Faster olfactory adaptation in patients with olfactory deficits: an analysis of results from odor threshold testing*

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Abstract

Background: Patients with olfactory deficits often report rapid and lasting olfactory adaptation compared to the time when they had normal olfactory function. However, this phenomenon receives little scientific attention. This retrospective study aimed to compare the patterns of olfactory adaptation in normosmic controls and patients with olfactory impairment by analyzing the trajectory of turning points in odor threshold tests based on the staircase technique.

Methods: 4120 subjects (1684 hyposmia, 1742 anosmia and 694 normosmic controls) were included in this study. Their odor threshold, odor discrimination and odor identification ability were assessed using the Sniffin' Sticks. We analyzed the trajectory of turning points in the odor threshold test.

Results: Current results suggested that patients with hyposmia needed significantly more trials to reach the final threshold scores than controls and anosmic group, and controls needed more trials than anosmic group. The difference between the first turning point and final threshold scores in the anosmic group was significantly larger than in the hyposmia group and in controls.

Conclusion: People with poor olfaction seem to adapt faster to olfactory stimuli. The trajectory of turning points in odor threshold test may serve as an indicator of olfactory adaptation and function of olfactory receptors. Olfactory adaptation may provide a new tool in the assessment of subtle olfactory loss.

Key words: Olfaction, olfactory adaptation, hyposmia, anosmia, normosmic

Introduction

Normal olfactory adaptation results in the temporary disability to perceive a particular odor after prolonged olfactory exposure. It reduces the sensitivity to perceive that odor and increases detection thresholds [(1)]. Olfactory adaptation happens on a peripheral and a cortical level [(2, 3)]. The decreased neural response over time during constant stimulation is usually defined as desensitization [(1)]. Following olfactory exposure sensitivity is gradually restored with time. Olfactory adaptation is of high significance because it prevents sensory overload, which allows people to respond to new olfactory stimuli [(4, 5)]. However, faster adaptation may be a disadvantage. For example, adapting to gas leakage too quickly may lead to failure to detect it and be very dangerous. In addition, adapting to foods very fast also leads to decreased enjoyment.

Abnormalities of the number or function of olfactory receptor neurons (ORN) may lead to abnormal olfactory adaptation (6). Findings by Stevens et al. suggest that older people tend to lose olfactory sensitivity faster under continuous exposure to an odorant and recover slower than younger people. Moreover, older people are less likely to detect a gradually increasing odor concentration [(6)]. With increasing age and developing neurodegeneration it is likely that the distribution of olfactory cells in the nasal epithelium becomes irregular and patchy, and is gradually replaced by respiratory epithelium, leading to a reduced number of ORNs in older people [(7, 8)]. It may be hypothesized that the relatively lower number of remaining ORN in older people are

quickly and completely occupied by odorant molecules, which are, in turn, inactivated so that there are no ORN available for responses to new stimuli [9]. Moreover, ORN in older people may function differently compared to younger people [10], and it may take longer time for occupied ORN to recover [6].

On a clinical level, we observe that many patients with olfactory deficits adapt faster to olfactory stimuli [11]. For example, many patients with hyposmia report that they can perceive an odour or a flavor when they experience it for the first time. However, the odours and flavors are much less intense when they are perceived a second time or for a longer period, respectively. Because of this relation between adaptation and olfactory sensitivity, olfactory adaptation may serve as an indicator of olfactory function in clinical practice. However, to the best of our knowledge, there has been no systematic investigation of this phenomenon. The current study aimed to measure olfactory adaptation by analyzing the trajectory of turning points in an odor threshold test in a large sample of patients with olfactory loss. We hypothesized that patients with olfactory deficits would adapt faster to olfactory stimuli.

Material and methods

Results from 4120 subjects were included in this retrospective study. Patients were examined at the Smell and Taste Clinic at the Department of Otorhinolaryngology of the TU Dresden, Germany from 2012 to 2019 at the same facility using the same techniques. They consisted of three groups: 1742 patients with anosmia, 1684 patients with hyposmia, and 694 normosmic controls. Exclusion criteria were major diseases (e.g., complicated diabetes, kidney disease, severe neurological and psychiatric diseases), or pregnancy.

All participants received a detailed otorhinolaryngological examination including nasal endoscopy, a structured history, and a standardized test for smell and taste function [12]. Controls were examined by a stepwise procedure. First, all subjects underwent interviews by an ENT specialist, and information including medical history, subjective evaluation of smell and taste function were collected. Subjects with diseases which may directly influence the sense of smell (e.g., renal disorders, neurodegenerative disorders) were excluded in the present study. Second, all subjects underwent the test of Sniffin' Sticks, and TDI scores higher than 31 were defined as normosmia. This retrospective study was conducted in accordance with the guidelines of the Declaration of Helsinki, the retrospective protocol was approved by the Ethics Committee at the TU Dresden (protocol number EK251112006).

Assessment of olfactory function – "Sniffin Sticks"

Orthonasal olfactory function was measured using the extended "Sniffin' Sticks" test which is based on odor-containing felt-tip pens [13]. This test consists of three subtests: odor threshold, odor discrimination, and odor identification test. For each subtest, the pen's cap was removed, and its felt-tip was presented about 2 cm in front of both nostrils of the subject for about 3 sec. The testing procedure began with the threshold test using a triple-forced choice paradigm where participants had to discriminate the odor (phenyl ethyl alcohol [PEA]) from 2 blanks (filled with solvent propylene glycol). Starting with the lowest PEA concentration, a staircase paradigm was used where 2 correct or 1 incorrect answer led to a decrease or increase of concentration, the so-called turning point, respectively. With the purpose of shorten the time of reaching the first turning point, 2 concentration levels are increased if subject make a mistake. The resulting threshold score could range from 1 to 16 and was the mean of the last 4 turning points in the staircase.

An additional two variables were computed from the threshold data. The first was the number of trials taken to reach the final threshold score, which was termed "Trials"; the second was the difference between the first turning point and threshold score was calculated, which was termed "Difference".
For the odor discrimination test, 2 pens with the same odor were presented while a third pen had a different scent which was the target pen. For the identification test, subjects were asked to choose the verbal item that described the odor best using a 4-alternative-forced choice task from flash cards that had both the picture and name of the object. Scores of both odor discrimination and identification tests could range from 0 to 16. The scores on the 3 olfactory subtests were then summed to produce the overall TDI score (Threshold, Discrimination and Identification) [14]. This TDI score was used to categorize the patients as normosmic, hyposmic, or functionally anosmic (further referred to as anosmic).

Statement of ethics

This retrospective study was conducted in accordance with the guidelines of the Declaration of Helsinki, the retrospective protocol was approved by the Ethics Committee at the TU Dresden (protocol number EK251112006).

Statistical analyses

The Statistical Package for Social Sciences version 22.0 (IBM SPSS 22.0, Chicago, IL, USA) was used for the statistical analyses. Differences in sex distribution between normosmic, hyposmic and anosmic groups were evaluated using the χ^2 test. Differences in olfactory-related scores were evaluated with analyses of covariance (ANCOVA), then age and sex were included as covariances. Associations between number of trials and olfactory scores were evaluated with Partial correlation analysis, with age and sex as covariances.

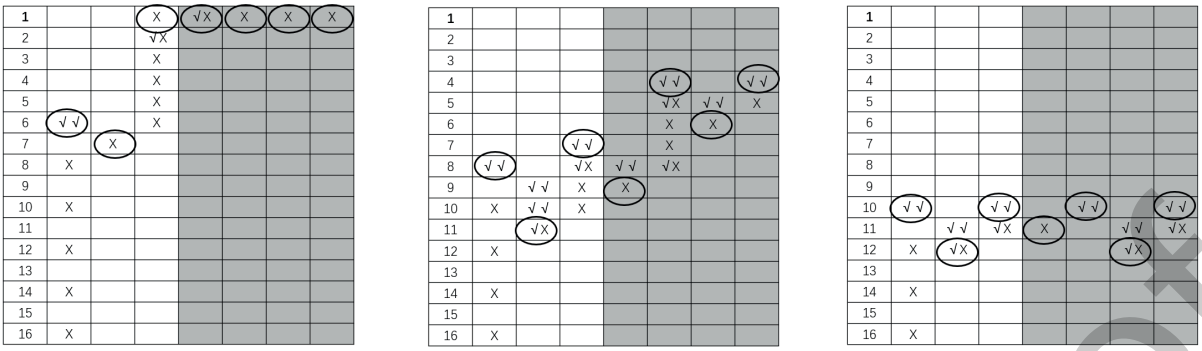

Figure 1. Typical examples of trajectories of olfactory threshold test in anosmia, hyposmia and normosmic controls. "√" means correct, and "X" means incorrect, circles "O" around the boxes means turning points. For the anosmia example, the threshold score is 1, there were 20 trials and the difference score is 5. For the hyposmia example, the threshold score is 5.75, there were 35 trials and the difference score is 2.25. For the normosmic controls example, the threshold is 10.75, there were 24 trials and the difference is 0.75.

Results

Typical records of threshold tests in normosmic controls, hyposmia and anosmia are shown in Figure 1. The hyposmic patients required significantly more trials to reach the final olfactory threshold than normosmic than anosmic group. The difference between the first turning point and the final threshold scores in patients with anosmia was significantly larger compared to the hyposmic and normosmic group (Table 1 and Figure 2).

In patients with functional anosmia, the number of trials was positively correlated with age (r=0.08, p=0.001) and olfactory function (threshold (r=0.50, p<0.001), discrimination (r=0.12, p<0.001), identification (r=0.01, p<0.001), and TDI scores (r=0.32, p<0.001)). In normosmic controls, the number of trials was positively correlated with age (r=0.09, p=0.02) and negatively correlated with olfactory function (threshold (r=-0.38, p<0.001), TDI scores (r=-0.30, p<0.001)). No such correlation was found in patients with hyposmia.

Discussion

The current study with a large sample size analyzed the trajectories of turning points in an odor threshold tests as an approximation of olfactory adaptation. We found the following main results: 1) hyposmic participants needed significantly more trials to reach the final threshold scores than normosmic controls and anosmic participants; 2) The difference between the first turning point and the final threshold scores in the anosmic group was significantly larger than that in hyposmic and normosmic participants; 3) the number of trials was positively correlated with olfactory function in patients with functional anosmia, while it was negatively correlated with olfactory function in normosmic controls.

The different trajectories of turning points in participants with various levels of olfaction may result from different patterns of olfactory adaptation. Previous studies have suggested that reduced or dysfunctional ORNs contribute to abnormal olfactory adaptation, which was shown by the faster adaptation to odor stimulus and slower recovery in older people compared with younger people [6]. The mechanism underlying olfactory adaptation may be a modulation of cAMP-gating which is mediated by Ca2+ feedback [15]. Starting with the interaction between odorant and olfactory receptors, the receptor-associated G-protein modulates the adenylate cyclase which increases intracellular cAMP concentration, which then opens the cyclic nucleotide-gated cation channel. With the influx of Ca^{2+} ions through this channel, the olfactory pathway is activated and forms the basis for the perception of odours. At the same time, the influence of Ca^{2+}/calmodulin-dependent protein kinase II or CaMK activation leads to repressed cation channels, inactivated adenylyl cyclase and activated phosphodiesterase which cleaves cAMP [16-18]. These series of actions desensitize ORNs and contribute to olfactory adaptation. After termination of stimulation, the activity of the adenylyl cyclase and the affinity of the CNG channel are restored with time, resulting the recovery of olfactory adaptation [1] (Figure 3). The extent of olfactory adaptation may be influenced by several factors, including the concentration of the substance used for adaptation, the duration of adaptation, the similarity of the odorant used for adaptation and subsequent stimulation [19], and the salience of the odor [1,20]. Additionally, neurogenesis plays an important role in the ability to adapt to odors. ORNs lost by normal turnover in the postnatal period are replaced by

Table 1. Comparison of olfaction among anosmia (A), hyposmia (B) and normosmic control (C).

	Anosmia (n=1742)	Hyposmia (n=1684)	Normosmic controls (n=694)	F/χ2	P	Post Hoc
Age	56.0±14.1	57.5±12.5	44.4±15.7	233.83	<0.001	B>A>C
Women/Men	962/780	1025/659	412/281	11.71	0.003	-
Threshold	1.4±1.0	4.1±2.5	8.9±3.1	1545.79	<0.001	C>B>A
Discrimination	6.1±2.1	10.2±2.1	13.1±1.6	1805.58	<0.001	C>B>A
Identification	4.4±2.0	8.9±2.5	13.4±1.8	2317.02	<0.001	C>B>A
TDI	11.3±3.2	23.1±4.0	35.4±3.5	6152.14	<0.001	C>B>A
Trials*	20.8±3.6	24.2±4.4	22.7±4.7	149.35	<0.001	B>C>A
Difference*	8.3±2.7	5.1±3.2	4.6±3.6	293.93	<0.001	A>B>C

Trials* means the number of trials of reaching final threshold scores. For Post Hoc, B>C (P<0.001), C>A (P<0.001), B>A (P<0.001). Difference* means the difference between the first turning point and final threshold scores. For Post Hoc, A>B(P<0.001), B>C (P<0.001), A>C (P<0.001).

new ones, as neurogenesis happens throughout the lifetime in the olfactory epithelium [21, 22]. Various factors may decrease neurogenesis, such as aging, viruses, smoking, and environmental factors [23,24]. When regeneration fails, ORNs undergo degeneration, resulting in partial or total neural anosmia [23]. In patients with post-traumatic anosmia, using olfactory fMRI a delayed activation of the primary orbitofrontal cortex was found, which may be associated with axonal injury and reduced numbers of ORNs [25].

During the threshold test of the Sniffin' Sticks in the current study, PEA of different concentrations was presented to the participants at short intervals. Therefore, the (presumably) limited number of ORNs in patients with anosmia may be totally occupied by odor molecules from the first stimulus and may not be capable to recover rapidly. As a result, it becomes difficult to perceive consecutive odorous stimuli, which may explain the steep decline of the threshold trajectories, leading to fewer trials needed to reach the final threshold scores, and causing a large difference between the first turning point and the final threshold scores. Conversely, normosmic controls may have enough available ORNs to perceive new smells. Their relatively larger number of ORNs may allow them to recover faster, and in the threshold test, it took fewer trials from one turning point to the next one. As a result, the turning points in in normosmic subjects showed less fluctuation.

The difference between first turning point and the final threshold scores in hyposmia was larger than that in the control group but smaller than that in anosmia. This suggested that their adaptation rate falls between these two groups. It appears to be in line with the reports by patients with hyposmia to have difficulties in detecting repetitive odorous stimuli. This may be due to their dysfunctional or a reduced number of ORNs. Hyposmia patients showed larger number of trials and more fluctuation in trajectory than anosmic patients and controls. Apart from the biological activity, it should be noted that the first turning point in some participants might have occurred at relatively low concentrations simply by chance. Participants were asked to discriminate the odor from 2 blanks successfully two times in a row, so they had a chance of 11% to answer correctly even they did not smell anything. This may contribute to the large "Difference" in anosmia, because many anosmia had final scores of 1. Therefore, present results should be interpreted with caution, because the Sniffin' Sticks are not originally designed for testing olfactory adaptation and limitations are inevitable. However, in clinical practice, many anosmic patients were certain that they can perceive the odor at a lower concentration at the beginning of testing, then their sensitivity fell down very quickly. Future studies are needed to develop specific assessment for olfactory adaptation, in order to better explore the characteristics of olfactory adaptation in anosmia, hyposmia and normosmia.

There were several limitations in the current study. First, current conclusion should be interpreted with caution because only one odor (PEA) was used, and some people may not be sensitive to one specific odor but still have normal perception of other odors. Although such specific anosmia apparently are rare [26], future studies using various odors could provide a better understanding about olfactory adaption. Second, in the threshold test of the Sniffin' Sticks, subjects were presented with brief exposures to weak olfactory stimuli and interspersed with exposure to blanks, which may not be the best experimental paradigm to investigate olfactory adaptation in healthy people. But for patients with olfactory impairment, these stimuli may be enough to cause olfactory adaptation, which resulted in different trajectories in their threshold tests, suggesting a differential effect between patients and controls. Third, the current

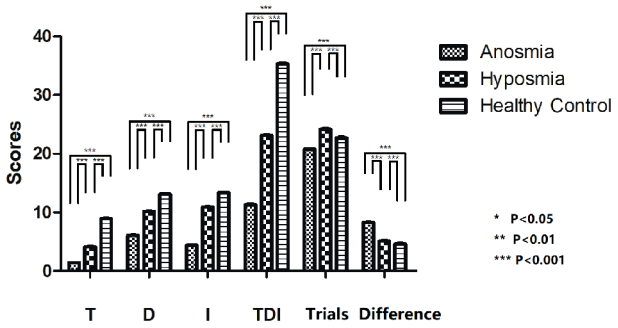

Figure 2. Comparison of olfaction among anosmia, hyposmia and normosmic control. T = threshold, D = discrimination, I = identification, and "TDI" means summed scores of threshold, discrimination and identification. "Trials" means the number of trials of reaching final threshold scores, and "difference" means the difference between the first turning point and final threshold scores.

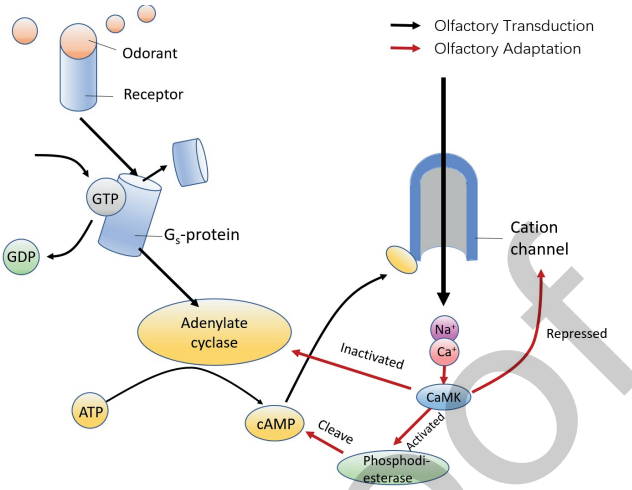

Figure 3. The mechanism of olfactory transduction and olfactory adaptation. GTP, guanosine triphosphate. GDP, guanosine diphosphate. ATP, adenosine triphosphate. cAMP, cyclic adenosine monophosphate. CaMK, calmodulin-dependent protein kinase.

investigation focused on the behavioral level, and no biological or physiological measures were taken to describe number and function of ORNs. As a result, current study was not able to exclude the effect of cognition, for example, the better cooperation, concentration and understanding in young subjects may contribute to the positive correlation between age and number of trials. Further studies including electro-olfactograms (EOG) [27] or biopsies from the olfactory epithelium [28] could be carried out to further explore the relationships among trajectory of olfactory threshold tests, function/number of ORNs and olfactory adaptation. Last, the recovery of olfactory perception after olfactory adaption was assessed by the trajectory of threshold tests results, but the exact time to recover remains unclear. Further measurement of the recovery time could provide a deeper understanding of olfactory adaptation.

Conclusion

In summary, the trajectory of olfactory threshold test scores may serve as an indicator of olfactory adaptation. The current results suggest that people with poor olfaction adapt faster to olfactory stimulation. Measuring olfactory adaptation may provide a new perspective for exploring olfactory function in clinical practice, because it has strong association with olfactory test scores, and can provide more information about olfaction and the patients' complaints.

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Authorship contribution

Ben Chen, conception and design, acquisition of data, analysis and interpretation of data; drafted the article; gave final approval of the version to be published. Antje Haehner: revised the manuscript critically for important intellectual content, gave final approval of the version to be published. Mehmet Kibris Mahmut: revised the manuscript critically for important intellectual content; gave final. Thomas Hummel: conception and design, acquisition of data, analysis and interpretation of data; revised the manuscript critically for important intellectual content, gave final approval of the version to be published.

Conflict of interest

The authors have no conflicts of interest to declare.

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