Effectiveness of Olfactory Training on Different Severities of Posttraumatic Loss of Smell

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Objective/Hypothesis: A common, lasting condition from traumatic brain injury is impairment to smell. In patients with olfactory impairment, recent meta-analyses have demonstrated that olfactory training consistently improves higher-order functions, such as odor identification. The focus of this work was to assess effects of olfactory training (OT) in posttraumatic olfactory loss patients through several metrics including psychophysical, olfactory bulb (OB) volume, and functional magnetic resonance imaging.

Study Design: Prospective cohort study.

Methods: Sniffin' Sticks were used to classify two patient groups (anosmic [N = 23] and hyposmic [N = 14]) and measure changes after OT. Additionally patients were asked the intensity, valence, and uncued identification of odors presented (coffee and peach) within the magnetic resonance imaging scanner before and after olfactory training. Olfactory training was performed twice daily with a four-odor training set for 24 weeks, and sets were replaced halfway through the entire training session (~12 weeks).

Results: Patients had an increase in test scores (threshold and identification) and in-scanner intensity ratings and identification. Anosmic patients showed improved olfactory thresholds to 2-phenylethanol, increased intensity ratings, and activation in the right superior frontal gyrus (SFG) to odors after OT. Hyposmic patients were able to identify odors better after training. This behavior was mirrored with increased, ipsilateral activations in semantic processing areas such as Broca's area, left angular gyrus, and left SFG.

Conclusions: Taken together, along with neither patient group showing changes in OB volumes, OT improves olfactory performance in patients with posttraumatic olfactory loss and seems to be driven, at least in part, by top-down processes (central) rather than bottom-up (peripheral).

Key Words: Smell, olfactory training, impairment, traumatic brain injury, imaging.

Levels of Evidence: 2

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INTRODUCTION

Decreased olfactory function is a common, lasting condition occurring after physical injury from an impact, diagnosed as posttraumatic olfactory loss.[1] The more serious the injury, the more often disturbances in smell functionality exist.[2,3] Several mechanisms may lead to olfactory impairment, including 1) Injuries of the nose and facial bones leading to damage of the olfactory epithelium,[4,5] 2) lesions of olfactory bulb (OB) or the fila olfactoria,[6–8] or 3) damage to central structures.[3,9]

Olfactory impairment from severe brain trauma puts patients in life-threatening conditions. Its olfactory complications fade into the background, and attention on the issue may only occur at the rehabilitation stage.[8] Natural recovery occurs, typically within the first 6 months to 1 year after the incidence.[1,10,11] However, the chances of improvement reduces after 2 years of loss.[12,13] This olfactory impairment can lead to a major loss in quality of life.[14] For instance, the decreased perception of flavor may lead to appetite and weight changes,[15] whereas an overall lower odor sensitivity decreases awareness of health-related hazards such as consumption of spoiled food and gas leakages or fires.[16] Therefore, research is needed to determine effective therapies that increase the recovery of smell loss.

For posttraumatic patients, spontaneous olfaction recovery may happen within the first weeks of the trauma incidence,[2] whereas extended natural recovery or treatment has resulted in a 10% to 39% improvement within periods of 14 months to 6 years from the traumatic event.[1,2,10,17] Therapies using corticosteroids have shown improvements, but no improvement different from spontaneous recovery has been shown.[18–20] Similarly a systemic use of vitamin A (10.000 IU daily) showed no positive effect[21]; however, improvement has recently been seen with the application of zinc gluconate.[22] Olfactory training seems to be promising and has been shown to help regenerate capacity of the olfactory system in both animal and human models[23–28] The limited neurological research in this area points to plasticity; however, the ways in which the brain reorganizes would differ among levels of olfactory dysfunction.

The focus of this work was to assess effects of olfactory training in posttraumatic patients with varying levels of olfactory loss (e.g., complete or partial loss) through several metrics including psychophysical measurements, OB volume, and functional magnetic resonance imaging (fMRI). The OB volumes of healthy individuals are larger compared to posttraumatic patients.[1,9,29] Structural and fMRI have been successful at revealing dysfunction in olfactory perception[29] and predicting increased olfactory functionality with rehabilitation practices such as olfactory training.[30–34] To our knowledge, this study is the first to measure functional changes in hyposmic patients after olfactory training. We hypothesize an increased identification ability after olfactory training among patients suffering olfactory loss after head trauma, with increased activation in related semantic processing areas. Additionally, this change may be more prevalent for hyposmic patients than anosmic patients showing increased activation in areas processing sensory integration or attention.

MATERIALS AND METHODS

Participants
Forty-two participants (20 women) ranging in age from 23 to 74 years (mean = 52.2 years, standard deviation = 12.1 years) were evaluated in the study. Participants were assigned to two patient groups (Table I) using the Sniffin' Sticks test battery,[35] which is comprised of tests for odor threshold, odor discrimination, and odor identification (TDI). Recruitment for patients with olfactory loss following head trauma was carried out over a period of 2 years with a standard ear, nose, and throat examination. All participants were right-handed[36] and had no major comorbidities. All participants provided written informed consent. The study was approved by the ethics committee of the medical faculty at the Dresden University of Technology. All subjects were instructed to not eat or drink an hour before the testing procedure.

Olfactory Training
Olfactory training was performed by both patient groups (hyposmic and anosmic) for at least a 24-week period or longer.[24] Four odorants (phenylethyl alcohol: rose odor, eucalyptol: eucalyptus odor, citronellal: lemon odor, and eugenol: cloves odor) were chosen. Cotton balls were impregnated with these odorants, placed in opaque bottles, and given to participants. For training, they were instructed to sniff each odor for approximately 15 seconds twice a day. Olfactory training bottles were replaced after 12 weeks.

Procedure
Each group underwent an fMRI scanning sequence with a block design in which two odors (peach and coffee; Frey & Lau, Henstedt-Ulzburg, Germany) were presented intranasally to the left and right nostril at neat concentrations while humidified air was used as the control.[37] The odor stimuli were presented with a mobile olfactometer[38] (flow 2 L/min). With a block design paradigm, odors were presented for 1 second with an interstimulus interval of 2 seconds in six blocks of 20 seconds (ON period) with intermittent 20 seconds OFF blocks (presenting only air). After each ON block, individuals were asked to verbally identify the odor and rate its intensity (0 to 10; not perceived to very strongly perceived) and pleasantness (−5 to +5; extremely unpleasant to extremely pleasant). Four series blocks were used for each condition: 1) peach on left side, 2) peach on right side, 3) coffee on left side, and 4) coffee on right side. Within an ON or OFF block, eight fMRI volumes (T2) were taken for a total of 96 images and prior to stimuli conditions a structural image (T1) was acquired. Following the block conditions, the participants were asked to close their eyes (to minimize any agitation) and a detailed image (T2) of the front and middle portion of the skull base was taken to capture the OB.[39]

After the fMRI session, participants were instructed on olfactory training and the follow-up fMRI session at least 6 months later. During the follow-up session, individuals were reevaluated with Sniffin' Sticks and repeated the exact fMRI sequence. After the follow-up session, a posttraining questionnaire about compliance with training procedure and experience with olfactory training was filled-out.

fMRI Scanning Parameters
A 1.5 T magnetic resonance imaging scanner (Siemens Sonata; Siemens, Erlangen, Germany) and a full-head eight-channel receiver coil were used for image acquisition. A gradient echo T2-sensitive echo planar imaging sequence was employed for 96 functional volumes/condition in thirty-three slice locations, covering the entire head (repetition time [TR]: 2500 ms, echo time [TE]: 40 ms, image matrix: 64×64, in-plane resolution: 3 mm, through-plane resolution: 3.75 mm). Images were acquired in the axial plane oriented parallel to the planum sphenoidale to minimize artifacts. TE was selected because it had been established for 1.5 Tesla scanners for the imaging of limbic structures.[40] A full brain (192 slices) T1-weighted turbo FLASH three-dimensional sequence was acquired to overlay functional data (TR: 2,180 ms, TE: 3.93 ms, slice thickness: 1 mm).

Additionally, the OB was captured using a T2-weighted fast spin-echo imaging sequence (TR: 4,800 ms, TE: 125 ms, slice thickness: 2 mm) without an interslice gap in the coronal plane covering the anterior and middle segments of the base of the skull.[39]

Structural Data Processing
The same preprocessing procedures were used for the high-resolution T2 OB images. OB volumetric measurements were done by manual segmentation of the coronal slices through the OBs using the AMIRA system (Visage Imaging, Carlsbad, CA). For reliability, the measurements of OBs always took place at least twice by the same examiner. If the volumes of the two measurements differed by more than 10%, a third measurement took place.[41]

TABLE I.
Olfactory Ability Classification and Patient Details of Participants in Study.

Group	No. (No. of Women)	Age Range, yr (Mean, SD)	TDI ± SD	Months Since Trauma ± SD
Hyposmic	18 (11)	29–74 (51.1, 11.8)	22.0 ± 4.1	34.2 ± 49.2
Anosmic	24 (9)	23–72 (54.2, 13.7)	11.3 ± 2.6	24.7 ± 20.6

SD = standard deviation; TDI = threshold, discrimination, and identification.

Functional Data Processing and Statistics

Pre- and postprocessing of the structural and functional data was performed using SPM8 (Statistical Parametric Mapping; Wellcome Centre for Human Neuroimaging, University College London, London, United Kingdom). Functional images were motion corrected and coregistered with the respective anatomical images, normalized (to Montreal Neurological Institute [MNI] template) and smoothed ($7 \times 7 \times 7$ mm^3 full width at half maximum Gaussian kernel). Alternating ON and OFF blocks within each condition were contrasted session-wise for each subject, the odor and nasal site was generalized, and the resulting data were fed into the group analyses.

In the group analysis, a paired t test was used to compare olfactory training within patient groups (hyposmic and anosmic). A voxel threshold of ≥ 6 was used (with an expected voxels/cluster of 3.9 and T threshold of 3.61).

Statistical Analysis

Data analysis was performed with JMP (version 13.0; SAS Institute; Cary, NC). Left and right OBs were compared separately within groups with a paired t test. Correlations according to Pearson were computed between OB volume and Sniffin' Sticks subtests.

An independent t test was done for pretraining between groups for Sniffin' Sticks composite TDI scores. Pre- and posttraining in-scanner valence and intensity ratings were evaluated within groups with a paired t test. Similarly, overall TDI test score and its subtests scores were compared within groups pre- and posttraining with a paired t test. To determine the probability of correctly identifying the name of the odor presented during fMRI sessions, training was regressed on correctness of verbal label given to that odor (yes or no) while controlling for trauma duration.

RESULTS

One male anosmic and four hyposmic patients (two males) were not evaluated in the follow-up session due to an absence or medical condition arising after the initial session (e.g., one patient had a stroke). Additionally, one male anosmic and two hyposmic patients (one male) were not included in the OB analysis due to artifacts.

Training Outcomes

On average, the duration of olfactory training between the initiation and final examination was 7.1 months ($\pm$ 1.4 months), with a minimum training duration of 6 months in both groups. Eighteen patients (50%) reported that they applied the training regularly twice a day as instructed, whereas 15 (40 %) used it once or twice a day, and four (10%) reported applying less than 7 times a week. There was no correlation between regularity of training and change in TDI value and bulb volume. Sixty-five percent of patients rated their sense of smell as a better than the start of training, whereas 35% rated their smell ability as unchanged.

Psychophysical Differences

Training increased overall TDI (t [36] = 2.85, P = .007), threshold scores (t [36] = 2.33, P = .03), and identification scores (t [36] = 2.14, P = .04) for olfactory impaired individuals (both anosmic and hyposmic patients). There were no improvements in discrimination scores (t [36] = 1.31, P = .2). Within the impaired groups, anosmic patients showed a significant increase in overall TDI from training from 11.53 ($\pm$ 2.92) to 15.10 ($\pm$ 6.47) (t [22] = 2.29, P = .03), whereas hyposmic patients had a nonsignificant improvement in functionality from 22.68 ($\pm$ 3.62) to 25.14 ($\pm$ 4.50) (t [13] = 1.68, P = .12). Specifically, there was a significant increase in threshold for anosmic patients (t [22] = 2.08, P = .049), and a trend toward increased identification for hyposmic patients (t [13] = 1.90, P = .08). There were no other significant findings within groups for the other olfactory subtests (P > .05).

One subject did not respond during the qualitative questions about odors presented within the scanner during the second posttraining session and was excluded. Looking across the impaired groups, individuals perceived higher odor intensities (t [35] = 3.83, P < .001) and could name the odors better after olfactory training (odds ratio: 1.73, χ^2(65) = 4.37, P = .04). There was no impact on the hedonics of the either odor (P > .05). Within the groups, anosmic (t [21] = 2.82, P = .01) and hyposmic patients (t [13] = 2.58, P = .02) perceived higher intensities of the odors, and anosmics trended toward an increased pleasantness of the odor (t [21] = 2.05, P = .053), unlike hyposmic patients (t [13] = 0.06, P = .95). On average, anosmic patients were still unable to name one of the two odors pre- (7% correct) and posttraining (15% correct), whereas hyposmic patients increased their ability to name odors posttraining from 45% to 61%. Figure 1 shows the intensity, hedonics, and probability of identifying odors presented within the scanner for each impaired patient group.

Structural Brain Differences

There were no significant volume differences pre- and posttraining within hyposmic nor anosmic patient groups for the left (respectively, t [11] = 0.76, P = .47 and t [18] = 0.98, P = .34) and right (respectively, t [14] = 1.02, P = .33 and t [19] = 0.1, P = .92) OBs. There were no significant correlations between changes in threshold with changes in OB volumes for anosmic (r = −0.05, P = .82, left side; r = 0.01, P = .98, right side) and hyposmic patients (r = 0.10, P = .75, left side; r = −0.07, P = .86, right side). Similarly, no significant correlations existed for discrimination and identification (P > .05).

Functional Brain Differences

For hyposmic patients, a large region in the right dorsal anterior cingulate was activated after olfactory training (t = 5.72) (Fig. 2). Table II shows the other activations after training, which were predominantly in the left hemisphere including the left pars triangularis (Broca's area), left angular gyrus, left medial frontal gyrus, and left superior frontal gyrus. For anosmic patients, only the right superior frontal gyrus was significantly more active after olfactory training (t = 6.41; coordinates: x: 12mm, y: 35mm, z: 53mm).
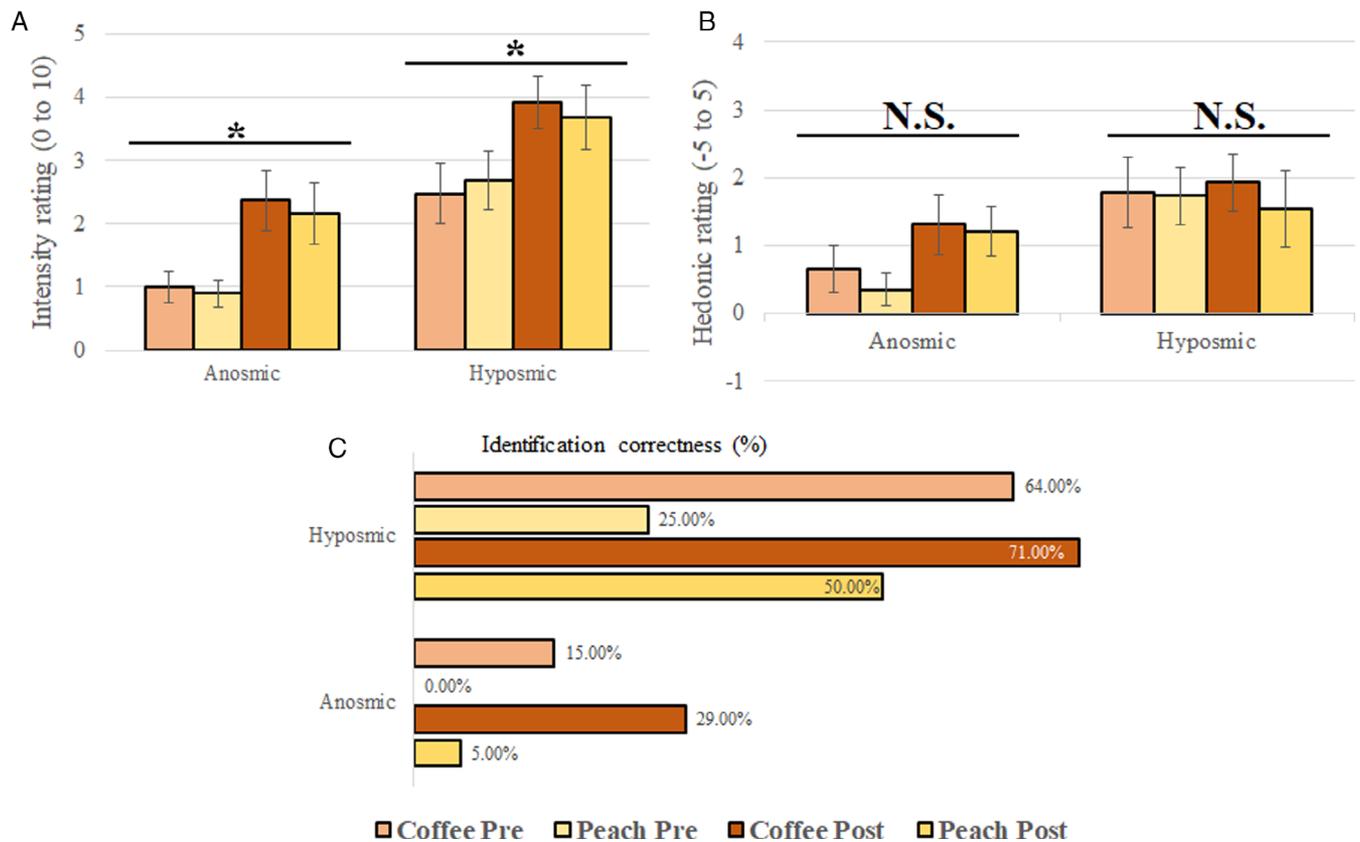
Fig. 1. Ratings of intensity (A), liking (B), and identification (C) of odor presented within the scanner. N.S. = Not significant. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

DISCUSSION

Olfactory training has proved to increase olfactory ability among patients with olfactory impairment. In our study, we add to this growing body of work showing increases in olfactory performance in patients with post-traumatic olfactory impairment. Impaired groups had increased olfactory tests scores and reported an increase in intensity and ability to identify odors. Interestingly, anosmic patients saw greater improvements in threshold, whereas identification seemed to improve more for hyposmic patients.

Hyposmic Olfactory Improvement

Although identification scores only trended toward an improvement, in-scanner measurements of intensity and uncued identification showed major improvements after olfactory training. For instance, hyposmic patients doubled their percentage of correct identification for peach odor from 25% to 50%.[27,28] This behavioral change was mirrored by increased activity in semantic processing centers such as left pars triangularis, or Broca's area,[42] and activations of several areas with well-defined pathways to this area (left angular gyrus[43] and left superior frontal gyrus[44]).

The angular gyrus (AG) connects to ipsilateral frontal areas via the superior longitudinal fasciculus.[45] Semantic processing is the most consistent function that activates the left AG.[46–50] Similar to the AG, the left superior frontal gyrus is strongly connected to Broca's area,[44] and is associated with semantic functions.[51] Our study saw activations in the posterior superior frontal gyrus, which has anatomical connections with the thalamus, precentral gyrus, and inferior frontal gyrus.[52] In a recent study, training individuals for 3 days to associate a specific smell with lexicosemantic features generated large activations in the superior frontal gyrus (SFG) and AG compared to perceptual learning or no training. Training effects showed increased ability in a semantic task that positively correlated with SFG activations.[47] Additionally, another study using a yes-no odor recognition paradigm showed the middle frontal gyrus, cingulate, and AG to be activated during odor recognition.[53] In the current study, we show activation in these areas after olfactory training for hyposmic patients whose ability to identify the odors presented increased.

The increased intensity and identification of odors would make them more familiar and detectable to patients. This change did not impact subjective hedonics, but may explain the activation in the right dorsal anterior cingulate cortex (dACC). In an early positron emission tomography study, participants were presented several odors and asked if they could detect it and if it was familiar. Contrasting the familiarity with the detection trail scans, there were significant activation in the right medial frontal gyrus, left inferior frontal gyrus, left SFG, and right dACC.[54] Interestingly, increased conflict monitoring of the dACC has been reported with an increased complexity of
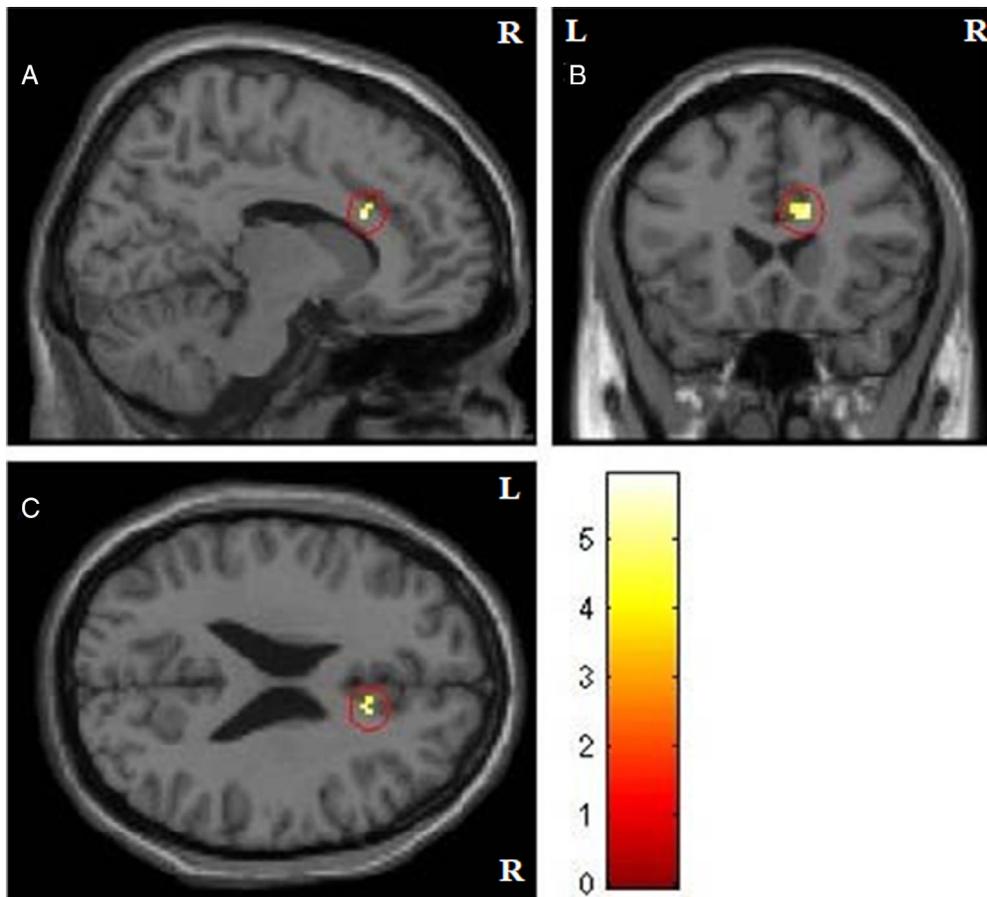
Fig. 2. Activated right anterior cingulate for paired comparison of hyposmic patients before and after olfactory training. (A–C) Sagittal, coronal, and horizontal plane depictions of activated area in the brain, respectively. The activation cluster of right anterior cingulate ($t = 5.72$) is marked by the red circle in the standardized brain, for comparison according to prior olfactory training of hyposmic patients. L = left; R = right.

odors.[48] In our study, hyposmic patients most likely acknowledged more features in the odors adding complexity and increasing their ability to identify them.

Anosmic Olfactory Improvement

For anosmic patients, in line with previous studies,[24,32,34,55] thresholds improved whereas identification showed some improvement, but still less than

TABLE II.
Significant Activated Clusters After Olfactory Training for Hyposmic Patients.

Region	x	y	z	Voxel	Peak T
Right dorsal anterior cingulate	12	22	24	18	5.72
Left pars triangularis	−46	38	8	14	5.6
Left superior frontal gyrus	0	34	42	12	5.39
Left angular gyrus	−46	−66	48	11	5.37
Left medial frontal gyrus	−26	12	46	7	4.38
Left globus pallidus	−20	−6	4	6	4.27

Shown are the calculated clusters from the group hyposmia analysis comparing before and after application of olfactory training. All clusters present were significant (uncorrected, $P < .001$).

chance. However, the current study showed no increase in OB size. Thus, what is driving the lower detection threshold and subsequent increased intensity scores observed in the fMRI scanner? Previously, Kollndorfer and colleagues showed functional connectivity changes after olfactory training in a group of patients with anosmia after upper respiratory infections.[32,33] In one of those studies, one purely trigeminal (CO_2) and two highly bimodal odors (menthol and cinnamaldehyde) were presented pre- and posttraining, and the connectivity of three seed regions representing the olfactory network (caudate nucleus), integrative network (insular cortex), and the somatosensory network (supramarginal gyrus) were obtained. After training, anosmic patients showed an increase in functional connectivity for all networks. In our study, these seed connections may have been established, but the connected regions did not show an increased activation. Instead, significant activation was seen in the right SFG, which may explain the increase in intensity (coinciding with a threshold decrease).[56]

Training Effects on OB

It is important to point out that the improvements in olfactory ability with training did not reflect changes

in the OBs for either patient group.[30,34] Our nonsignificant changes to OB volumes are at odds with studies showing increases in olfactory patients undergoing medical treatment,[29,31] spontaneous recovery,[57] and studies in healthy subjects.[58] The current findings seem to suggest that improvements induced through training in olfactory-impaired individuals may be, at least in part, a top-down effect through plasticity of the central nervous system and increased attention.

Limitations

Our study points to several conclusions that could benefit from additional investigation due to some limitations. We show different functional changes in impairment groups after olfactory training; however, we cannot know how this differs from healthy subjects, as no control was used. Another limitation is the size of the patient group, especially the hyposmic patient group. Future studies should include a control and larger patient sample in their design to measure changes across all levels of olfactory functionality. Furthermore, our study was not designed specifically to measure the amount of processing type involved in functional changes resulting from olfactory training. Thus, future studies should address top-down (central) versus bottom-up (peripheral) processing involved with changes in olfactory perception during training.

CONCLUSION

With neither patient group showing changes in OB volumes, OT improves olfactory performance in patients with posttraumatic olfactory loss and seems to be driven, at least in part, by top-down processes (central) rather than bottom-up (peripheral).

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