receptor gene expression or differentiation of olfactory receptor neurons from basal cells. In addition, due to increased awareness the processing of odorous impressions may be facilitated.

Primary odors, first described by Henning (1916) using the odor prism, are traditionally used for olfactory training. The question arose as to whether, other than repeated short-term exposure, the use of odors of differing molecular weight could further improve olfactory ability.

Differences in olfactory receptor binding capacity for light and heavy weight odorants have been assumed for quite some time. In relation to this, two hypotheses exist in the literature: (a) heavy molecules bind to a limited range of olfactory receptors due to their large size that would not fit into binding pockets (Amoore, 1964) and (b) heavy molecules exhibit many binding sites and therefore activate a broad range of receptors (Araneda, Kini, & Firestein, 2000; Gaillard et al., 2002; Xu et al., 2003).

More recent studies seem to be in favor of the first hypothesis showing that older people are less sensitive to heavy molecules (Sinding, Puschmann, & Hummel, 2014) and likewise a higher percentage of specific anosmias is shown for heavy molecules compared with light molecules (Croy et al., 2015).

The aim of this study was to find out whether there is a difference regarding olfactory improvement after training with light weight molecules (LWM) or heavy weight molecules (HWM). We hypothesized that the olfactory performance after training improved to a greater extent using LWM as compared with training with HWM.

Methods

The study was performed according to the Declaration of Helsinki and was approved by the Ethics Committee of the TU Dresden (application number EK123042013). All patients were recruited from the Smell and Taste Clinic at the Department of Otolaryngology of the "Technische Universität" (TU) Dresden. After detailed explanation of the study and thorough evaluation regarding inclusion and exclusion criteria, patients provided written

informed consent before inclusion. The primary outcome measure was defined as the comparison of the change of olfactory performance (threshold, discrimination, and identification, TDI, score) 5 months after olfactory training between the two training groups (LWM and HWM groups). Secondary outcome measures were specified as the comparison of the following parameters between the two training groups: change of odor threshold, odor discrimination, and odor identification. Furthermore, the differences of olfactory performance (TDI) between the two etiologies (PVOL and PTOL) within the two training groups were investigated. Additionally, a comparison of the intensity rating of the training odors at baseline was undertaken between the two training groups and between the two etiologies within the training groups.

Inclusion/Exclusion Criteria

The following inclusion criteria were applied:

- Female and male outpatients from 18 years of age
- Postviral or posttraumatic olfactory loss

Patients meeting any of the following criteria had to be excluded from the study:

- Age less than 18 years
- Female patients seeking to become pregnant, pregnancy, and lactation period
- Normosmia
- Current acute or chronic sinunasal disease
- Chronic disease causing smell disorders like Parkinson's disease or chronic renal failure
- Low compliance or inability to understand instructions or study documents

Participants

A total number of 96 patients (56 females and 40 males) with either PVOL ($n = 70$) or PTOL ($n = 26$) were prospectively included in this study. The mean age was 59.4 years, ranging from 26 to 80 (12.6 SD). Patients were distributed equally in a pseudo-randomized manner into two training groups to rule out differences in age and sex distribution between the groups. Each group consisted of 48 patients. The LWM training group consisted of 37 patients with PVOL and 11 patients with PTOL, 27 females, 21 males, mean age 59.5 years (± 11.4 *SD*), and the HWM training group of 33 patients with PVOL and 15 patients with PTOL, 29 females, 19 males, mean age 59.2 years (± 13.8).

Olfactory Training With LWM and HWM

All odors were presented in brown glass jars, which contained a cotton wool pad soaked with 4 ml of odor. Patients in each group were directed to expose themselves to three different odors for 10 s twice in the morning and twice in the evening over a period of 5 months.

Intensity Rating

Additionally, patients were instructed to rate the intensity of LWM and HWM odors on a visual numeric scale (0 to 10: no smell to maximum intensive) at baseline.

Table 1. Set of Odors Used for Olfactory Training.

LWM	HWM
cis-3-hexenol	*Fructone*
Mw: 140.14 g/mol	Mw: 174.19 g/mol
Quality: cut grass	Quality: green apple
CAS # 4940-11-8	CAS # 6413-10-1
Ethyl maltol	*Ethyl vanilline*
Mw: 140.14 g/mol	Mw: 166.18 g/mol
Quality: caramelized sugar	Quality: vanilla
CAS # 4940-11-8	CAS # 121-32-4
Pinene alpha	*Gardocyclene*
Mw: 136.23 g/mol	Mw: 220.31 g/mol
Quality: essential oil	Quality: herbaceous, woody
CAS # 7785-70-8	CAS # 67634-20-2
Ocimene	*Irone alpha*
Mw: 136.23 g/mol	Mw: 206.32 g/mol
Quality: citrus	Quality: floral fruity
CAS #13877-91-3	CAS # 79-69-6

Note. LWM = light weight molecules; HWM: heavy weight molecules.

Two different categories of odors were used during the training (Table 1). One set consisted of LWM (molecular weight <150 g/mol) and the other of HWM (molecular weight >150 g/mol).

Olfactory Testing

Olfactory testing was performed before and after completing olfactory training using the ''Sniffin' Sticks'' test (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). This test involved three different tasks, containing an odor threshold, odor discrimination, and odor identification part. Here, felt-tip pen-like odor dispensers were presented to a blinded subject.

Odor threshold was tested in a 3-alternative forced choice (3AFC) procedure using Phenyl Ethyl Alcohol (PEA) as the target odor. Subjects had to detect the odorized pen among three samples with the other two pens containing odorless propylene glycol.

Odor discrimination was tested using 16 triplets of pens with each triplet containing two identical and one different odor. Subjects had to identify the different odor.

The odor identification task was based on the identification of 16 common odors. Patients had to choose from a list of four descriptors in a 4-alternative forced choice (4AFC).

The sum of the three tests accounted for the TDI score with a maximum score of 48 points (Kobal et al., 2000).

Statistical Analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences, version 14.0, SPSS Inc., Chicago, IL, USA). The level of significance was set at 0.05. For comparison of two groups t tests and Chi-squared tests were used. Concerning the psychophysical data analyses of variance (ANOVA) were performed to compare olfactory function within

(within-subject-factor: "Sniffin' Sticks," odor TDI) and between (between-subject-factor: molecule weight, light, heavy) the groups.

To analyze the rated intensity of odors again, ANOVAs and t tests were applied.

Results

Olfactory Training in General

Compared with baseline olfactory training in general was associated with olfactory improvement (which was defined as TDI improvement $\geq$5.5 points; Gudziol, Lötsch, Hähner, Zahnert, & Hummel, 2006) in both patient groups (PVOL: 45%; PTOL: 16%) with a significantly higher number of patients improving with PVOL (χ^2 [1] = 6.47, $p = .015$). The better outcome of PVOL patients could also be shown in a significantly higher improvement in the TDI score (t [93]) = 2.35, $p = .021$; PVOL: $M = 4.66$, $SD = 4.88$; PTOL: $M = 2.17$; $SD = 3.83$) and PEA threshold (t [93] = 4.01, $p < .001$; PVOL: $M = 1.84$, $SD = 2.84$; PTOL: $M = 0.05$, $SD = 1.46$) compared with patients with PTOL.

Training With LWM and HWM

There was no significant difference in age, cause of olfactory loss, and sex distribution between the training groups (age: t test: $t_{94} = 0.12$, $p = .90$; cause of olfactory loss: χ^2 [1] = 0.84, $p = .49$; sex: χ^2 [1] = 0.17, $p = .84$). Olfactory improvement could be shown in 36% of patients trained with LWM (Lm group) and in 38% of patients trained with HWM (Hm group); there was no statistically significant difference between the two training groups (χ^2 [1] = 0.13, $p = 1.00$). Considering the cause of olfactory loss, we demonstrated that PVOL patients in the HWM training group had a significantly higher improvement of PEA threshold as compared with PVOL patients training with LWM (Mann-Whitney U test: $p = .004$). However, such significant differences were not seen for other tests or for PTOL patients ($p > .05$). Olfactory test results before and after olfactory training with LWM and HWM are demonstrated on Figure 1 color coded by the etiology of smell loss.

Intensity Rating

At baseline, patients from the LWM group-rated LWM odors as significantly more intense than those from the HWM group (t [94] = 2.82, $p = .006$). Considering the etiologies of olfactory loss, no such significant difference in intensity rating appeared between the two training groups ($p > .05$).

Discussion

Major results found in this study were the following: (a) Improvement of olfactory function after olfactory training in general could be confirmed in patients with PVOL and PTOL. This improvement was more pronounced in PVOL patients. (b) There was no significant difference in olfactory improvement between LWM and HWM groups. (c) But specific differences appeared in PVOL patients where olfactory training with HWM odors appeared to be superior over LWM odors in improving PEA threshold, which was contrary to our hypothesis.

In line with several studies (Damm et al., 2014; Hummel et al., 2009; Konstantinidis et al., 2013) investigating the olfactory improvement after repeated short-term exposure to odors,

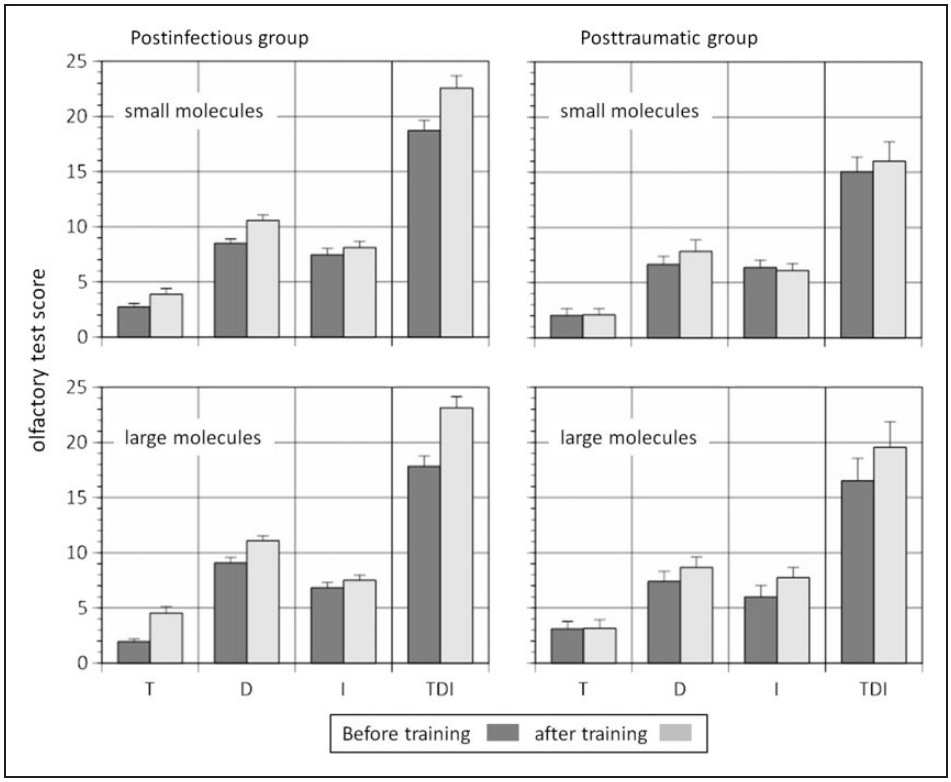

Figure 1. Olfactory test score before and after olfactory training with small molecules (LWM) and large molecules (HWM) color coded by the etiology of smell loss.

we could confirm the improvement in olfaction after olfactory training over a period of 5 months. Furthermore, this improvement was three times higher for PVOL patients compared with PTOL patients (45% vs. 16%), which was consistent with the literature (Reden et al., 2006). The physiological mechanism of improvement is yet to be studied but changes seem to occur at different levels of olfactory processing (olfactory epithelium, olfactory bulb, or further central olfactory centres; Wang et al., 2004).

Contrary to our hypothesis, PEA threshold improvement was observed for HWM training but not for LWM training. This relative superiority of HWM training was, however, only seen in the PVOL group. From electron microscopic observations of the olfactory mucosa, a decreased number of intact olfactory receptor neurons (ORN) could be demonstrated in PVOL patients (Moran, Jafek, Eller, & Rowley, 1992) assuming a destruction of ORN through the virus. Therefore, since the greatest damage was supposed to be in the periphery or at the level of the ORN, we would expect the greatest improvement to occur in this region. Hence, a possible interpretation of an isolated PEA threshold improvement in PVOL patients could be a partial recovery of the ORN, as there might be a potential association between the odor threshold value and the peripheral olfactory activity.

So far two hypotheses existed regarding the molecular size-dependent receptor binding capacity of odors as mentioned earlier (Amoore, 1964; Araneda et al., 2000; Gaillard et al., 2002; Xu et al., 2003). Two recent studies showing lower olfactory sensitivity to HWM in older subjects, (Sinding et al., 2014) and a higher rate of specific anosmia for HWM

(Croy et al., 2015) indicated that heavy molecules might bind to a limited range of olfactory receptors. Nevertheless, no dramatic difference in olfactory performance change could be attributed to the molecular weight of odors used for training.

However, the results of our study need to be put into perspective as we were not only comparing odors of different molecular weight but using entirely different odor types for training purposes. Therefore, differences for instance in solubility might interfere or even cover the effect of molecular weight of odors on olfactory improvement. Considering the change of olfaction from baseline after olfactory training in general as shown in our study, a further limitation of this study is that there was no non-training control group in order to distinguish the effect of spontaneous recovery or test–retest effects from training effects.

An alternative way to activate more olfactory receptors (ORs) might relate to the model provided by Altundag et al. (2015). In that case, the use of a wider number of different odors (and not a few) would increase olfactory abilities by cognitive changes leading to improved odor perception.

Thinking of further olfactory training strategies, the use of mixed odors containing olfactory and trigeminal components might be taken into account as an interaction between these two systems is already well-documented (Bensafi, Frasnelli, Reden, & Hummel, 2007; Kollndorfer et al., 2015).

Considering the significant improvement in olfaction using a larger number of odorants (Altundag et al., 2015), varying the training strategy seems to effectively improve olfactory recovery, although the underlying physiological mechanism is not understood.

As to whether different modes of sniffing (normal, rapid, and forced) might have an influence on the amount of molecules reaching the olfactory region, and therefore, activating ORs should be subject to further investigations (Beauchamp, Scheibe, Hummel, & Buettner, 2014; Zhao, Dalton, Yang, & Scherer, 2006).

Conclusion

Overall, olfactory training was associated with olfactory improvement. With the exception of threshold scores in PVOL, there were no significant differences between LWM and HWM groups.

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Declaration of Conflicting Interests

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