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A threshold-like measure for the assessment of olfactory sensitivity: the "random" procedure

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Abstract Many tests of olfactory dysfunction are either too complex, too expensive, or too time-consuming to be of use in routine clinical testing. Thus, the present multicenter study was undertaken to investigate a new approach, the so-called "random" test. In this test different concentrations of citronellal and phenyl ethyl alcohol are applied according to a pre-established order; patients are asked to identify the odor if possible. The test score is the sum of correctly identified odors. Test administration takes about 10 min. Two studies were performed. Basic characteristics of the test were explored in experiment 1 in 176 healthy subjects (76 male, 100 female; age 12–85 years, mean age 30 years), namely test–retest reliability, correlation with other measures of olfactory sensitivity, and sensitivity of the test to differences in age and gender. In the second experiment the test was tried in 97 patients (45 male, 52 female; age 19–78 years, mean age 47 years) in a clinical environment to investigate its usefulness in diagnosing olfactory loss. The "random"-test was found (1) to exhibit a test–retest reliability similar to that reported for established measures of olfactory function ($r = 0.71$; $P < 0.001$), (2) to correlate with other measures of olfactory sensitivity ($0.82 > r > 0.60$; $P < 0.001$), (3) to differentiate between expected differences in olfactory sensitivity in relation to gender ($t > 2.602$, $P < 0.011$), and (4) to discriminate between different degrees of olfactory loss ($F > 36.6$, $P < 0.001$). Based on these data, and the fact that the new test requires little time and is easy to use, this approach can be expected to suit clinical needs.

Keywords Olfaction · Thresholds · Aging · Gender · Anosmia

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Introduction

Numerous tests are available for olfactory testing in a clinical environment [for review see 3]. However, many of these tests are poorly validated, take too much time to administer, are too expensive for routine application, provide questionable results when used several times in the same subject, or are annoying to patients with olfactory loss or staff involved in administration/evaluation. Partly initiated by the needs of the Working Group Olfaction and Gustation of the German Society for Oto-Rhino-Laryngology, Head and Neck Surgery, during the last 5 years the "Sniffin' Sticks" test has been developed. This test of nasal chemosensory function is based on pen-like odor-dispensing devices. It consists of three tests of olfactory function, namely tests for odor threshold, odor discrimination, and odor identification [7, 10]. The test should utilize the subjects' sniffing behavior [12] rather than administration of squeeze bottles. Normative data from a multi-center study of more than 1000 subjects have been published recently [11].

Administration of this elaborate test of olfactory function, however, appears to be too lengthy to appeal to practitioners. In addition, as it is entirely based on forced choice tasks it has frequently been criticized by both patients with olfactory loss and medical personnel who have to deal with these complaints. For example, many anosmic patients feel uncomfortable/frustrated in situations where they are forced to select a certain odor descriptor for an odorous probe which they do not perceive. Thus, the present concept

was developed to remedy this situation with a test in which patients are asked to label different concentrations of the two odorants citronellal (CIT; a citrus-like fresh odor) and phenyl ethyl alcohol (PEA; a rose-like odor) with either "lemon", "rose", or "no odor present".

Material and methods

The study consisted of two experiments. Basic characteristics of the test were explored in experiment 1, namely test–retest reliability, correlation with other measures of olfactory sensitivity, and investigation of the sensitivity of the test to differences in age and gender. In the second experiment the test was tried in a clinical environment to investigate the usefulness of this approach in the diagnosis of olfactory loss. This experiment focused on both correlations with established measures of olfactory sensitivity and discrimination between groups with varying degrees of olfactory loss. Investigations were performed according to the Declaration of Helsinki (Summerset West amendment). All subjects provided written consent.

Subjects/patients

A total of 176 volunteers participated in experiment 1, which was divided into two sessions performed on two different days (76 male, 100 female; age range 12 to 85 years, mean age 30.4 years). All subjects were in excellent health; upon questioning none of them reported the presence of olfactory disturbances. One group of subjects (n = 100; 45 male, 55 female; age range 12 to 85 years, mean age 34.3 years) were investigated birhinally. The remaining 76 subjects (31 male, 45 female; age range 20 to 61 years, mean age 25.2 years) were studied separately for the left and right nostril. This experiment was performed at the Department of Pharmacology, University of Erlangen-Nürnberg, Erlangen, Germany.

Ninety-seven subjects participated in experiment 2 (45 male, 52 female; age range 19 to 78 years, mean age 47 years) which consisted of a single session. All of the subjects were inpatients at the Department of Otorhinolaryngology at the Municipal Hospital in Riesa, Germany. The major disorders of participating patients were as follows: chronic sinusitis (n = 21), acute hearing loss (n = 12), tinnitus (n = 10), vertigo (n = 6), septal surgery (n = 5), head trauma (n = 3), facial paralysis (n = 3), chronic tonsillitis (n = 3), and other causes (n = 31). Thirty-four patients reported that their olfactory sensitivity was reduced; the remaining 63 patients indicated that their olfactory sensitivity was normal or better than normal. The patients' history was taken using a standardized questionnaire. To exclude the presence of dementia, all patients received a "Mini-Mental-State Examination" (MMSE) [6] with scores from 0–30; only patients with a score higher than 27 were allowed to enter the study. All of these patients had received a thorough physical examination of the upper respiratory airways by an experienced otorhinolaryngologist. Based on their score in the Sniffin' Sticks odor test ([7, 11]; see below) they were grouped into anosmics (n = 14; 6 male, 8 female; age range 37 to 70 years, mean age 52 years), hyposmics (n = 31; 10 male, 21 female; age range 26 to 78 years, mean age 57 years), and normosmics (n = 52; 29 male, 23 female; age range 19 to 65 years, mean age 35 years).

Odor presentation

Odorants were presented in commercially available felt-tip pens. The pens had a length of approximately 14 cm, and the inner diameter of the cylindrical pens was 1.3 cm. Instead of liquid dye the tampon was filled with liquid odorants or odorants dissolved in propylene glycol, up to a total volume of 4 ml. For odor presentation the cap was removed by the experimenter for approximately 3 s and the pen's tip was placed 1–2 cm in front of both nostrils. Subjects were blindfolded to prevent visual identification of the odor-containing pens [for details see 7, 10].

For threshold measurements two odorants (PEA, rose-like odor; CIT, citrus-like odor) were presented in dilution series. Each series consisted of 16 dilutions made in 1:2 dilution ratios, starting from 100% PEA solutions and 50% CIT solutions, respectively, in propylene glycol.

Thresholds – "staircase" procedure

Using a triple forced-choice paradigm, detection thresholds for CIT and PEA were determined using a "staircase" method [7]. Three pens were presented in a randomized order. Two pens contained the solvent and one the odorant in a certain dilution. The subject's task was to identify the pen with the odorant. Presentation of the triplets to a subject occurred every 20 s, until the subject had correctly discerned the odorant in two successive trials, which triggered a reversal of the staircase. The mean of the last four staircase reversal points of a total of seven reversals was used as the threshold estimate [7]. It will be referred to as the staircase thresholds for CIT (staircase threshold$_{CIT}$) or for PEA (staircase threshold$_{PEA}$) with scores ranging from 0 to 16. staircase thresholds for citronellal were only collected during experiment 1.

Thresholds – "random" procedure

During testing all 32 odor pens were presented which contained either PEA or CIT at 16 concentrations each. Presentation of odorants and odor concentrations followed a pseudo-randomized order. This sequence was maintained for all participating subjects/patients. The interval between presentations was approximately 20 s. After presentation of one pen at a time subjects were asked to indicate whether the pen contained CIT, PEA, or no odor. The sum of correctly identified items was used as a measure of olfactory sensitivity. These scores were computed for both odorants together and for the two odorants separately. They will be referred to as the "random" thresholds, either separately for CIT (random threshold$_{CIT}$) or PEA (random threshold$_{PEA}$) with scores in the range between 0 and 16, or for both CIT and PEA together (random threshold$_{CIT + PEA}$) with scores in the range between 0 and 32.

Odor discrimination

In the odor discrimination task [compare 7], 16 triplets of pens were presented in a randomized order, with two containing the same odorant and the third a different odorant. Subjects had to determine which of three odor-containing pens smelled different. The presentation of triplets was separated by 20–30 s. The interval between presentation of individual pens of a triplet was approximately 3 s. As a total of 16 triplets were tested the subjects' scores ranged from 0 to 16. Subjects were blindfolded to prevent visual identification of some of the odorant-containing pens.

Odor identification

Odor identification was assessed by means of 16 common odors [compare 7]. Using a multiple choice task, individual odorants were identified from a list of four descriptors each. The interval between odor presentations was 20–30 s. Again, the subjects' scores ranged from 0 to 16.

TDI score

Results of three subtests obtained by means of the Sniffin' Sticks were also analyzed as a composite "TDI score" which was derived from the sum of the results obtained for staircase threshold$_{PEA}$, odor discrimination, and odor identification measures. This score was compiled with reference to normative data put together in more than 1000 healthy subjects [11].

Statistical analyses

Data were analyzed using SPSS 9.0 for Windows. Paired *t*-tests were used to explore group differences in age or gender. Correlational analyses were performed using Pearson statistics. For comparisons between groups of patients ANOVAs were employed (between-subject factor "group"). Bonferroni tests were used for post hoc comparisons. The alpha level was set at 0.05.

Results

Experiment 1

As explained above. one group of subjects (n = 100) was investigated birhinally by means of both random and staircase procedures. An additional 76 subjects were studied separately for the left and right nostril. Results from all 176 subjects were used for the correlational investigation of test–retest reliability. As more subjects were tested birhinally (n = 100), than were tested monorhinally (n = 76) only the results of the better nostril were used [compare 9]. The sequence of testing with the random or the staircase procedure was randomized across all participating subjects; however, intraindividually this sequence was the same for both sessions. Normative values were derived from results obtained for birhinal function in 176 subjects (Table 1).

Age-related differences in olfactory sensitivity

To investigate differences in relation to age, two groups were formed according to the group's mean age of 34 years (group a: mean age 23 years, age range 12–32 years; group b: mean age 51 years, age range 34–85 years). As a rule, younger subjects were more sensitive than older ones. However, differences between groups a and b were only found for staircase threshold$_{PEA}$ determined during the first session (t = 3.31, df = 98, P = 0.001). For staircase threshold$_{PEA}$ determined during the second session this difference was no longer present.

Gender-related differences in olfactory sensitivity

Differences between men and women were present, with female subjects being more sensitive. This became significant for all sensitivity measures obtained by the random procedure (t > 2.602, df = 98, P < 0.011). For sensitivity measures determined by means of the staircase procedure this effect was less pronounced. No gender-related differences could be found for staircase threshold$_{PEA}$ determined during the first session (t = 0.91, df = 98, P = 0.36), whereas this was significant for staircase threshold$_{PEA}$ during session 2 (t = 2.17, df = 98, P = 0.032) and for staircase threshold$_{CIT}$ obtained in the first and second session (t > 2.602, df = 98, P < 0.011).

Test–retest reliability

Correlation between results obtained during sessions 1 and 2 was slightly larger for thresholds determined by means of the staircase procedure (PEA: r_{99} = 0.77, P < 0.001; CIT: r_{100} = .72, P < 0.001) than for results obtained by means of the random procedure (r_{176} = 0.71; P < 0.001) (Fig. 1).

Experiment 2

Differences between anosmic, hyposmic, and normosmic subjects

For all measures of olfactory sensitivity the differences between the three groups became statistically significant (staircase threshold$_{PEA}$: $F_{(2,94)}$ = 136.2, P < 0.001; odor discrimination: $F_{(2,94)}$ = 130.1, P < 0.001; odor identification: $F_{(2,94)}$ = 156.4, P < 0.001; random threshold$_{PEA}$: $F_{(2,94)}$ = 36.7, P < 0.001; random threshold$_{CIT}$: $F_{(2,94)}$ = 43.3, P < 0.001; random threshold$_{PEA + CIT}$: $F_{(2,94)}$ = 67.4, P < 0.001) (Fig. 2). When the source of these main effects was further investigated, in all cases Bonferroni post hoc testing indicated significant differences between all three

Table 1 Normative values obtained in 176 healthy subjects investigated in experiment 1. Results are listed for scores in the random test for both citronellal (CIT) and phenyl ethyl alcohol (PEA) (results for birhinal testing and results for the best nostril, respectively)

		Test score
Median		23
Minimum		12
Maximum		30
Percentile	10	18
	20	20
	30	21
	40	22
	50	23
	60	24
	70	25
	80	25
	90	27

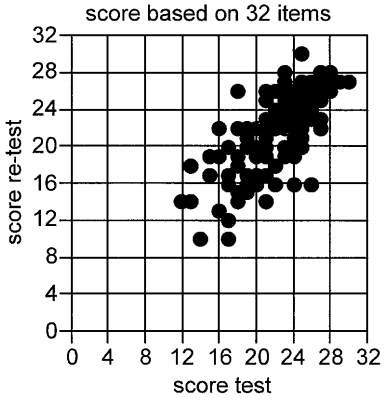

Fig. 1 Test–retest reliability of olfactory sensitivity as assessed by means of the random technique

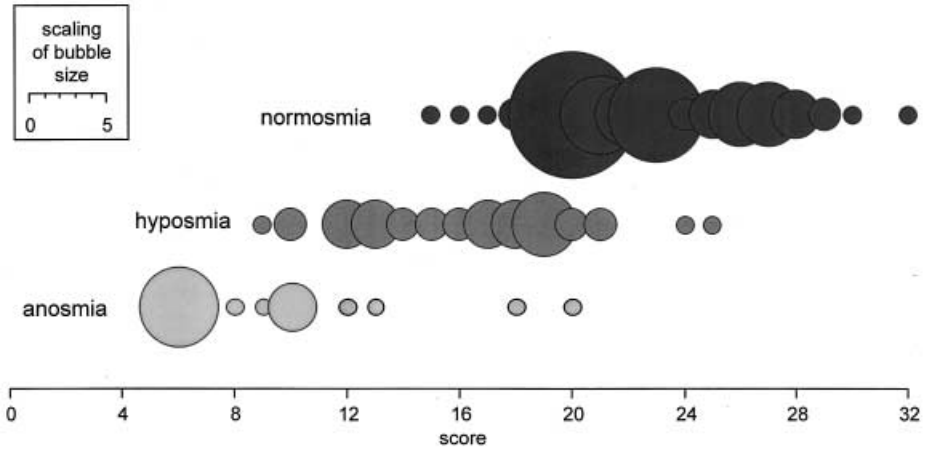

Fig. 2 Scores of subjects/patients with anosmia *(bottom)*, hyposmia *(middle)*, and normosmia *(top)* shows as a bubble graph. The diameter of the bubble is linearly correlated (see *insert*) to the number of subjects with the random odor test score indicated on the *y* axis

Table 2 Coefficients of correlations between olfactory tests (n = 97; *Thr* Thresholds established by means of the staircase method; *Dis* scores in odor discrimination; *Id* scores in odor identification; *TDI* summated scores from testing of odor thresholds, odor discrimination, and odor identification as used in the Sniffin' Sticks test [11]; *Random* combined scores of the random test procedure for CIT and PEA; *CIT* scores from the random test for citronellal; *PEA* scores from the random test for phenyl ethyl alcohol). All correlations were significant ($P < 0.001$)

	Dis	Id	Random	CIT	PEA
Thr	0.69	0.75	0.77	0.65	0.70
Dis		0.79	0.71	0.69	0.60
Id			0.74	0.69	0.65
TDI			0.82	0.74	0.72
CIT					0.67

groups ($P <$ = 0.001). In contrast, no significant differences between groups were found for the MMSE ($F_{(2,94)}$ = 0.84, P = 0.43).

Correlations between olfactory tests

All tests of olfactory function exhibited significant correlations ($r_{97} > 0.60$; $P < 0.001$) (Table 2); they were found to be largest for correlations between the TDI score and the random threshold$_{CIT + PEA}$ (r_{97} = 0.82)

Discussion

Results from the present study indicate the potential usefulness of this newly developed concept for routine clinical testing. The method was found (1) to exhibit a test–retest reliability similar to that found for established measures of olfactory thresholds, (2) to correlate with other measures of olfactory sensitivity, (3) to differentiate between expected differences in olfactory sensitivity in relation to gender, and (4) to discriminate between different degrees of olfactory loss. Thus, it seems that this test fulfills basic requirements needed for clinical applications.

In comparison to existing tests of olfactory function the random test offers advantages. These advantages include the time of approximately 10 min needed for its application. This is considerably shorter than that needed, e.g., for Sniffin' Sticks [7, 11] administration, which typically requires 20–30 min.

Another advantage in routine clinical testing may be that patients have the choice of selecting a "no odor" option. The background of this is that many anosmic patients are not very interested in olfactory tests and may even become annoyed by them. This everyday clinical observation is supported on a behavioral level by the scratching behavior of anosmic patients in a "Scratch and Sniff" odor identification test [5]. In these tests odors are released by scratching pads, the surface of which is covered with microencapsulated odors. It can be shown that anosmics at first scratch the pads at a relatively high intensity. However, after only a few trials they appear to lose interest, as indicated by a rapid decrease in scratch intensity. Similarly, in a clinical environment many patients with limited olfactory function are not in favor of a situation where they anticipate after a few trials that their response is not based on sensory experience but on guessing.

Furthermore, the random test can be used repetitively in a single individual at relatively short intervals. This may be of special interest when it comes to the assessment of drug effects on the sense of smell. These investigations often require frequent testing of the same individual [e.g. 8, 13] which seems to be difficult to accomplish with odor identification tests.

And finally, as with the Sniffin' Sticks [7, 11] or the Connecticut Chemosensory Clinical Research Center test [1, 2], the random test can be used repetitively in several different patients, which in turn keeps costs of olfactory testing in check. This seems to be especially important as health insurance companies in most countries of the world would not reimburse the practitioner for olfactory testing.

A limitation of this newly developed approach is that it may not be useful in medico-legal cases when malingering has to be detected – which appears to be possible, to some degree, by means of forced-choice odor identification tests like the University of Pennsylvania Smell Iden-

tification Test [4] or other olfactory tests that use forced-choice approaches [e.g. 7]. Future studies are expected to focus on investigations in potential malingers.

In conclusion, based on the present results the random test can be expected to meet clinical needs in a number of respects.

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