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SHORT COMMUNICATION

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Comparison of trigeminal lateralization with differing stimulants

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Abstract

Trigeminal-specific stimulants have been shown to activate different receptors preferentially and this likely accounts for variation in sensory perception. It is unclear whether trigeminal sensitivity is similar across different transient receptor potential (TRP) receptors or if dysfunction of different receptors results in differing patient symptoms. Therefore, a prospective cohort study was conducted, consisting of trigeminal lateralization testing with three different stimulants (eucalyptol, isothiocyanate, acetic acid), olfaction testing with Sniffin' Sticks, and measurement of various patient-reported outcome measures (PROMs). A total of 50 participants were enrolled across the olfactory spectrum. Mean TDI score was 27.1 ± 8.3 (range 7.0–39.5) with 38% normosmic and 62% dysosmic. Mean trigeminal lateralization scores out of 20 in the overall cohort were 16.18 (2.78) for eucalyptol, 14.94 (3.49) for mustard oil, and 15.28 (3.68) for vinegar. Eucalyptol showed a significant correlation with threshold scores of Sniffin' Sticks. A significant correlation was found between acetic acid and various PROMs. None of the lateralization scores of the trigeminal stimulants correlated to each other significantly and there was no correlation to age. The lack of correlation suggests that the measured sensitivity of one type of TRP receptor may not translate to similar sensitivity of the other receptors. Additional investigations with TRPV1 and TRPA1 agonists are needed to corroborate our findings.

KEYWORDS

chemosensory, olfaction, trigeminal, TRP receptor

Key Points

It is unclear whether trigeminal sensitivity is similar across different TRP receptors or if dysfunction of different receptors results in differing patient symptoms. A prospective cohort study was conducted, consisting of trigeminal lateralization testing with three different stimulants (eucalyptol, isothiocyanate, acetic acid), olfaction testing with Sniffin' Sticks, and measurement of various patient-reported

outcome measures. None of the lateralization scores of the trigeminal stimulants correlated to each other significantly. The lack of correlation suggests that the measured sensitivity of one type of TRP receptor may not translate to similar sensitivity of the other receptors. Additional investigations with TRPV1 and TRPA1 agonists are needed to corroborate our findings.

INTRODUCTION

The trigeminal system is involved with nasal perception of odorants and airflow.[1] Trigeminal dysfunction has been noted in patients with olfactory loss and some rhinologic conditions, including empty nose syndrome, chronic rhinosinusitis, and allergic rhinitis.[1] Trigeminal function has been measured using various methods, including lateralization of trigeminal activating stimulants or gaseous CO_2.[2] Trigeminal-specific stimulants have been shown to activate different receptors preferentially and this likely accounts for variation in sensory perception. For example, eucalyptol activates transient receptor potential melastatin 8 (TRPM8) with a cool sensation, isothiocyanate (mustard oil) activates transient receptor potential (TRP) ankyrin 1 (TRPA1) with a warm or stinging sensation, and acetic acid (vinegar) activates TRP vanillanoid 1 (TRPV1) with a burning sensation.[3] It is unknown whether trigeminal sensitivity is similar across these receptors or if dysfunction of different receptors results in differing patient symptoms. Therefore, this study aims to perform trigeminal lateralization with three inhaled stimulants known to activate different TRP receptors and correlate testing between each stimulant, to psychophysical olfactory testing, age, and various patient reported outcome measures (PROMs).

METHODS

This prospective cohort study was approved by the Medical University of South Carolina's institutional review board (Pro00109603). Subjects aged 18+ years who were able to consent and complete study questions in English were enrolled. We aimed to enroll participants from a pool of clinic patients, research patients, and staff members, across the olfactory spectrum, as established by Sniffin' Sticks Threshold, Discrimination and Identification (TDI) total score of ≥31 defined as normosmic and <31 defined as dysosmic. Exclusion criteria were as follows: any transient otolaryngologic condition in the last 2 weeks, history of nose bleeds, crusting, ulceration or perforation, use of topical decongestant within the last week, pregnancy, immunocompromise/immunosuppression, allergy/sensitivity to silicone or testing devices, and medical conditions that would prevent study completion.

Each subject completed all study procedures in one to two sessions within a week. Testing consisted of trigeminal lateralization with 20 trials of each stimulant described below, olfaction testing with Sniffin' Sticks, and various PROMs. Trigeminal lateralization was performed with two 250 mL bottles containing 30 mL of stimulant. Bottles were squeezed simultaneously to deliver a 15 mL puff of air via nasal spout. Participants were instructed to identify which nostril had the stimulant. The following stimulant concentrations as previously described in the literature were mixed with 1, 2 propanediol: 60% v/v eucalyptol, 0.75% isothiocyanate, and 12.5% acetic acid.[3,4] Lateralization was scored as percent correct out of 20.

PROMs included Questionnaire for Olfactory Disorders (QOD-NS) and visual analog scales (VAS, from 0to10 cm, where 0 = *no symptoms* and 10 = *worst possible symptoms*).

Data analysis was performed using SPSS v27.0.1 (IBM Corporation). After assessing normality with Shapiro–Wilk tests, outcomes were correlated with Spearman's rank correlation. A $P < 0.05$ was considered statistically significant.

RESULTS

Demographics

Fifty participants were enrolled, of which 28 (56%) were female. The mean age was 40.5 years, ranging from 22 to 77. Previous history of sinus surgery was reported by seven (14%) participants and nasal surgery by eight (16%).

Psychophysical testing results

Mean TDI score was 27.1 ± 8.3 (range 7.0–39.5) with 38% normosmic and 62% dysosmic. Mean trigeminal lateralization scores in the overall cohort were 16.18 (2.78) for eucalyptol, 14.94 (3.49) for mustard oil, and 15.28 (3.68) for vinegar. Mean scores by olfactory status (normosmic vs. dysosmic) are listed in Table 1.

TABLE 1 Mean trigeminal lateralization scores and standard deviations by olfactory status.

Groups	Eucalyptol	Acetic acid	Isothiocyanate
Dysosmics	15.71 (2.98)	15.00 (3.54)	15.23 (3.82)
Normosmics	16.95 (2.73)	14.84 (3.50)	15.37 (3.53)
P value	0.104	0.878	0.894

TABLE 2 Spearman rank correlations between trigeminal testing and olfactory testing.

Item	Trigeminal stimulants Eucalyptol	Vinegar	Mustard
Trigeminal stimulants			
Eucalyptol	1.000	0.105	−0.166
vinegar	0.105	1.000	0.161
mustard	−0.166	0.161	1.000
Threshold	0.314*	0.095	0.072
Sniffin' Sticks			
Discrimination	0.116	0.195	−0.230
Identification	0.050	0.096	0.037
TDI total	0.212	0.143	0.008

Abbreviation: TDI, Threshold, Discrimination and Identification.
*$P < 0.05$.

Relationship between different trigeminal stimulants and olfaction

Eucalyptol showed a significant correlation with threshold scores of Sniffin' Sticks. None of the lateralization scores of the trigeminal stimulants correlated to each other significantly (Table 2).

When comparing lateralization scores by olfactory status, there were no significant differences (Table 1).

Correlation between different trigeminal stimulants, age, and PROMs

A significant correlation was found between acetic acid and PROMs, mainly VAS of the impact of smell loss and specific questions of QOD-NS. Mustard was correlated to some VAS of the impact of sensory loss (Table 3). Correlation to age was not significant.

DISCUSSION

While it is known that activation of various TRP receptors results in a spectrum of sensory perception, it is unknown if the function of these receptors varies. We found that lateralization between the different trigeminal stimulants did not correlate. Our findings contrast those reported by Frasnelli et al.,[3] who found significant correlations between menthol, eucalyptol, and mustard. However, it is difficult to make direct comparisons due to differing cohort size, inclusion criteria, and number of trials for each stimulant lateralization. In addition, their stimulants only tested two different TRP receptors. Our results suggest that different aspects of the trigeminal nerve should be tested in each individual to assess the nerve's function as a whole. The lack of correlation

TABLE 3 Spearman rank correlations between trigeminal testing and PROMs.

Item	Trigeminal stimulants Eucalyptol	Vinegar	Mustard
Age	−0.163	−0.158	0.051
VAS symptoms in last 3 months			
Nasal obstruction	0.112	0.057	0.246
Nasal drainage	0.081	−0.232	0.030
Facial pain	0.007	−0.254	0.117
Smell loss	0.061	−0.174	0.058
How often do you do the following?[a]			
Notice your memory of things smelled/tasted different from present	−0.005	−0.344*	−0.070
Feel you miss certain fragrances that you can no longer smell	−0.162	−0.271	0.135
Find those around you notice smells that you cannot	−0.191	−0.237	0.091
VAS Impact of Smell loss on:			
Mood	0.167	−0.322*	0.043
Food	0.037	−0.254*	0.252
Social	0.019	−0.386*	0.155
Gas leak	0.135	−0.302*	0.212
Hygiene	−0.034	−0.322*	0.056
Sex	0.066	−0.197	0.177
Cooking	0.187	−0.212	0.193
Appetite	0.350*	−0.256	0.057
Weight	0.196	−0.261	0.146
Overall smell	−0.115	−0.238	0.133
VAS Impact of sensory loss			
Warmth in mouth	0.041	0.038	0.312*
Coolness in mouth	0.063	−0.002	0.267
Warmth in nose	0.189	−0.190	0.214
Coolness in nose	0.091	−0.055	0.145
Warmth on skin	0.131	−0.101	0.155
Coolness on skin	0.063	−0.047	0.208
Texture of food	0.090	−0.201	0.213
Spicy	0.101	−0.173	0.185
Light touch	0.071	−0.052	0.253
Painful touch	0.302*	−0.063	0.293*
Overall sensory	−0.076	0.011	0.359*
QOD-NS total	−0.059	−0.277	0.143

Abbreviations: PROM, patient-reported outcome measures; QOD-NS, Questionnaire of Olfactory Disorders-Negative Statements; VAS, visual analog scale.
[a]scale of 0 (*never*), 1 (*rarely*), 2 (*sometimes*), 3 (*often*), 4 (*always*);
*$P < 0.05$.

suggests that the measured sensitivity of one type of TRP receptor may not translate to similar sensitivity of the other receptors. In this study, we used previously published concentrations of known stimulants, but it may be that using different concentrations or stimulants would demonstrate stronger correlations.

Similar to prior studies, we found that eucalyptol significantly correlated to olfaction, specifically threshold. We did not find a correlation between psychophysical olfaction and acetic acid or mustard, which has not been previously studied.[5–7] Prior studies have also reported correlation of trigeminal testing with age, but again, most of these studies examined eucalyptol or other TRPM8 activators and have not examined other stimulants.[5–8] As this is a preliminary, exploratory study, we recommend that additional investigations with TRPV1 and TRPA1 agonists and varying concentrations are needed to corroborate our findings.

Acetic acid had a significant correlation to PROMs, though the strength of association was weak. This may indicate that TRPV1 receptor function has the greatest impact on quality of life and subjective symptoms. Since TRPV1 is known to play a role in nociception and has been shown to be positively correlated to pain scores, it is not surprising that TRPV1-specific stimulants are correlated to other PROMs. Further studies with other TRPV1-specific stimulants are needed to confirm the impact of TRPV1 receptor function.

AUTHOR CONTRIBUTIONS

Tiffany Chen: Data collection, data analysis, manuscript drafting and editing. **Nicolas S. Poupore**: Data collection, manuscript drafting and editing. **Michael C. Shih**: Data collection, manuscript drafting and editing. **Thomas S. Edwards**: Data analysis, manuscript drafting and editing. **Shaun A. Nguyen**: Data analysis, manuscript drafting and editing. **Zachary M. Soler**: Study design, manuscript drafting and editing. **Rodney J. Schlosser**: Study design, data collection, data analysis, manuscript drafting and editing.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Professor Shaun A. Nguyen is a member of World Journal of Otorhinolaryngology – Head & Neck Surgery (WJOHNS) editorial board and is not involved in the peer review process of this article. [Correction added on 10 November 2023, after first online publication: The section CONFLICT OF INTEREST STATEMENT was revised.]

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by and follows all regulations stipulated by the Medical University of South Carolina's institutional review board (Pro00109603).

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