JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Association of Olfactory Training With Neural Connectivity in Adults With Postviral Olfactory Dysfunction

Pawina Jiramongkolchai, MD; Michael S. Jones, PhD; Andrew Peterson, MSci; Jake J. Lee, MD; Adam Liebendorfer, BS; Cristine N. Klatt-Cromwell, MD; John S. Schneider, MD, MA; Andrew J. Drescher, MD; M. Allison Ogden, MD; Joseph D. Brunworth, MD; Dorina Kallogjeri, MD, MPH; Sara Kukuljan, BS, RN; Jonathan E. Peelle, PhD; Jay F. Piccirillo, MD

IMPORTANCE Viral upper respiratory tract infections are a major cause of olfactory loss. Olfactory training (OT) is a promising intervention for smell restoration; however, a mechanistic understanding of the changes in neural plasticity induced by OT is absent.

OBJECTIVE To evaluate functional brain connectivity in adults with postviral olfactory dysfunction (PVOD) before and after OT using resting-state functional magnetic resonance imaging.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study, conducted from September 1, 2017, to November 30, 2019, recruited adults with clinically diagnosed or self-reported PVOD of 3 months or longer. Baseline olfaction was measured using the University of Pennsylvania Smell Identification Test (UPSIT) and the Sniffin' Sticks test. Analysis was performed between December 1, 2020, and July 1, 2020.

INTERVENTIONS Participants completed 12 weeks of OT using 4 essential oils: rose, eucalyptus, lemon, and clove. The resting-state functional magnetic resonance imaging measurements were obtained before and after intervention.

MAIN OUTCOME AND MEASURES The primary outcome measure was the change in functional brain connectivity before and after OT. Secondary outcome measures included changes in UPSIT and Sniffin' Sticks test scores, as well as patient-reported changes in treatment response as measured by subjective changes in smell and quality-of-life measures.

RESULTS A total of 16 participants with PVOD (11 female [69%] and 14 White [88%]; mean [SD] age, 60.0 [10.5] years; median duration of smell loss, 12 months [range, 3-240 months]) and 20 control participants (15 [75%] female; 17 [85%] White; mean [SD] age, 55.0 [9.2] years; median UPSIT score, 37 [range, 34-39]) completed the study. At baseline, participants had increased connectivity within the visual cortex when compared with normosmic control participants, a connection that subsequently decreased after OT. Furthermore, 4 other network connectivity values were observed to change after OT, including an increase in connectivity between the left parietal occipital junction, a region of interest associated with olfactory processing, and the cerebellum.

CONCLUSIONS AND RELEVANCE The use of OT is associated with connectivity changes within the visual cortex. This case-control cohort study suggests that there is a visual connection to smell that has not been previously explored with OT and that further studies examining the efficacy of a bimodal visual and OT program are needed.

Viewpoint page 497

Supplemental content

Author Affiliations: Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine in St Louis, St Louis, Missouri (Jiramongkolchai, Jones, Peterson, Lee, Liebendorfer, Klatt-Cromwell, Schneider, Drescher, Ogden, Brunworth, Kallogjeri, Kukuljan, Peelle, Piccirillo); Statistics Editor, *JAMA Otolaryngology—Head and Neck Surgery* (Kallogjeri); Department of Otolaryngology–Head and Neck Surgery, St Louis University School of Medicine, St Louis, Missouri (Brunworth); Editor, *JAMA Otolaryngology—Head and Neck Surgery* (Piccirillo).

Corresponding Author: Pawina Jiramongkolchai, MD, Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine in St Louis, 660 S Euclid Ave, Campus Box 8115, St Louis, MO 63110 (pawina@wustl.edu).

JAMA Otolaryngol Head Neck Surg. 2021;147(6):502-509. doi:10.1001/jamaoto.2021.0086
Published online March 18, 2021.

Postviral olfactory dysfunction (PVOD) is involved in up to 40% of cases of impaired olfaction[1] and is characterized by the sudden onset of anosmia or hyposmia after an upper respiratory tract infection.[2] Up to one-third of individuals with PVOD have improvement in olfactory function within 12 months.[3-6] However, recovery is often incomplete, and, to date, there is no cure.

Anosmia has emerged as a defining symptom of coronavirus disease 2019 (COVID-19), an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[7,8] Given the rapid and widespread transmission of COVID-19 in the US, many US residents infected with SARS-CoV-2 will undoubtedly experience olfactory dysfunction, creating an unprecedented need for effective management and treatment of PVOD.

Olfactory training (OT) is a promising intervention for smell restoration. First described by Hummel et al in 2009,[5] OT involves repeated daily exposure to essential odors representative of common smells (eg, flowery, fruity, or aromatic). Although the underlying mechanism of OT is not well understood, OT is thought, in part, to exploit the unique and dynamic neuroplasticity of the olfactory system. From rodent to primate models, olfactory tract cells, especially at the level of the olfactory bulb, undergo lifelong regeneration and neurogenesis.[9,10]

Task-based functional magnetic resonance imaging (fMRI) studies have been performed to evaluate olfactory processing within the primary olfactory cortex and associated regions of interest. Task-based fMRI measures changes in blood oxygen level-dependent signal in response to a stimulus. Odor-stimulated fMRI, first introduced by Yousem et al,[11] has been used to study olfactory loss in neurodegenerative disorders as well as congenital and acquired hyposmia.[12-16] Using fMRI, OT alters neuronal connectivity for patients with PVOD, with studies[17,18] demonstrating reorganization within the olfactory network and associated somatosensory network. However, these task-based fMRI studies[19,20] have been limited by habituation or desensitization to odors administered during the task, restricting visualization of olfactory activation.

Unlike in task-based fMRI, images in resting-state fMRI (rs-fMRI), also known as functional connectivity MRI, are acquired in the absence of a stimulus. Resting-state fMRI allows multiple networks to be studied at once rather than just specific brain regions activated by a deliberate task. Resting-state fMRI has been used to study how brain connectivity can become disorganized and disrupted by neurodegenerative conditions, such as Alzheimer disease, depression, autism, and schizophrenia.[21,22] In addition, Park et al[23] used rs-fMRI to characterize olfactory dysfunction in patients with traumatic anosmia and found that although intranetwork connectivity of the olfactory network was decreased when compared with control participants, internetwork connectivity of both the olfactory network and whole-brain networks increased. However, the findings of this study were limited by the potential confounder of nonolfactory traumatic brain injury. To date, rs-fMRI has not been used to investigate changes in functional connectivity in patients with PVOD undergoing OT. The objectives of this study were to characterize baseline functional connectivity in adults with PVOD and evaluate the effects of OT on neural connectivity to further elucidate the pathogenesis of PVOD and mechanism of OT.

Key Points

Question What is the baseline functional connectivity in adults with postviral olfactory dysfunction (PVOD), and what changes in functional connectivity are observed after 3 months of olfactory training (OT)?

Findings In this prospective cohort study of 16 adults with PVOD and 20 control participants, an increased connectivity within the visual cortex was observed at baseline in those with PVOD. After 3 months of OT, this connectivity in the visual cortex decreased and was replaced with an increased connection between regions of the brain involved in olfaction.

Meaning These findings suggest a bimodal interaction between the visual and olfactory cortex during OT and that further understanding of the association between these 2 senses for adults with PVOD may be useful to enhance existing OT programs.

Methods

Participants provided written informed consent, and all data were deidentified. This single-institution, prospective cohort study was approved by the Washington University School of Medicine in St Louis Institutional Review Board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The analysis was performed between December 1, 2020, and July 1, 2020.

Participants

Adults 18 to 70 years of age with clinically diagnosed or self-reported postviral olfactory loss of 3 months or longer were eligible to participate. Individuals were excluded if they (1) were a current smoker or had a history of smoking within the past 6 months; (2) had nasal polyps; (3) had exposure to head and/or neck radiotherapy or chemotherapy; (4) had been diagnosed with neurologic disorders; (5) were experiencing a upper respiratory tract infection during the study enrollment; and/or (6) were pregnant or had MRI contraindications. Participants were recruited from September 1, 2017, to November 30, 2019.

Eligible participants were evaluated in the office, and a detailed head and neck history was obtained. Anterior rhinoscopy was performed to evaluate for nasal masses, and the University of Pennsylvania Smell Identification Test (UPSIT; Sensonics International) and the Sniffin' Sticks test (Burghardt) were administered to assess baseline olfactory function.

Control participants sex and age matched (±5 years) to participants with PVOD had normal smell as determined by UPSIT and were recruited for baseline neuroimaging. Individuals with MRI contraindications were excluded.

Interventions and Imaging

Budesonide Nasal Irrigation

Enrolled participants completed a 30-day run-in course of budesonide nasal irrigation to minimize any possible subclinical inflammation that could be contributing to smell loss. Participants were provided with a 1-month supply of budesonide capsules (Genesis Pharmacy), an 8-oz sinus rinse bottle (NeilMed Pharmaceuticals Inc), and a 1-month supply of commercially prepared isotonic salt packets. Participants were instructed to dissolve 2 budesonide capsules (0.5 mg per capsule) into the sinus rinse bottle along with the saline mixture and then irrigate both nasal cavities once daily. After completion of budesonide lavage, participants were reevaluated with UPSIT and the Sniffin' Sticks test. If participants scored below normal on either of the tests, they underwent OT. If participants were treated with corticosteroids by their referring physician before enrollment and had persistent objective olfactory dysfunction, they also began OT.

Olfactory Training

Participants were given 4 opaque vials with 1 mL of 4 essential oils: rose (phenyl ethyl alcohol), eucalyptus (eucalyptol), lemon (citronella), and clove (eugenol), as described by Hummel et al.[5] They were instructed to sniff each of the odors for 20 to 30 seconds twice a day for 12 weeks and to keep a journal to monitor their progress. Participants were also contacted routinely to assess adherence.

fMRI Imaging Acquisition

The MRI data were acquired using an MRI scanner (Siemens Prisma scanner, Siemens Medical Systems) at 3T before and after OT. Scan sequences began with a T1-weighted structural volume using a magnetization-prepared rapid gradient-echo sequence; fMRI images were acquired using a multiband echo planar imaging sequence[24] (repetition time, 1100 milliseconds; echo time, 33 milliseconds; flip angle, 84°; voxel size, 2.6-mm isotropic; multiband factor, 4). After acquisition of the structural scans, 40 minutes of resting-state data were collected in four 10-minute runs.

Primary Outcome Measure

The primary outcome measure was the change in functional connectivity in participants with PVOD, using measurements taken before and after OT. A set of 164 regions of interest (ROIs) from the CONN toolbox[25] were used, supplemented with 23 ROIs determined by prior studies[26,27] to be associated with olfactory processing. The eAppendix in the Supplement gives a full list of the ROIs and coordinates.

Secondary Outcome Measures

Secondary outcome measures included changes in objective sense of smell and patient-reported responses to the intervention. Objective changes in olfaction were measured using UPSIT and the Sniffin' Sticks test. UPSIT has high reliability and applicability across multiple populations[28-30]; UPSIT consists of 4 odor-impregnated booklets that participants scratch and sniff to identify various odors, and scores account for differences in sex.[28] Hyposmia is defined as a score of 19 to 34 for females and 19 to 33 for males. Anosmia for either sex is defined as a score below 18. A score below 5 is highly suggestive of malingering.[28] For UPSIT, an increase by 4 points or more from baseline indicates a clinically meaningful improvement.[31] Like UPSIT, the Sniffin' Sticks test is a reliable and validated tool to assess olfactory function.[32,33] Sniffin' Sticks are odor-encapsulated markers that are used to measure odor detection threshold, discrimination, and identification (TDI). Normosmia is defined as a TDI score >30.5. An increase by 5.5 points or more from baseline is considered meaningful improvement.[34] There appears to be a geographic preference to the use of these tests, with UPSIT most commonly used in North America and the Sniffin' Sticks test most commonly used in Europe. The Sniffin' Sticks test was used in addition to UPSIT to gain familiarity with the former.

Patient-reported secondary outcome measures included patient global response to treatment using a 4-point Likert scale with anchors of 0 (no change) to 4 (total change), subjective change in smell based on a visual analog scale, and changes in scores on the Questionnaire for Olfactory Dysfunction–Negative Statements (QOD-NS).[35] The QOD-NS is a validated 17-item questionnaire that pertains to olfactory-specific quality of life domains adversely impacted by olfactory dysfunction and is inversely scored (maximum score of 51), with higher scores reflective of more impaired quality of life. A standardized minimal clinically important difference for the QOD-NS for PVOD has not been determined.

Statistical Analysis

The sample size for this study was based on feasibility. To date, there is no known effect size for the impact of 30 days of budesonide irrigation followed by OT on the recovery of olfactory function and neuroplasticity for patients with PVOD.

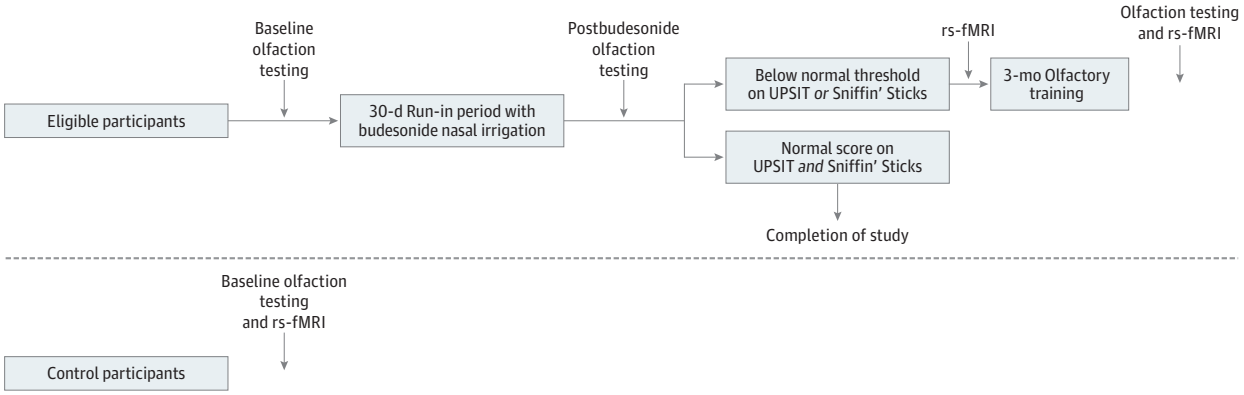
Clinical Data

Standard descriptive statistics were used to describe the study population and distribution of pre- and post-OT scores on UPSIT and the Sniffin' Sticks test. A paired-sample, 2-tailed *t* test or its nonparametric equivalent, the Wilcoxon signed rank test, was used to compare within-subject preintervention and postintervention changes. Median differences in primary and secondary outcome measures before and after intervention and 95% CIs around the point estimate were calculated and reported. All statistical analyses were performed in SPSS statistical software, version 25 (IBM Corp).

Neuroimaging

Resting-state connectivity was analyzed using the CONN toolbox version 18b (https://web.conn-toolbox.org/) and SPM12, version 7487 (Wellcome Trust Centre for Neuroimaging). Preprocessing consisted of realignment of functional images, registration of functional and structural images, segmentation and normalization into MNI (Montreal Neurological Institute) space, smoothing using an 8-mm full-width at half-maximum gaussian kernel, and finally linear detrending followed by bandpass filtering (0.01-0.1 Hz). A histogram of randomly selected functional connectivity pairs for each study participant was then used to guide the selection

Figure 1. Study Flow Diagram



rs-fMRI Indicates resting-state functional magnetic resonance imaging; UPSIT, University of Pennsylvania Smell Identification Test.

of denoising regressors. The final set consisted of (1) 6 motion parameters (linear and quadratic terms) and their first derivatives, (2) signal from white matter and cerebrospinal fluid (mean and first 4 principal components) obtained from anatomical component-based noise correction[36]; (3) frames tagged for scrubbing by the CONN Artifact Detection Tool; and (4) whole-brain global signal.

Functional connectivity values (Fisher *z*-transformed Pearson correlation coefficients) were compared using a paired, 2-tailed *t* test and corrected for multiple comparisons (false discovery rate). $P < .05$ was considered statistically significant. Pretreatment and posttreatment differences were analyzed using a repeated-measures, paired, 2-tailed *t* test. Participant β values for network connections demonstrating a significant change after treatment were correlated against clinical measures.

Results

Patient Characteristics

A total of 20 control participants and 31 participants with PVOD were enrolled in the study (**Figure 1**). Two eligible PVOD participants were excluded on in-office testing because 1 participant had right nasal polyps on anterior rhinoscopy and 1 had an idiopathic cause for smell loss on further questioning. Five participants with PVOD were lost to follow-up. None of the participants improved to normosmia after budesonide lavage. Because of the worsening psychiatric illness unrelated to the study, 1 participant with PVOD was excluded from final analysis. In addition, of the total 23 participants with PVOD who completed smell training and rs-fMRI, 7 were excluded from final neuroimaging analysis because of excessive artifact. Thus, the final study included a total of 16 participants with PVOD (11 female [69%]; 14 White [88%]; mean [SD] age, 60.0 [10.5] years; median duration of smell loss, 12 months [range, 3-240 months]) who completed 3 months of OT and pre- and post-OT rs-fMRI (**Table 1**) and 20 control participants (15 [75%] female; 17 [85%] White; mean [SD] age, 55.0 [9.2] years; median UPSIT score, 37 [range, 34-39]) who completed baseline rs-fMRI. Baseline olfactory function and subjective reports of sense of smell and quality of life are presented in Table 1.

Table 1. Baseline Characteristics of the Participants With Postviral Olfactory Dysfunction[a]

Characteristic	Finding (n = 16)
Age, median (range), y	63 (30-70)
Sex	
Male	5 (31)
Female	11 (69)
Race	
White	14 (87.5)
Black	2 (12.5)
Duration of smell loss, mo	
Median (range)	12 (3-240)
3-12	9 (56)
13-96	4 (25)
97-240	3 (19)
UPSIT score, median (range)	21 (10-33)
TDI score, median (range)	19.0 (8-27.25)
T	1.0 (1.0-4.25)
D	10 (4-12)
I	7 (3-14)
VAS sense of smell score, median (range)	12.0 (0-50)
QOD-NS score, median (range)	11.4 (3.4-16.5)

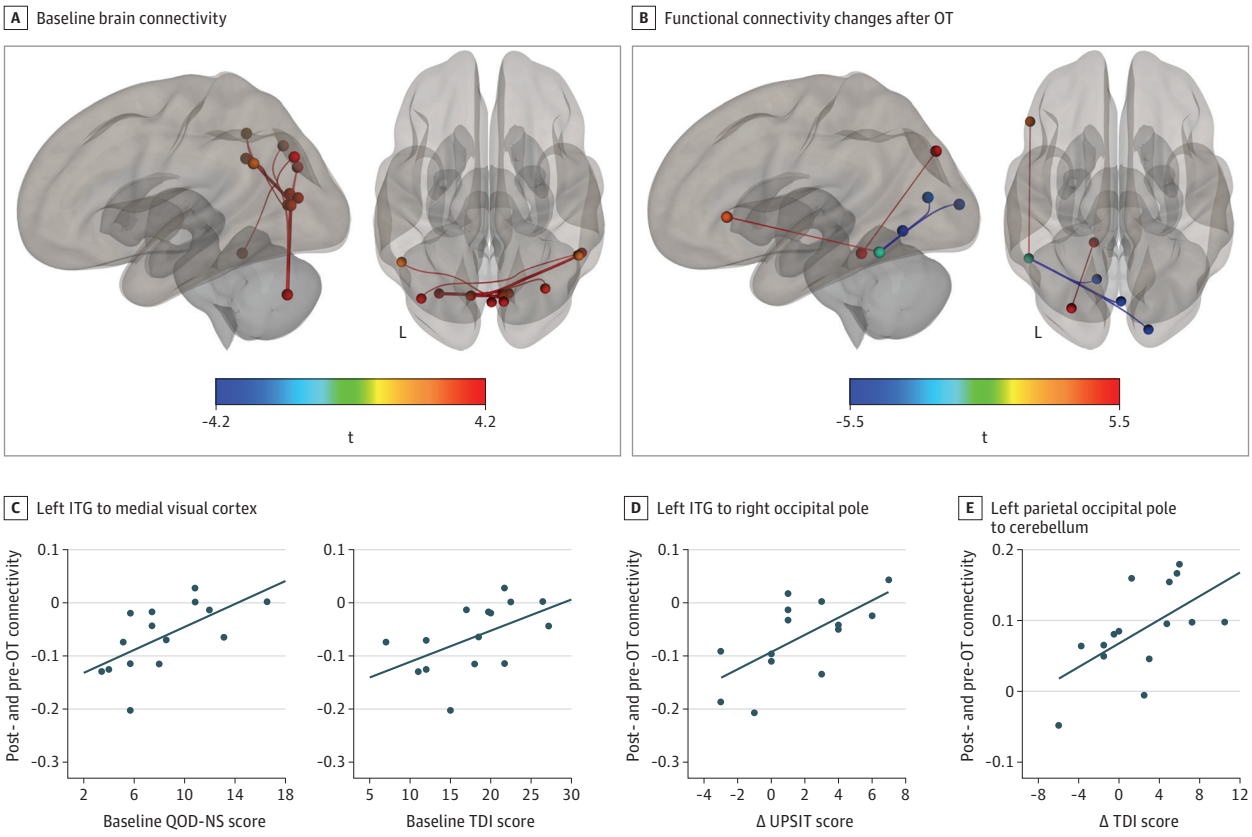
Abbreviations: QOD-NS, Questionnaire for Olfactory Dysfunction–Negative Statements; TDI, threshold, discrimination, and identification; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

[a] Data are presented as number (percentage) of participants unless otherwise indicated.

Baseline Functional Connectivity

Connectivity differed significantly between pretreatment participants and control participants in 13 ROI pairings (**Figure 2**A and **Table 2**). These ROIs primarily involved the visual cortex (left intracalcarine cortex vs network frontoparietal posterior

Figure 2. Changes After Olfactory Training



A, Differences (aggregate) in brain connectivity between participants with postviral olfactory dysfunction (PVOD) and control participants at baseline. Warm colors indicate greater connectivity in control participants than in participants with PVOD. B, Changes (aggregate) in functional connectivity after olfactory training (OT). Warm colors indicate increased connectivity, and cool colors indicate decreased connectivity. C through E, Of the 5 connections showing a significant change after OT, 4 showed correlations with clinical measures. ITG indicates inferior temporal gyrus; TDI, threshold, discrimination, and identification; QOD-NS, Questionnaire for Olfactory Dysfunction–Negative Statements; UPSIT, University of Pennsylvania Smell Identification Test.

parietal cortex: $\Delta z = 0.12$; $P = .04$), cerebellum (left cerebellum crus vs right intracalcarine cortex: $\Delta z = 0.19$; $P = .04$), and angular gyrus (right angular gyrus vs right intracalcarine cortex: $\Delta z = 0.14$; $P = .04$). In addition, changes in the default mode and frontal-parietal networks—2 classic resting-state networks—were observed. Specifically, an increase in connectivity between the right inferior temporal gyrus and the left lateral parietal node of the default mode network ($\Delta z = 0.18$; $P = .03$) and between the left intracalcarine cortex and right posterior parietal cortex node of the frontal-parietal network ($\Delta z = 0.12$; $P = .04$) was observed.

Network Connectivity Changes After OT

Five network connectivity values changed after OT (Figure 2B and Table 2). These changes included increases in connectivity between the inferior temporal gyrus and the left inferior frontal gyrus ($\Delta z = 0.07$; $P = .02$) and between the left parietal occipital junction (an olfactory ROI) and the cerebellum ($\Delta z = 0.09$; $P = .01$). Decreases in connectivity were noted between the inferior temporal gyrus and the medial visual network ($\Delta z = -0.07$; $P = .04$), left lingual gyrus ($\Delta z = -0.08$; $P = .03$), and occipital pole ($\Delta z = -0.08$; $P = .04$).

Olfactory Performance

Overall, 9 individuals had clinically meaningful improvement in smell after completion of OT as measured by UPSIT or the Sniffin' Sticks test. The median change in UPSIT was 1.5 points (95% CI, 0-3.0), and the median change in threshold, discrimination, and identification (TDI) was 1.25 points (95% CI, −0.62 to 3.0) (**Table 3**).

On completion of OT, the median visual analog scale score for sense of smell increased by 66%, with an absolute 9.5% increase. The QOD-NS scores also improved after OT, with a 14% relative improvement and 1.2-point absolute difference.

Correlation of Neuroimaging and Clinical Measures

To assess whether any of the changes in brain connectivity associated with OT were attributable to clinical measures, a series of exploratory correlations between the statistically significant brain connections and clinical measures was conducted, resulting in 4 correlations that reached a significance level of $P < .05$, uncorrected for multiple tests (Figure 2C-E). In all cases, participants who at baseline had a better sense of smell as defined by higher scores on UPSIT and/or the Sniffin' Sticks test demonstrated a larger increase in functional con-

Table 2. Functional Connectivity Differences Before OT and Network Changes After OT

ROI 1	ROI 2	Δz	*P* value
Functional connectivity differences before OT			
Inferior temporal gyrus (R)	Network default mode LP (L)	0.18	.03
Intracalcarine cortex (L)	Network frontoparietal PPC (R)	0.12	.04
Angular gyrus (R)	Intracalcarine cortex (R)	0.14	.04
Angular gyrus (R)	Intracalcarine cortex (L)	0.15	.04
Angular gyrus (R)	Supracalcarine cortex (R)	0.13	.04
Angular gyrus (R)	Visual medial (R)	0.15	.04
Angular gyrus (L)	Intracalcarine cortex (R)	0.13	.04
Cerebellum crus 2 (L)	Intracalcarine cortex (R)	0.19	.04
Cerebellum crus 2 (L)	Intracalcarine cortex (L)	0.17	.04
Cerebellum crus 2 (L)	Supracalcarine cortex (R)	0.17	.04
Cerebellum crus 2 (L)	Cuneal cortex (R)	0.17	.04
Cerebellum crus 2 (L)	Visual medial (R)	0.18	.04
Cerebellum crus 2 (L)	Lateral occipital cortex	0.15	.04
Network changes after OT			
Inferior temporal gyrus (L)	Inferior frontal gyrus (L)	0.07	.02
Inferior temporal gyrus (L)	Lingual gyrus (L)	−0.08	.03
Inferior temporal gyrus (L)	Visual medial network	−0.07	.04
Inferior temporal gyrus (L)	Occipital pole	−0.08	.04
Parietal-occipital juncture (L)	Cerebellum	0.09	.01

Abbreviations: LP, lateral parietal; OT, olfactory training; PPC, posterior parietal cortex; ROI, region of interest; Δz, Fisher *z*-transformed Pearson correlation coefficient.

Table 3. Objective and Patient-Reported Outcome Measures After Budesonide Nasal Irrigation and OT

	Median (range)		
Measure	After budesonide	After OT	Median difference (95% CI)[a]
UPSIT score	19.0 (5 to 40)	19.0 (9 to 40)	1.5 (0 to 3.0)
TDI score	17.5 (7.0 to 27.2)	18.3 (7.0 to 34.5)	1.25 (−0.62 to 3.0)
T	1.0 (1.0 to 5.8)	1.50 (1.0 to 7.5)	0.25 (0 to 1.12)
D	8.50 (5.0 to 14.0)	8.0 (3.0 to 15.0)	0.0 (−1.0 to 1.0)
I	7.0 (1.0 to 12.0)	8.0 (2.0 to 14.0)	1.0 (0 to 2.0)
VAS sense of smell score	14.3 (0 to 49.5)	23.8 (0 to 83.8)	12.0 (4.5 to 18.5)
QOD-NS score	8.6 (3.4 to 23.4)	7.4 (0 to 17.1)	−1.7 (−2.85 to −0.28)

Abbreviations: OT, olfactory training; QOD-NS, Questionnaire for Olfactory Dysfunction–Negative Statements; TDI, threshold, discrimination, and identification; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

[a] Median difference is calculated as the difference between postbudesonide and post-OT values.

nectivity after OT. The connection between the left inferior temporal gyrus and medial visual cortex correlated with baseline QOL-NS score (Pearson *r* = 0.63; 95% CI, 0.17-0.86) and baseline TDI (Pearson *r* = 0.53; 95% CI, 0.02-0.82). The connection between left inferior temporal gyrus and the right occipital pole correlated with ΔUPSIT scores (Pearson *r* = 0.65; 95% CI, 0.19-0.88), and a region of left parietal-occipital junction (previously associated with olfaction) and the cerebellum correlated with ΔTDI scores (Pearson *r* = 0.59; 95% CI, 0.02-0.85).

Safety

No adverse events occurred during the study. Five participants had incidental MRI findings, and all 5 were notified. Two participants with PVOD had incidental extra-axial meningiomas. Two of the control participants had cavernomas, and 1 control participant had a pleomorphic adenoma.

Discussion

In this single-institution, prospective cohort study, significant differences in baseline brain connectivity between participants with PVOD and normosmic control participants were observed, most notably with an increase in functional connectivity in the visual cortex among the participants. Interestingly, after OT, this connectivity in the visual cortex decreased and was replaced with an increased connection between regions of the brain involved in olfaction, such as the left parietal occipital junction.

Postviral olfactory dysfunction is a common cause of olfactory dysfunction. In the current COVID-19 pandemic, anosmia is now a major defining symptom of active viral infection and has emerged as a major public health issue. This study characterizes baseline rs-fMRI in participants with PVOD, which has not been previously studied, as well as changes in rs-fMRI after OT. Similar to the study by Park et al[23] that used rs-fMRI in patients with posttraumatic anosmia, this study found that at baseline participants with PVOD also demonstrated an increase in the visual cortex and motor connectivity, which suggests that loss of a vital organ sense may lead to adaptation, remodeling, and heightening of a closely related sense, namely, vision. Of interest, in patients with Parkinson disease with anosmia, rs-fMRI did not reveal any functional connectivity differences within the olfactory, default mode, salience, or central executive networks compared with control participants.[22]

These different studies[22,23] demonstrate that the cause of anosmia may affect the underlying rs-fMRI and may hold important clues to disease pathogenesis and treatment.

Although prior task-based fMRI studies[17,37] have observed changes in the olfactory and somatosensory networks after OT, to date, no study has examined how OT can affect whole-brain connectivity using rs-fMRI. The functional connectivity results of this study suggest that before OT patients with PVOD have increased connectivity in visual regions compared with normosmic patients, possibly because of heightened visual cues to compensate for their olfactory sensory deficit. Sensory deprivation leads to neural reorganization and adaptive behaviors.[38] Congenitally blind individuals, for example, demonstrate increased odor awareness compared with normal-sighted individuals.[39] Furthermore, the overall decrease in connections with the visual cortex after OT corresponds to an observed improvement in smell, possibly reflective of the bimodal effect of OT on the visual and olfactory cortex.

Limitations

Limitations of this study include a lack of control group for OT. The objective and subjective changes observed in this study could be attributable to spontaneous improvement or to the act of sniffing alone and not the essential odors. However, the corresponding changes in neuroimaging support the study's behavioral data. Another limitation is the small sample size, which limited the ability to perform subgroup analysis to determine the association of duration of smell loss with functional connectivity. However, because the effect size of a 30-day course of budesonide nasal irrigation followed by OT on olfaction for patients with PVOD is unknown, the sample size was based on feasibility. The findings from this study can be used to power a larger placebo-controlled randomized clinical trial.

Despite these limitations, by examining the effects of OT on whole-brain connectivity using rs-fMRI, this study supports the concept that the olfactory system has significant plasticity and ability to develop new neural connections and highlights the dynamic association between olfaction and vision for adults with PVOD.

Conclusions

In this prospective cohort study, neural reorganization most prominently in the visual cortex was observed for adults with PVOD who completed 3 months of OT. The observed increased connectivity within the visual cortex at baseline, which then decreased after OT, suggests that there is a bimodal association between vision and smell during OT that warrants further investigation. By further understanding the role of visual processing in smell for adults with PVOD undergoing OT, more effective therapies for PVOD may be identified.

ARTICLE INFORMATION

Accepted for Publication: January 21, 2021.

Published Online: March 18, 2021. doi:10.1001/jamaoto.2021.0086

Author Contributions: Drs Jiramongkolchai and Jones had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Jiramongkolchai, Brunworth, Kallogjeri, Kukuljan, Peelle, Piccirillo.
Acquisition, analysis, or interpretation of data: Jiramongkolchai, Jones, Peterson, Lee, Liebendorfer, Klatt-Cromwell, Schneider, Drescher, Ogden, Peelle, Piccirillo.
Drafting of the manuscript: Jiramongkolchai, Kukuljan, Peelle, Piccirillo.
Critical revision of the manuscript for important intellectual content: Jiramongkolchai, Jones, Peterson, Lee, Liebendorfer, Klatt-Cromwell, Schneider, Drescher, Ogden, Brunworth, Kallogjeri, Peelle, Piccirillo.
Statistical analysis: Lee, Kallogjeri, Peelle.
Obtained funding: Jiramongkolchai, Piccirillo.
Administrative, technical, or material support: Peterson, Lee, Liebendorfer, Kukuljan, Peelle.
Supervision: Klatt-Cromwell, Ogden, Peelle, Piccirillo.

Conflict of Interest Disclosures: Dr Jiramongkolchai reported receiving a CORE Resident Research Award from the American Academy of Otolaryngology–Head and Neck Surgery Foundation during the conduct of the study. Dr Klatt-Cromwell reported serving as a consultant for Medtronic and Intersect ENT outside the submitted work. Dr Peelle reported serving on the Scientific Advisory Committee of the Fondation pour l'Audition service outside the submitted work. Dr Piccirillo reported a patent with royalties paid for SNOT-22 from Washington University in St Louis. No other disclosures were reported.

Funding/Support: This study was supported by the American Academy of Otolaryngology–Head and Neck Surgery Foundation CORE Resident Research Award (Dr Jiramongkolchai), the Development of Clinician/Researchers in Academic ENT T32 DC00022 from the National Institute on Deafness and Other Communication Disorders (Drs Jiramongkolchai and Lee), and award TL1TR002345 from the National Center for Advancing Translational Sciences of the National Institutes of Health (Dr Peterson).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclaimer: Dr Kallogjeri is the Statistics Editor and Dr Piccirillo is the Editor of *JAMA Otolaryngology—Head and Neck Surgery*, but they were not involved in any of the decisions regarding review of the manuscript or its acceptance.

Additional Contributions: Thomas Hummel, MD, Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany, provided the Questionnaire for Olfactory Dysfunction. He was not compensated for this work.

REFERENCES

1. Welge-Lüssen A, Wolfensberger M. Olfactory disorders following upper respiratory tract infections. *Adv Otorhinolaryngol*. 2006;63:125-132. doi:10.1159/000093758

2. Seiden AM, Duncan HJ. The diagnosis of a conductive olfactory loss. *Laryngoscope*. 2001;111(1):9-14. doi:10.1097/00005537-200101000-00002

3. Altundag A, Cayonu M, Kayabasoglu G, et al. Modified olfactory training in patients with postinfectious olfactory loss. *Laryngoscope*. 2015;125(8):1763-1766. doi:10.1002/lary.25245

4. Reden J, Mueller A, Mueller C, et al. Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. *Arch Otolaryngol Head Neck Surg*. 2006;132(3):265-269. doi:10.1001/archotol.132.3.265

5. Hummel T, Rissom K, Reden J, Hähner A, Weidenbecher M, Hüttenbrink KB. Effects of olfactory training in patients with olfactory loss. *Laryngoscope*. 2009;119(3):496-499. doi:10.1002/lary.20101

6. Damm M, Pikart LK, Reimann H, et al. Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *Laryngoscope*. 2014;124(4):826-831. doi:10.1002/lary.24340

7. Spinato G, Fabbris C, Polesel J, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA*. 2020;323(20):2089-2090. doi:10.1001/jama.2020.6771

8. Kaye R, Chang CD, Kazahaya K, Brereton J, Denneny JC III. COVID-19 anosmia reporting tool: initial findings. *Otolaryngol Head Neck Surg*. 2020;163(1):132-134. doi:10.1177/0194599820922992

9. Wilson DA, Best AR, Sullivan RM. Plasticity in the olfactory system: lessons for the neurobiology of memory. *Neuroscientist*. 2004;10(6):513-524. doi:10.1177/1073858404267048

10. Ming GL, Song H. Adult neurogenesis in the mammalian central nervous system. *Annu Rev Neurosci*. 2005;28(1):223-250. doi:10.1146/annurev.neuro.28.051804.101459

11. Yousem DM, Williams SC, Howard RO, et al. Functional MR imaging during odor stimulation: preliminary data. *Radiology*. 1997;204(3):833-838. doi:10.1148/radiology.204.3.9280268

12. Levy LM, Henkin RI, Lin CS, Hutter A, Schellinger D. Odor memory induces brain activation as measured by functional MRI. *J Comput Assist Tomogr*. 1999;23(4):487-498. doi:10.1097/00004728-199907000-00001

13. Schneider F, Habel U, Reske M, Toni I, Falkai P, Shah NJ. Neural substrates of olfactory processing in schizophrenia patients and their healthy relatives. *Psychiatry Res*. 2007;155(2):103-112. doi:10.1016/j.pscychresns.2006.12.004

14. Westermann B, Wattendorf E, Schwerdtfeger U, et al. Functional imaging of the cerebral olfactory system in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2008;79(1):19-24. doi:10.1136/jnnp.2006.113860

15. Wang J, Eslinger PJ, Doty RL, et al. Olfactory deficit detected by fMRI in early Alzheimer's disease. *Brain Res*. 2010;1357:184-194. doi:10.1016/j.brainres.2010.08.018

16. Vasavada MM, Martinez B, Wang J, et al. Central olfactory dysfunction in Alzheimer's disease and mild cognitive impairment: a functional MRI study. *J Alzheimers Dis*. 2017;59(1):359-368. doi:10.3233/JAD-170310

17. Kollndorfer K, Fischmeister FP, Kowalczyk K, et al. Olfactory training induces changes in regional functional connectivity in patients with long-term smell loss. *Neuroimage Clin*. 2015;9:401-410. doi:10.1016/j.nicl.2015.09.004

18. Kollndorfer K, Kowalczyk K, Hoche E, et al. Recovery of olfactory function induces neuroplasticity effects in patients with smell loss. *Neural Plast*. 2014;2014:140419. doi:10.1155/2014/140419

19. Sobel N, Prabhakaran V, Zhao Z, et al. Time course of odorant-induced activation in the human primary olfactory cortex. *J Neurophysiol*. 2000;83(1):537-551. doi:10.1152/jn.2000.83.1.537

20. Poellinger A, Thomas R, Lio P, et al Activation and habituation in olfaction—an fMRI study. *Neuroimage*. 2001;13(4):547-560. doi:10.1006/nimg.2000.0713

21. Zhang D, Raichle ME. Disease and the brain's dark energy. *Nat Rev Neurol*. 2010;6(1):15-28. doi:10.1038/nrneurol.2009.198

22. Georgiopoulos C, Witt ST, Haller S, et al. A study of neural activity and functional connectivity within the olfactory brain network in Parkinson's disease. *Neuroimage Clin*. 2019;23:101946. doi:10.1016/j.nicl.2019.101946

23. Park M, Chung J, Kim JK, Jeong Y, Moon WJ. Altered functional brain networks in patients with traumatic anosmia: resting-state functional MRI based on graph theoretical Analysis. *Korean J Radiol*. 2019;20(11):1536-1545. doi:10.3348/kjr.2019.0104

24. Feinberg DA, Moeller S, Smith SM, et al. Multiplexed echo planar imaging for sub-second whole brain FMRI and fast diffusion imaging. *PLoS One*. 2010;5(12):e15710. doi:10.1371/journal.pone.0015710

25. Whitfield-Gabrieli S, Nieto-Castanon AJ. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect*. 2012;2(3):125-141. doi:10.1089/brain.2012.0073

26. Gottfried JA, Deichmann R, Winston JS, Dolan RJ. Functional heterogeneity in human olfactory cortex: an event-related functional magnetic resonance imaging study. *J Neurosci*. 2002;22(24):10819-10828. doi:10.1523/JNEUROSCI.22-24-10819.2002

27. Karunanayaka P, Eslinger PJ, Wang JL, et al. Networks involved in olfaction and their dynamics using independent component analysis and unified structural equation modeling. *Hum Brain Mapp*. 2014;35(5):2055-2072. doi:10.1002/hbm.22312

28. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. 1984;32(3):489-502. doi:10.1016/0031-9384(84)90269-5

29. Doty RL. Office procedures for quantitative assessment of olfactory function. *Am J Rhinol*. 2007;21(4):460-473. doi:10.2500/ajr.2007.21.3043

30. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys*. 1989;45(5):381-384. doi:10.3758/BF03210709

31. Doty RL, Yousem DM, Pham LT, Kreshak AA, Geckle R, Lee WW. Olfactory dysfunction in patients with head trauma. *Arch Neurol*. 1997;54(9):1131-1140. doi:10.1001/archneur.1997.00550210061014

32. Hummel C, Zucco GM, Iannilli E, Maboshe W, Landis BN, Hummel T. OLAF: standardization of international olfactory tests. *Eur Arch Otorhinolaryngol*. 2012;269(3):871-880. doi:10.1007/s00405-011-1770-0

33. Gudziol V, Lötsch J, Hähner A, Zahnert T, Hummel T. Clinical significance of results from olfactory testing. *Laryngoscope*. 2006;116(10):1858-1863. doi:10.1097/01.mlg.0000234915.51189.cb

34. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin' sticks": screening of olfactory performance. *Rhinology*. 1996;34(4):222-226.

35. Frasnelli J, Hummel T. Olfactory dysfunction and daily life. *Eur Arch Otorhinolaryngol*. 2005;262(3):231-235. doi:10.1007/s00405-004-0796-y

36. Behzadi Y, Restom K, Liau J, Liu TTJN. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage*. 2007;37(1):90-101. doi:10.1016/j.neuroimage.2007.04.042

37. Kollndorfer K, Kowalczyk K, Hoche E, et al. Recovery of olfactory function induces neuroplasticity effects in patients with smell loss. *Neural Plast*. 2014;2014:140419. doi:10.1155/2014/140419

38. Merabet LB, Pascual-Leone A. Neural reorganization following sensory loss: the opportunity of change. *Nat Rev Neurosci*. 2010;11(1):44-52. doi:10.1038/nrn2758

39. Beaulieu-Lefebvre M, Schneider FC, Kupers R, Ptito M. Odor perception and odor awareness in congenital blindness. *Brain Res Bull*. 2011;84(3):206-209. doi:10.1016/j.brainresbull.2010.12.014