Normative data for the lateralization task in the assessment of intranasal trigeminal function

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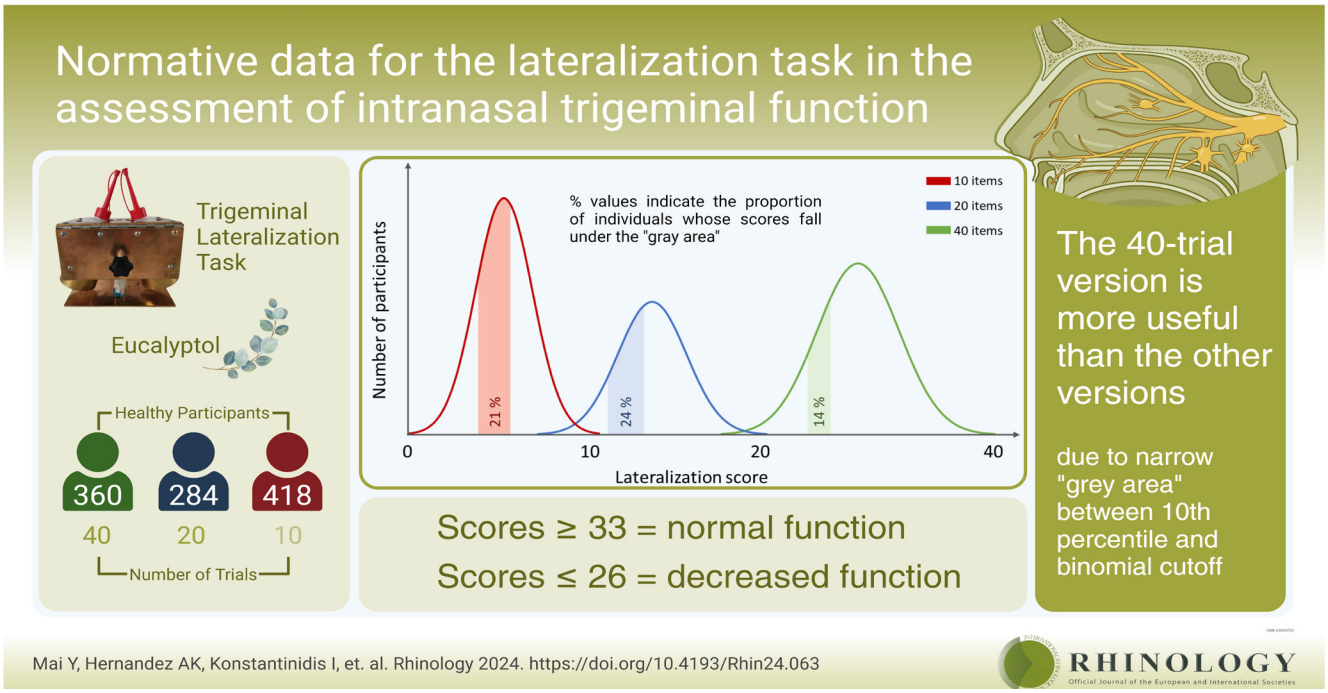

Abstract

Aim: To provide normative data for the lateralization task in the assessment of intranasal trigeminal function, as well as to investigate potential effects of age, sex and olfactory function.

Methods: The lateralization task using eucalyptus as target stimulus was performed to assess intranasal trigeminal function. Data were collected from: 360 healthy adult participants (mean age 37.5±17.4) for the 40-trial version; 284 participants (mean age 32.6±14.1) for the 20-trial version; and 418 participants (mean age 42.6±15.6) for the 10-trial version. The "Sniffin' Sticks" test was used to measure olfactory function.

Results: The mean scores were 35.46±4.50 for the 40-trial version, 15.64±3.65 for the 20-trial version, and 8.14±2.16 for the 10-trial version. In the reference group aged 18-25 years, the 10th percentiles were 33 for the 40-trial version, 11 for the 20-trial version, and 6 for the 10-trial version. Significant effects of age and odor discrimination score were observed on lateralization performance.

Conclusions: We provide reference scores for the lateralization task, in large sample of healthy participants. Among the three examined tasks (40, 20 and 10), the 40-trial task yielded the most reliable information. For the 40-trial version, scores equal or higher to 33 points indicate a normal lateralization ability, whereas scores between 27 and 32 may warrant further assessment. Scores below 27 possibly point towards a decreased trigeminal function. The lateralization task serves as surrogate marker of intranasal trigeminal functions and further studies with pathological cases are needed to explore its clinical usefulness.

Key words: odor lateralization, trigeminal function, trigeminal sensitivity, binomial test, olfactory function

Introduction

Measurement of intranasal trigeminal function has attracted increasing attention over the past decade [1–6]. One common method of assessing trigeminal function is using the odor lateralization task, which involves the correct detection of the stimulated nostril following the delivery of an odor to a single nostril. This task is grounded in the principle that odor lateralization largely relies on the trigeminal system [7–10], although improvement at localizing pure odorants can be achieved through training or by using a mix of pure odorants and "trigeminal" odors (which induce trigeminal sensations like irritation) [11,12]. Until now, the task has been introduced over 30 years ago by Kobal et al. [7], and is widely used in published studies [3,13] especially in the recent 10 years.

The odor lateralization task involves a trigeminal odor delivered to one nostril while an odorless stimulus is delivered to the other nostril. Participants, through a forced-choice response, are required to indicate which nostril received the trigeminal odor [7,14,15]. The task typically includes 40 [16] trials, with half of the trials presented to each side of the nose in a randomized sequence. In more recently published studies, 20-trial [17] and 10-trial [18] versions were also getting popular. The odor lateralization performance is calculated by summing the correct responses. A common way to determine an individual's performance relies on the idea that whether participants score statistically above chance level [8,11,19]. According to the binomial test, individuals achieving ≥27 correct responses out of 40 trials, ≥15 out of 20 trials, or ≥9 out of 10 trials is statistically above chance level. However, the actual performance distribution within the healthy population and the level of performance that the majority of the healthy population can reach has not been reported yet. The increasing clinical significance of trigeminal system in the field of rhinology and the widespread use of lateralization test also calls for normative values established among healthy individuals.

Aim of this study was to provide normative data for odor lateralization tasks in quantitative assessing intranasal trigeminal function, as well as to examine the relationships between odor lateralization performance and age, sex, and olfactory function.

Materials and methods

Participants

Data were obtained from a total of 1014 independent healthy adult participants without any chemosensory complaints. This included unpublished data from 194 participants and previously published data from 820 participants [16–18,20–27]. Of these, 360 independent participants completed the 40-trial version, 278 completed the 20-trial version, and 376 completed the 10-trial version. To maximize the data pool, where available, scores from the first 20 trials of the 40-trial version were included in the 20-trial analysis; and scores from the first 10 trials of the 20-trial and 40-trial versions were included in the 10-trial analysis. For practical reasons, individual trial records were available for only 36 participants from the 20-trial version and 6 participants from the 40-trial version. Therefore, scores from the first 10 trials of these 42 participants were extracted and added to the 10-trial data pool, resulting in a total of 418 cases. Scores from the first 20 trials of the 6 participants who completed 40 trials were added to the 20-trial data pool, resulting in a total of 284 cases. Participants were asked to avoid smoking, drinking or eating anything with strong smells prior to the test. Informed consent was obtained from all participants. Data were collected at the Smell and Taste Clinic of TU Dresden and Aristotle University of Thessaloniki. Ethical approval for unpublished data was obtained from the Ethics Committees at the Medical Faculty of TU Dresden, Germany (EK558122019, BO-EK-141032023, BO-EK-430102023) and Aristotle University of Thessaloniki, Greece (1446/19.10.21). Published data included an ethical statement in each corresponding article. All procedures followed the Declaration of Helsinki.

Measurements

Odor lateralization task

The test utilized a mechanically operated "squeezer" device with two 250ml compressible polypropylene bottles(28). During each test, one nostril received an odor stimulus, while the other received air/solvent (propylene glycol). The odor stimulus in our study was eucalyptol in its neat concentration (99%; C80601, Merck, Darmstadt, Germany; CAS number: 8000-48-4), a prototypical bimodal stimulant that activates the trigeminal receptor TRPM8 and induces a cooling sensation(5,6). The volumes of eucalyptol in the 250ml propylene bottles ranged from 10 to 30 ml across the studies, while the volume delivered to participants per nostril in each trial was set at approximately 15ml. To minimize potential mechanical irritation at the nares, bottles were equipped with spouts and soft silicone tubing (inner diameter 4mm). Participants were instructed to hold the tubing in place, ensuring they reached beyond the nasal valve, and breathe normally (similar to resting breathing) during the test. After each stimulus, participants indicated the side of stimulation. During the test, a total of 40, 20, or 10 trials (with half of the trials on each side of the nose in a randomized order) were applied to blindfolded participants at an interstimulus interval of 30-40s. It took approximately 30 mins to complete the 40-trial version, 15 mins for 20-trial version, and 7 mins for 10-trial version. The score was the sum of correct responses. Practice trials were conducted prior to the formal test.

Olfactory function

Olfactory function was assessed using the "Sniffin' Sticks" [29,30]. It includes subtests for olfactory threshold (OT), discrimination (OD), and identification (OI), each with a maximum score of 16.

The sum of the three tests constitutes the composite TDI score (range 1-48). All the tests were performed birhinally.

Data analysis

Data were analyzed using SPSS 29 software (SPSS Inc., Chicago, IL, USA). Descriptive analyses were conducted to summarize demographic information, Sniffin' Sticks score, and lateralization score in the total sample and different age groups. To provide data distribution in relation to specific age groups, we calculated the 5th, 10th, 25th, 50th, 90th and 95th percentiles of the lateralization score distribution for each age group. Based on previous studies in similar fields, the 10th percentile score was considered the cutoff for determining normal or decreased lateralization ability [31–35]. Participants were divided into six age groups: 18-25 years; 25.1-35 years; 35.1–45 years; 45.1-55 years; 55.1–65 years; and over 65 years. The effect of age group was examined using analysis of variance (ANOVA), with Bonferroni correction applied for multiple post-hoc comparisons. The effect of sex was investigated using independent t-tests. Additionally, Pearson correlation analyses were conducted with Bonferroni correction applied to the p-values. Further, we exploratively identified factors predicting participants with better odor lateralization (>10th percentile) versus participants with poor odor lateralization (≤10th percentile) using logistic regression analyses. Both individual models (each predictor entered individually) and merged models (all predictors entered together) were built. Predictors included age, sex (male and female), study origin (Germany and Greece), OT, OD, and OI. All the analyses were conducted respectively for the 40-trial, 20-trial, and 10-trial versions of the lateralization task.

Results

Descriptive results and normative data for odor lateralization task

As shown in Table 1, we included a total of 360 healthy adult participants who completed the 40-trial version (female=189) with a mean age of 37.5±17.4 years and a mean TDI score of 35.19±3.51. A total of 284 healthy adults completed the 20-trial version (female=172) with a mean age of 32.6±14.1 and a mean TDI score of 34.35±4.75. Lastly, we also included 418 healthy participants who completed the 10-trial version (female=257) with a mean age of 42.6±15.6 and a mean OI score of 14.03±1.09 (no TDI score was available from this group).

For participants who completed the 40-trial version of the lateralization test, the mean score was 35.46±4.50, and no statistical difference was observed between Germany (n=320, 35.43±4.51) and Greece (n=40, 35.67±4.47; t=-0.32, p=0.75). The 10th percentiles for individuals aged 18-25 years: 33; 25-35 years: 31; 35-45 years: 26.4; 45-55 years: 29.7; 55-65 years: 26.8; and >65 years: 22. For participants who completed the 20-trial version, the mean score was 15.64±3.65. The 10th percentiles for individuals aged 18-25 years: 11; 25-35 years: 11; 35-45 years: 8.4; 45-55 years: 9.1; 55-65 years: 8; and >65 years: 8. For participants who completed the 10-trial version, the mean score was 8.14±2.16. The 10th percentiles for individuals aged 18-25 years: 6; 25-35 years: 5; 35-45 years: 5; 45-55 years: 5; 55-65 years: 4; and >65 years: 4 (Table 1, Figures 1 and 2).

Relationship between odor lateralization and age, sex and olfactory function

A significant effect of age was found for odor lateralization performance in both 40-trial ($F=7.74$, $p<0.001$) and 10-trial versions ($F=6.26$, $p<0.001$), but only a marginal significance in the 20-trial version ($F=2.23$, $p=0.052$). For the 40-trial version, post-hoc tests highlighted significantly higher scores for individuals aged 18-25 years, 25-35 years and 35-45 years compared to those >65 years (Mean difference [MD]=3.50 to 4.87, p's<0.05); and significantly higher scores for individuals aged 18-25 years compared to those who were 55-65 years (MD=2.38, p=0.01). For the 10-trial version, post-hoc tests highlighted significantly higher scores for individuals aged 18-25 years, 25-35 years, and 35-45 years compared to those >65 years (MD=1.28 to 1.79, p's<0.05); and significantly higher scores for individuals aged 18-25 years, and 25-35 years compared to those aged 55-65 years (MD=1.18 to 1.54, p's<0.05) (Figure 3 and Table 2).

No significant sex effect was found across the whole sample and for each age group in both the 40-trial (t=0.02 to 1.56, p's>0.05) and 10-trial versions (t=0.08 to 1.18, p's>0.05). However, in the 20-trial version, female (16.01±3.68) significantly performed better than male (15.07±3.56, t=2.12, p=0.04). Specifically, female (16.62±3.35) performed better than male (14.69±3.45) in the 18-25 years age group (t=2.88, p=0.005), while no significant differences were found in other age groups (t=0.21 to 2.34, p's>0.05).

Pearson correlation analysis consistently showed a negative correlation between lateralization score and age across the 40-trial (r=-0.30, p<0.001), 20-trial (r=-0.16, p=0. 028), and 10-trial versions (r=-0.26, p<0.001). Furthermore, positive correlations were observed between lateralization and OD score in both the 40-trial (r=0.24, p=0.007) and 20-trial versions (r=0.25, p=0.025). In the 40-trial version, positive correlations were also found between lateralization and OI score (r=0.21, p=0.025), as well as lateralization and TDI score (r=0.25, p<0.001) (Figure 4).

Factors predicting better versus poor lateralization performance

As shown in Table 3, when each predictor was analyzed individually, younger age significantly predicted better lateralization performance across the 40-trial, 20-trial, and 10-trial versions

Table 1. Descriptive statistics and normative values for odor lateralization task.

	Age (in years)	18-25	25-35	35-45	45-55	55-65	>65	Total
	N	144	70	27	36	53	30	360
	Mean	36.67	35.87	35.3	34.72	34.28	31.8	35.46
	Median	37	37	37	35.5	36	33.5	37
	SD	3.44	4.11	5.21	3.89	4.99	6.38	4.50
	Minimum	22	20	21	22	21	19	19
	Maximum	40	40	40	40	40	40	40
	Percentiles							
	5	29.25	25.55	22.2	27.1	23.4	20.1	26
	10	33	31.1	26.4	29.7	26.8	22	29
	25	35	34	33	32	30.5	27	33
40 trials	50	37	37	37	35.5	36	33.5	37
	75	40	39	39	38	38	38	39
	90	40	40	40	39	40	39.9	40
	95	40	40	40	39.15	40	40	40
	Age	22.51±1.75	28.58±2.85	40.62±2.73	50.79±2.63	60.38±2.73	71.10±5.24	37.50±17.41
	M : F	67:77	31:39	13:14	16:20	27:26	17:13	171:189
	TDI	36.39±3.14	35.49±3.48	36.75±3.69	35.51±2.92	33.52±3.44	32.92±2.98	35.19±3.51
	OT	8.17±1.89	8.46±2.27	8.07±1.61	7.55±1.79	7.65±1.84	7.04±1.28	8.00±1.92
	OD	12.86±1.78	12.32±1.82	14.20±1.64	13.12±1.24	12.45±1.82	12.42±2.09	12.81±1.82
	OI	14.31±1.51	14.44±1.57	14.55±1.15	14.40±1.23	13.97±1.24	13.79±1.08	14.27±1.37
	N (%) [≥27] [a]	141(98%)	66 (94%)	25 (93%)	35 (97%)	48 (91%)	24 (80%)	339 (94%)
	Age (in years)	**18-25**	**25-35**	**35-45**	**45-55**	**55-65**	**>65**	**Total**
	N	125	90	13	20	27	9	284
	Mean	16.06	15.86	14.46	14.3	15.37	13	15.64
	Median	17	16.5	16	13.5	17	12	17
	SD	3.48	3.37	4.16	3.84	4.32	4.27	3.65
	Minimum	5	6	8	8	8	8	5
	Maximum	20	20	20	20	20	20	20
	Percentiles							
	5	9.3	10	8	8.05	8	8	9
	10	11	11	8.4	9.1	8	8	10
	25	14	13	10.5	11	12	10	13
20 trials	50	17	16.5	16	13.5	17	12	17
	75	19	19	18	18	20	16.5	19
	90	20	20	19.6	19	20	-	20
	95	20	20	-	19.95	20	-	20
	Age	23.11±1.78	28.54±2.44	39.59±3.79	51.82±2.27	60.22±3.04	70.85±6.38	32.64±14.10
	M : F	36:38	44:46	4:9	8:12	14:13	6:3	112:172
	TDI	36.28±4.75	35.37±3.67	36.94±3.54	34.31±4.03	31.69±4.33	30.56±6.28	34.35±4.75
	OT	8.71±2.48	8.22±2.25	9.55±2.30	7.31±3.07	6.31±3.17	5.78±3.37	8.01±2.76
	OD	13.38±1.57	13.04±1.85	13.33±1.00	13.15±1.60	11.89±2.04	11.89±1.83	12.82±1.82
	OI	13.95±1.36	13.88±1.15	13.77±1.17	13.85±1.31	13.48±1.31	12.89±2.21	13.83±1.32
	N (%) [≥15] [a]	82 (66%)	57 (63%)	7 (54%)	8 (40%)	17 (63%)	4 (44%)	173 (61%)

Continued on next page

Table 1. Descriptive statistics and normative values for odor lateralization task.

	Age (in years)	18-25	25-35	35-45	45-55	55-65	>65	Total
	N	71	85	91	72	58	40	418
	Mean	8.82	8.46	8.31	8.22	7.28	7.03	8.14
	Median	10	10	9	9	7	7	9
	SD	1.667	2.102	2.096	1.966	2.512	2.304	2.162
	Minimum	3	1	2	3	0	3	0
	Maximum	10	10	10	10	10	10	10
	Percentiles							
	5	5	5	4	4	2.95	3	4
	10	6	5	5	5	4	4	5
	25	8	7	7	7	5	5	7
10 trials	50	10	10	9	9	7	7	9
	75	10	10	10	10	10	9.75	10
	90	10	10	10	10	10	10	10
	95	10	10	10	10	10	10	10
	Age	21.68±2.40	30.95±2.93	39.89±2.71	50.42±2.61	60.41±3.01	70.75±4.64	42.60±15.61
	M : F	19:52	33:52	38:53	23:49	28:30	19:21	160:257
	TDI	-	-	-	-	-	-	-
	OT	-	-	-	-	-	-	-
	OD	-	-	-	-	-	-	-
	OI	14.05±1.03	14.09±1.34	13.50±2.12	-	-	-	14.03±1.09
	N (%) [≥9] [a]	51 (72%)	53 (62%)	53 (58%)	40 (56%)	23 (40%)	14 (35%)	234 (56%)

N: sample size; SD: standard deviation; N, Mean, Median, SD, Minimum, Maximum and Percentiles describe odor lateralization scores for all the participants and across each age group; M= male, F=female; TDI: "Sniffin' Sticks" composite odor threshold, discrimination, and identification score, OT: "Sniffin' Sticks" odor threshold score, OD: "Sniffin' Sticks" odor discrimination score, OI: "Sniffin' Sticks" odor identification score. Age, TDI, OT, OD and OI presented as mean ± SD. [a] the number and percentage of participants with a lateralization score above the cutoff values suggested by binomial distribution.

(Exp(B)=0.96 to 0.97, p<0.001). In the 40-trial version, higher OD (Exp(B)=1.36, p<0.001) and TDI (Exp(B)=1.13, p=0.003) scores also significantly predicted better performance. When all predictors were entered into a single model, OD score remained a significantly positive predictor in the 40-trial version (Exp(B)=1.31, p=0.005).

Discussion

The lateralization task is widely used to measure intranasal trigeminal function, but as of yet no normal values have been reported. The present data provide the distribution of eucalyptus lateralization performance for the 40-, 20-, and 10-trial versions in a healthy population, thereby showing the approximate percentile of a given score. We observed that the mean lateralization scores were 35±5 points for the 40-trial, 16±4 points for the 20-trial, and 8±2 points for the 10-trial version. Compared to the above-chance cutoff based on binomial statistics, even the lower boundary of the 40-trial mean (mean-SD, i.e. 35-5) was 3 points higher than the above-chance cutoff of ≥27 points. This suggests that while a score of 27 is sufficient to consider an individual capable of lateralizing trigeminal odors statistically better than at random, healthy individuals on average achieve an even higher level of 35±5 points. However, the mean scores for the 20-trial version (16±4 points) overlapped with the above-chance cutoff of ≥15 points, as did those for the 10-trial version (8±2 points) with the above-chance cutoff of ≥9 points. With fewer trials, it is difficult to judge a participant's score because there is less clear differentiation between performance due to chance and actual ability. These highlight the benefits of having more trials compared to the shorter versions in the lateralization task. In addition to the statistical effect of a given accuracy being less likely to be above chance for fewer repetitions in a binomial distribution, this discrepancy might originate from the low error tolerance of the shorter versions compared to the 40-trial version, possibly related to task familiarity, practice or training effects [12,17].

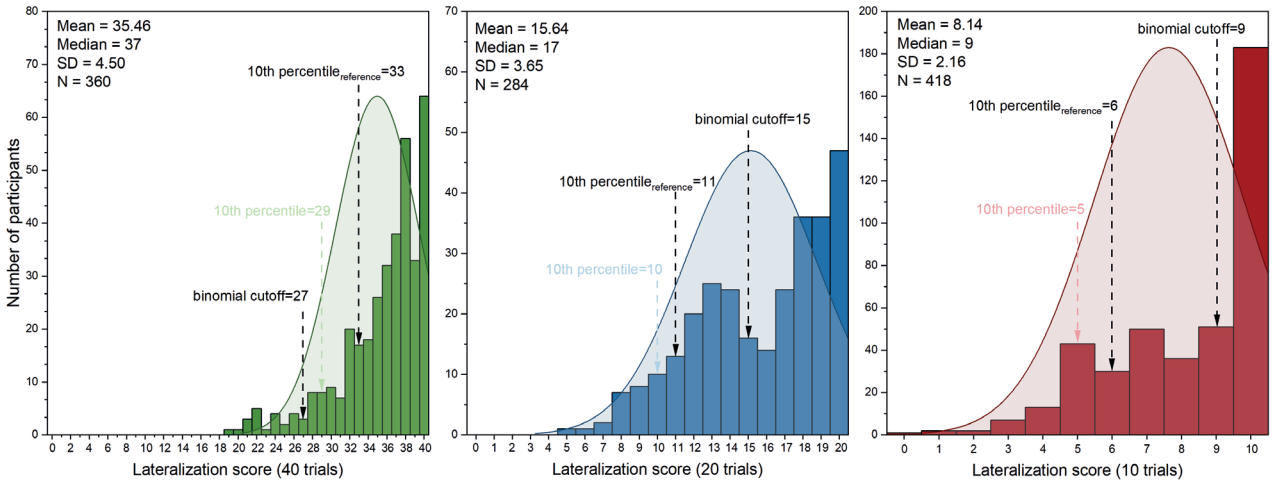

Figure 1. Distribution of lateralization scores for 40-, 20-, and 10-trial versions. This figure displays the distribution of lateralization scores for three different trial versions: 40-trial (left panel), 20-trial (middle panel), and 10-trial (right panel). X-axis: lateralization score; Y-axis (frequency): number of participants achieving a specific score. Binomial cutoff: thresholds for considering lateralization performance as statistically significant above chance level (including the cutoff value); 10th percentile: lower bound of typical performance for the sample showing the corresponding distribution; 10th percentile reference: lower bound of typical performance for the reference group aged 18-25 years. SD: standard deviation, N: sample size.

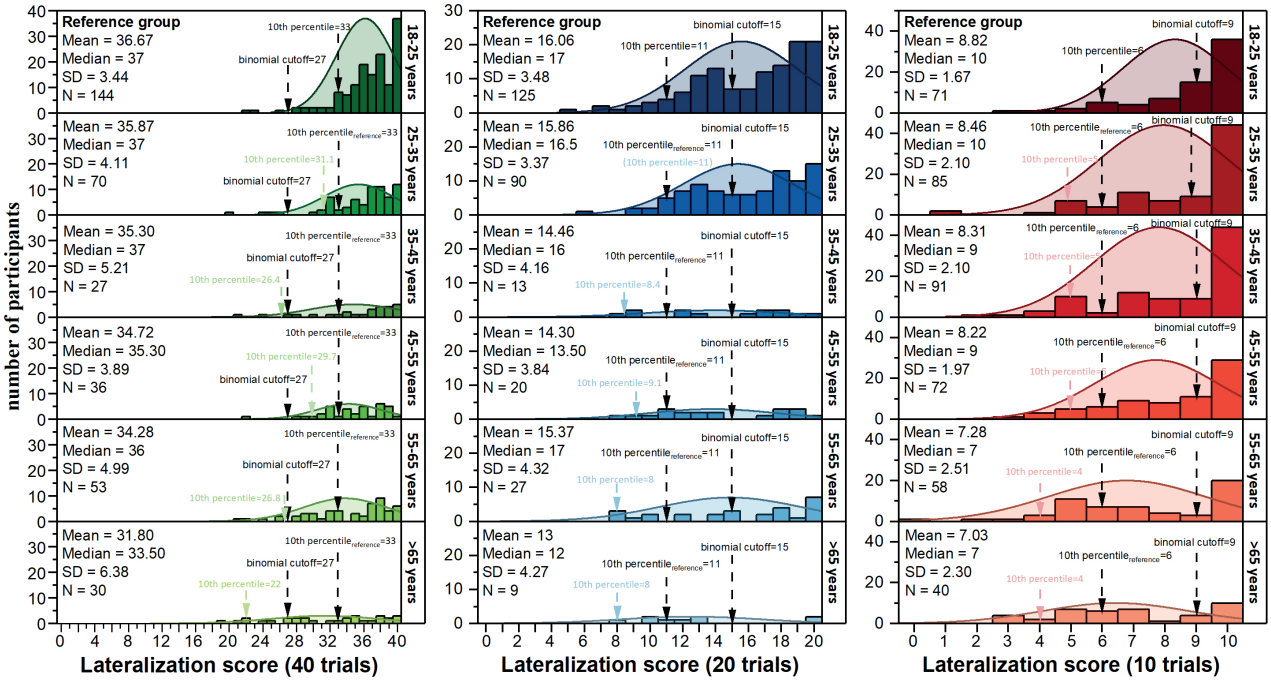

Figure 2. Distribution of lateralization scores by age group for 40-, 20-, and 10-trial versions. This figure displays the distribution of lateralization scores by age group for three different trial versions: 40-trial (left panel), 20-trial (middle panel), and 10-trial (right panel). X-axis: lateralization score; Y-axis (frequency): number of participants achieving a specific score. Binomial cutoff: thresholds for considering lateralization performance as statistically significant above chance level (including the cutoff value); 10th percentile: lower bound of typical performance for the sample showing the corresponding distribution; 10th percentile reference: lower bound of typical performance for the reference group aged 18-25 years. SD: standard deviation, N: sample size.

Researchers and clinicians may be interested in establishing a boundary to distinguish between "normal" and "decreased" lateralization ability. Previous studies in similar fields suggested that this boundary could be set at the 10th percentile in the reference age group with the best performance for considering the absolute performance [31–35]. This cutoff indicates that the majority (90 percent) of healthy individuals without trigeminal-related complaints in the reference age group can perform at

Table 2. Mean difference of lateralization score between age groups and their post-hoc test significance.

			A				
		Age (in years)	**18-25 (n=144)**	**25-35 (n=70)**	**35-45 (n=27)**	**45-55 (n=36)**	**55-65 (n=53)**
		25-35 (n=70)	0.8				
		35-45 (n=27)	1.37	0.58			
40 trials	**B**	45-55 (n=36)	1.94	1.15	0.57		
		55-65 (n=53)	**2.38****	1.59	1.01	0.44	
		>65 (n=30)	**4.87*****	**4.07*****	**3.50***	2.92	2.48
		Age (in years)	**18-25 (n=125)**	**25-35 (n=90)**	**35-45 (n=13)**	**45-55 (n=20)**	**55-65 (n=27)**
		25-35 (n=90)	0.21				
		35-45 (n=13)	1.6	1.39			
20 trials	**B**	45-55 (n=20)	1.76	1.56	0.16		
		55-65 (n=27)	0.69	0.49	-0.91	-1.07	
		>65 (n=9)	3.06	2.86	1.46	1.3	2.37
		Age (in years)	**18-25 (n=71)**	**25-35 (n=85)**	**35-45 (n=91)**	**45-55 (n=72)**	**55-65 (n=58)**
		25-35 (n=85)	0.36				
		35-45 (n=91)	0.51	0.15			
10 trials	**B**	45-55 (n=72)	0.59	0.24	0.09		
		55-65 (n=58)	**1.54*****	**1.18***	1.03	0.95	
		>65 (n=40)	**1.79*****	**1.43****	**1.28***	1.2	0.25

Note. The numbers in the table represent the mean difference between two age groups (A-B). n: sample size. *: p<0.05, **: p<0.01, ***: p<0.001. Bonferroni method was used to correct the p-values.

least at this level. In our results, the 10th percentile cutoff value for the reference group aged 18-25 was 33 points for the 40-trial version, 11 points for the 20-trial version, and 6 points for the 10-trial version. Scores <33 points out of 40 trials, <11 points out of 20 trials, or <6 points out of 10 trials indicate a distributional "decreased" lateralization ability.

However, for taking clinical action, we recommend a more conservative way to interpret the scores, that is, considering both the distributional cutoff and the above-chance cutoff. In the 40-trial task, the 10th percentile cutoff is 33 points, and the above-chance cutoff is 27 points. A "normal" function must be above both cutoffs, i.e., a score of ≥33. However, scoring below 33 points could be divided into two parts: 1) scores <27 could be regarded as a "decreased" lateralization ability, as it indicates that an individual cannot lateralize the odor statistically above chance nor reach a level that is achieved by 90% of the healthy population. 2) the scoring range between 27 and 33 could be regarded as a "grey area", indicating that those participants could perform the lateralization task significantly better than what is achieved with random guessing but still worse than 90% of the healthy population. If only based on the distribution cutoff, this overlap proportion would be categorized as "abnormal". However, without observations from patients with pathologies, it is difficult to determine if this score reflects normal variation or a true decrease in trigeminal sensitivity. In such cases, more comprehensive assessments [6,14], such as CO_2 threshold measurement, trigeminal event-related potentials, or negative mucosal potentials to trigeminal stimuli, may provide more information.

In the 20- and 10-trial versions, the distribution cutoffs were 11 and 6 points, while the above-chance cutoffs were 15 and 9 points, respectively. Unlike the 40-trial version, their distribution cutoffs are lower than their above-chance cutoffs. In these cases, scoring <11 points out of 20 trials or <6 points out of 10 trials suggests a "decreased" lateralization ability, as the score is both below the above-chance threshold and the distributional threshold. However, scoring ≥11 points out of 20 trials or ≥6 points out of 10 trials could be divided into two parts: 1) scores higher than both above-chance cutoff and distribution cutoff (i.e., ≥15 out of 20 trials or ≥9 out of 10 trials), indicate a "normal" lateralization ability because the correct lateralization responses are significantly better than both cutoffs. 2) scores between the above-chance cutoff and the 10th percentile cutoff (i.e., ≥11 to <15 points out of 20 trials, or ≥6 to <9 out of 10 trials) are in a "grey zone". If only based on the distribution cutoff, they would be considered as having "normal" ability. However, although scores within this range indicate that the performance is better

Table 3. Logistic regression of better (>10th percentile) versus poor lateralization performance (≤ 10th percentile).

40 trials								
$n_{>10th\ percentile}$=267	**Exp (B)**	**95% CI**		**p**	**Exp (B)**	**95% CI**		**p**
$n_{\leq 10th\ percentile}$=93		**Lower**	**Upper**			**Lower**	**Upper**	
Age (n=360)	0.97	0.95	0.98	**<0.001**	0.99	0.97	1.01	0.51
Sex [a] (n=360)	0.88	0.55	1.42	0.60	0.80	0.41	1.57	0.52
Origin [b] (n=360)	1.45	0.64	3.26	0.37	1.99	0.77	5.16	0.16
OT (n=236)	1.06	0.91	1.23	0.46	1.10	0.91	1.34	0.33
OD (n=176)	1.36	1.13	1.64	**<0.001**	1.31	1.08	1.59	**0.005**
OI (n=176)	1.19	0.95	1.50	0.14	1.07	0.84	1.37	0.57
TDI (n=265)	1.13	1.04	1.22	0.003		[c]		
20 trials								
$n_{>10th\ percentile}$=242	**Exp (B)**	**95% CI**		**p**	**Exp (B)**	**95% CI**		**p**
$n_{\leq 10th\ percentile}$=42		**Lower**	**Upper**			**Lower**	**Upper**	
Age (n=284)	0.97	0.95	0.99	**<0.001**	1.00	0.98	1.03	0.97
Sex [a] (n=284)	0.83	0.42	1.64	0.59	0.87	0.36	2.09	0.75
OT (n=201)	1.07	0.94	1.21	0.29	1.00	0.86	1.16	0.99
OD (n=121)	1.20	0.96	1.50	0.10	1.24	0.97	1.60	0.089
OI (n=274)	1.03	0.81	1.32	0.80	0.90	0.67	1.20	0.45
TDI (n=90)	1.03	0.95	1.03	0.45		[c]		
10 trials								
$n_{>10th\ percentile}$=320	**Exp (B)**	**95% CI**		**p**	**Exp (B)**	**95% CI**		**p**
$n_{\leq 10th\ percentile}$=98		**Lower**	**Upper**			**Lower**	**Upper**	
Age (n=417)	0.96	0.95	0.98	**<0.001**	0.85	0.68	1.07	0.18
Sex [a] (n=417)	1.17	0.74	1.86	0.51	0.34	0.03	3.44	0.36
OT (n=0)	-	-						
OD (n=0)	-	-						
OI (n=18)	1.85	0.73	4.68	0.19	1.93	0.74	5.06	0.18
TDI (n=0)	-	-						

[a] male was set as the reference, [b] Germany was set as the reference to compare to Greece, [c] TDI was not included in the merged model due to its the severe collinearity with OT, OD and OI.

than the lower tail of the distribution, these scores could still be obtained by random responses based on chance. Consequently, it is incorrect to categorize these individuals as having a "normal" lateralization ability. Therefore, individual scoring within this "grey zone" may warrant further assessment before clinical action is taken. When comparing the three trial versions, 14% (n=52) of the population in the 40-trials version, 24% (n=69) of population in the 20-trial version, and 21% (n=86) of the tested population falls within this "grey zone", pending further assessments. The 40-trial version, therefore, seems to be more useful, as it leaves fewer individuals in the "grey zone", where additional information is needed.

It is important to note that while the lateralization task reflects significant aspects of trigeminal function, it may not encompass the entire scope. This is because intranasal trigeminal function is not only involved in the ability to lateralize irritants but also in aspects such as perceptions of temperature, chemical irritants, and nasal airflow [5]. Additionally, there is currently no gold standard for assessing trigeminal function, making it more challenging to diagnose based solely on lateralization task cutoffs. The cutoff scores in this study estimate an aspect of intranasal trigeminal function. However, a combination of multiple indicators for trigeminal function seems promising, as each aspect of trigeminal function may require different measurements. In this context, odor lateralization could serve as a valid and reliable adjunctive indicator.

We observed an age-related effect in the 40-trial and 10-trial versions. Most pronouncedly, individuals aged 18-45 years

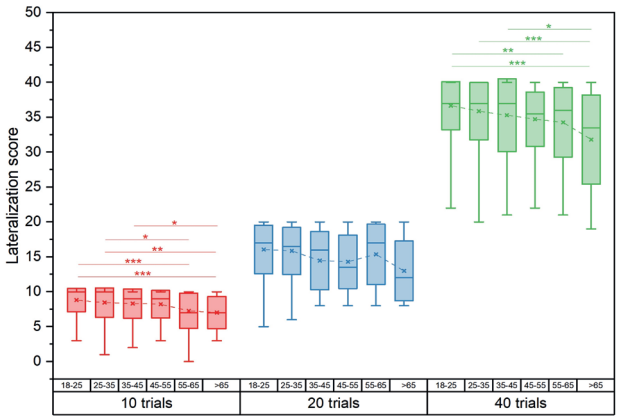

Figure 3. Comparisons of odor lateralization scores between age groups. Odor lateralization scores were compared between age groups for the 10-trial, 20-trial, and 40-trial versions, respectively. The box: standard deviation (box), The cross on the boxes: mean value, Solid line on the box: median value, Whiskers: range of maximum to minimum values. *: p<0.05, **: p<0.01, ***: p<0.001.

significantly outperformed those aged >65 years. However, the 20-item version showed a trend but was not statistically significant (p=0.052), probably related to the small sample size in the age group of >65 years (n=9), which had the lowest score.

Nevertheless, both correlation and regression results consistently indicated that poor lateralization performance correlated with older age across different trial versions. Such observations were largely in line with previously published studies [26,36]. However, it is challenging to determine whether the superior lateralization performance in younger participants was independent of their olfactory function [37]. In fact, in addition to the significantly correlations between lateralization performance and age, we also found significant correlations between olfactory function and lateralization ability, and between olfactory function and age. In the merged logistic regression for the 40-trial version, the significant effect of age became non-significant while the effect of odor discrimination remained significant. This suggests that the effect of age may overlap with odor discrimination, with the latter appearing as a more dominant predictor. However, more evidence is needed to confirm this relationship. Among the three dimensions of olfactory function, olfactory discrimination was most closely and consistently associated with lateralization performance. This could be explained by the general discrimination ability required for both tasks, though they are not completely the same. In the olfactory discrimination task, participants distinguish the target odor from two identical odors; while in the lateralization task, they distinguish whether the odor is delivered to the left or right side, simultaneously using the

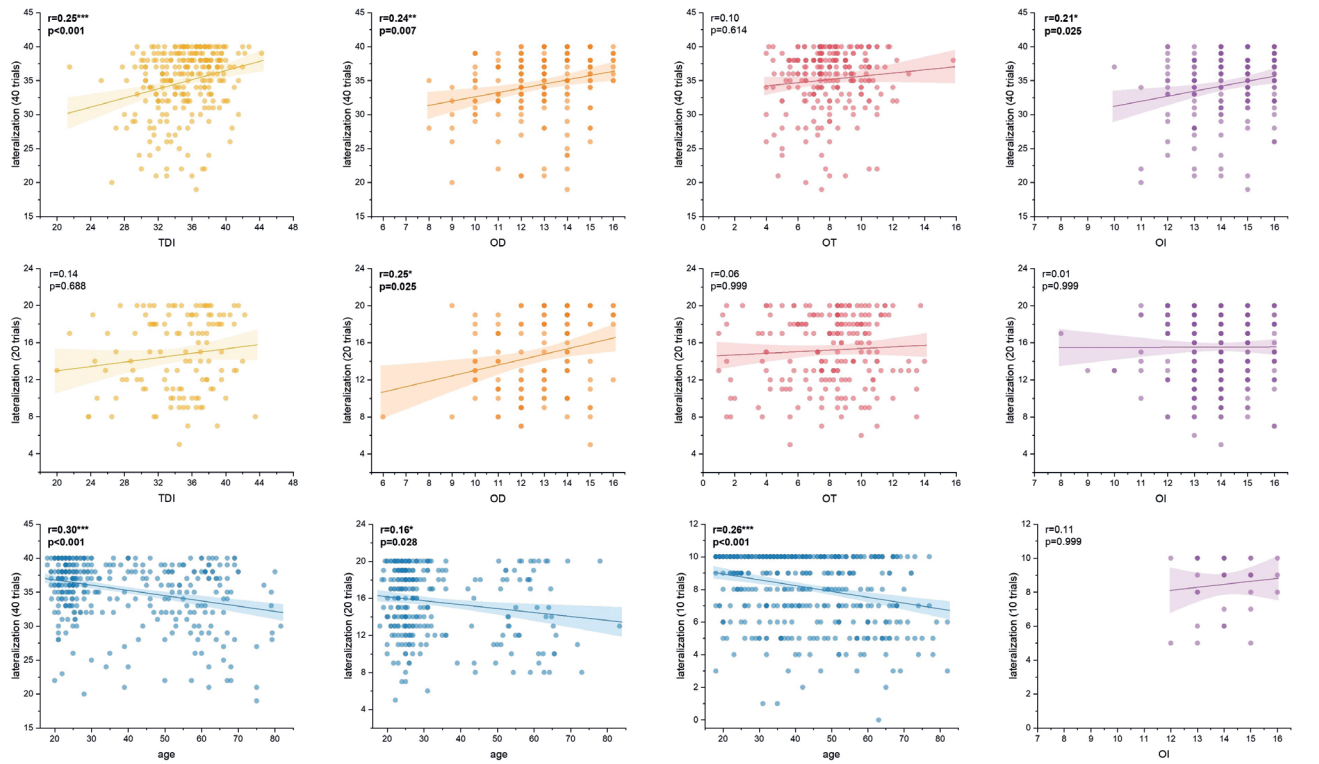

Figure 4. Correlations between lateralization scores and various measures. The density of data points is indicated by the shading intensity, where darker shades represent a higher number of overlapping points. The linear trends are indicated by solid lines, with shadow areas representing the 95% confidence intervals. TDI: "Sniffin' Sticks" composite threshold, discrimination, and identification score, OT: "Sniffin' Sticks" odor threshold score, OD: "Sniffin' Sticks" odor discrimination score, OI: "Sniffin' Sticks" odor identification score; *: p<0.05, **: p<0.01, ***: p<0.001.

exclusion principle to identify which side received the odorless stimulus, which is also part of the discrimination process. Women and men showed similar performance in the 40-trial and 10-trial versions across all age groups. However, in the 20-trial version, women aged 18-25 outperformed men, likely due to better odor discrimination scores. The other age groups did not show sex differences in odor discrimination or lateralization performance. We thus still consider that lateralization ability is overall comparable between men and women.

Several limitations should be discussed. Firstly, while the study established normative values with an appropriate sample size for each trial version, some age groups had small sample sizes, such as the 20-trial version for those over 65 years, which included only 9 participants. To confirm the stability of these cutoff values, larger sample sizes are needed. Secondly, the study focused on healthy individuals and did not include participants with pathologies or compare lateralization performance to other trigeminal-related tests. To examine the clinical usefulness, future research should include patients with chronic nasal obstruction or rhinosinusitis [13,38,39], and compare odor lateralization with other tests, such as nasal patency ratings or CO_2 threshold tests [17,18,37]. Additionally, the normative data were based on eucalyptol, which activates TRPM8 trigeminal receptors but also has a strong olfactory component. Comparing these cutoff values with those from other irritants, like menthol, which also activates TRPM8 but has a different olfactory component, would be valuable. Further research could also explore irritants that activate other trigeminal receptors, like TRPV1, TRPV3, or TRPA1, to better understand intranasal trigeminal function. Finally, as the lateralization test can be conducted using various instruments, it might be valuable to assess the repeatability of these results with other devices (e.g. olfactometer).

Conclusion

Our data provide a reference distribution of the eucalyptus lateralization task, showing the approximate percentile of a given score relative to the performance of healthy individuals. Considering both the above-chance cutoff and the actual distribution cutoff, the 40-trial version is more useful than the 20-trial and 10-trial versions. For the 40-trial version, scores of ≥33 indicate a normal range of trigeminal lateralization ability; scores between 27 and 32 fall into a "grey area" for further assessments; and scores below 27 suggest decreased lateralization ability. For the 20-trial and 10-trial versions, scores of <6 out of 10 items or <11 out of 20 items indicate "decreased" ability, while scores of ≥9 out of 10 items or ≥15 out of 20 items indicate a "normal" lateralization ability. Scores between 6-8 out of 10 items or 11-14 out of 20 items warrant further assessment. The 40-trial lateralization task could serve as an adjunctive examination of intranasal trigeminal functions, but future studies should include pathological cases to examine its clinical usefulness.

Authorship contribution

YM: data analysis and interpretation, manuscript drafting and revision, and final approval of the manuscript; AH: data acquisition, manuscript revision, and final approval of the manuscript; AKH: manuscript revision and final approval of the manuscript; IK: data acquisition, manuscript revision and final approval of the manuscript; TH: study conception, data acquisition, manuscript revision, and final approval of the manuscript.

Conflict of interest

The authors declare no competing financial interests.

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