Sinonasal surgery alters brain structure and function: Neuroanatomical correlates of olfactory dysfunction

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Funding information
This work was supported by the Deutsche Forschungsgemeinschaft (DFG HU441/18-1).

Abstract
Olfactory dysfunction (OD) is more common than hearing loss, partial blindness, or blindness and can have a significant impact on the quality of life. Moreover, unexplained OD is an early biomarker in neurodegenerative diseases and increases 5-year mortality risk. Structural alterations in olfactory eloquent brain regions may represent the neuroanatomical correlates of OD. Previous studies have demonstrated reduced gray matter (GM) volume in areas of presumed olfactory relevance in patients with OD. However, being cross-sectional in nature, these studies do not provide evidence of causality, for which longitudinal work is required. At present, however, longitudinal studies addressing olfactory structural plasticity are limited, both in number and methodological approach: to our knowledge, such work has not included parallel functional imaging to confirm the relevance of structural change. We therefore performed a longitudinal multimodal neuroimaging study investigating structural and functional plasticity in 24 patients undergoing surgical treatment for chronic rhinosinusitis, compared with 17 healthy controls. We demonstrated functionally significant structural plasticity within the orbitofrontal, anterior cingulate and insular cortices, and temporal poles in patients 3 months after surgery. Of interest, GM volume decreased in these regions, in association with increased psychophysical scores and BOLD signal. To our knowledge, this is the first study to demonstrate both structural and functional plasticity of the central olfactory networks, thereby confirming these areas as neuroanatomical correlates of olfactory function/dysfunction.

KEYWORDS
chronic rhinosinusitis, cortical thickness, functional MRI, gray matter volume, olfaction

1 | INTRODUCTION

Prior to the emergence of SARS-CoV-2, olfactory dysfunction (OD) was known to affect approximately 20% of the general adult population, making it more common than blindness, partial blindness, or hearing loss (RNID, 2020; Slade, 2014). As loss of smell and taste are now well-established symptoms of COVID-19, this figure will likely increase in future years, making the projected global burden of this sensory deficit highly significant (Whitcroft & Hummel, 2020). As the sense of smell guides food intake, environmental navigation, and social communication, OD is associated with reduced quality of life, and can lead to depression in up to 40% of affected patients (Croy & Hummel, 2016). Moreover, unexplained OD is linked with disease: it is an early biomarker in neurodegenerative diseases such as Parkinson's...
or Alzheimer’s disease, and is more closely associated with 5-year mortality than cerebrovascular accident, myocardial infarction, or systemic conditions such as diabetes or cancer (Pinto et al., 2014).

It has been suggested that structural alterations in olfactory eloquent regions may represent the neuroanatomical correlates of OD. This has been particularly well studied in the olfactory bulb (OB), which is an easily identified structure that can be targeted for volumetric assessment using manual segmentation techniques. Reduced OB volume has been demonstrated in a number of disease conditions, including post-infectious, sinonasal, and idiopathic OD, as well as psychiatric and neurodegenerative conditions (Huart et al., 2013). Accordingly, definitions of OB hypo- and aplasia are provided for diagnostic purposes in the Position Paper on Olfactory Dysfunction (Hummel et al., 2017).

Structural differences in areas upstream of the OB are less well studied, likely in part due to increased difficulty in identification of anatomical boundaries within cortical and subcortical regions. This difficulty can, however, be circumvented by techniques which use automated parcellation and allow subsequent comparison of spatially aligned anatomical regions within and between participants. One such well-established technique, voxel-based morphometry (VBM), has been used to demonstrate differences in gray matter (GM) density or volume in patients with OD. Two early VBM studies from Bitter and colleagues found reduced GM volume in patients with OD of mixed cause, compared to age- and sex-matched controls (Bitter, Brüderle, et al., 2010; Bitter, Gudziol, et al., 2010). Although not directly compared, this group found patients with anosmia to have more spatially widespread GM loss than those with hyposmia, while both groups demonstrated reductions within areas of the primary (piriform cortex) and secondary olfactory network (orbitofrontal cortex, insula, anterior cingulate cortex, parahippocampus), as well as several other regions. Subsequent VBM work has confirmed GM volume reductions in patients with OD compared to controls, although the spatial extent of these losses is more limited where single etiologies are studied (Han et al., 2017, 2018; Peng et al., 2013; Yao et al., 2014, 2018).

While these studies are helpful in identifying potential neuroanatomical correlates of OD, they are limited by their cross-sectional nature, which makes attribution of causality difficult: reduced GM volume in an olfactory eloquent region may predispose to, rather than result from, OD (Patterson et al., 2015; Reichert & Schöpf, 2018). Longitudinal studies are superior in this respect. However, tracking GM reduction is logistically difficult outside of the context of aging and neurodegeneration—both of which confound neuroanatomical change. The olfactory system, however, offers a good model to investigate structural plasticity, given that subjects with dysfunction may have extended periods of deficit followed by partial or complete recovery after treatment. Such plasticity has been shown within the OB (Gudziol et al., 2009), but is less well studied in upstream regions.

A limited number of studies have addressed structural plasticity of the primary and/or secondary olfactory networks in patients undergoing treatment for OD. Increased GM volume in areas of the secondary olfactory network (e.g., the hippocampus and parahippocampus) has been demonstrated using VBM in patients with post-infectious OD after a program of olfactory training (Gellrich et al., 2017). Gullmar and colleagues further demonstrated white matter (WM) change as characterized through differences in diffusion tensor imaging parameters in patients who had also undergone surgical treatment for chronic rhinosinusitis (CRS—an umbrella term for persistent inflammatory conditions of the nose and paranasal sinuses) (Gullmar et al., 2017). In a pilot VBM study, we additionally demonstrated areas of GM volume change within the primary and secondary olfactory networks, also after surgical treatment for CRS (Whitcroft et al., 2018). While these studies provide evidence that structures within the primary and secondary olfactory networks can undergo plastic change, they provide limited evidence for the functional significance of such changes.

We aimed to build on this work by performing, to our knowledge, the first prospective multimodal neuroimaging study to assess functional, as well as structural plasticity, in patients undergoing treatment for OD. Accordingly, we performed voxel-based morphometry, analysis of cortical thickness (CT), and olfactory functional imaging in patients with CRS, before and after functional endoscopic surgery, as well as in a matched longitudinal healthy control group. In doing so, we hoped to further characterize the extent and nature of structural plasticity within the primary and secondary olfactory networks and the functional significance of any such change. We hypothesized that improved olfactory function will be associated with altered GM volume and/or CT within structures of the primary and/or secondary olfactory networks, and that structural changes will be accompanied by increased functional activity. Identification of such areas will ultimately help to confirm their role as neuroanatomical correlates of olfactory function and dysfunction.

## 2 | MATERIALS AND METHODS

### 2.1 | Experimental design

Treatment of CRS provides a particularly attractive neurobiological model to investigate structural plasticity of the central olfactory...
system: CRS is common—affecting 10.9% of the European population (Hastan et al., 2011); CRS can lead to OD in over 90% of patients, depending on subtype (Litvack et al., 2008; Rombaux et al., 2016); CRS-related OD can improve with treatment (Kohli et al., 2016) and surgical treatment of medically refractive CRS provides a temporally defined intervention that can be relatively well stereotyped across patients. Therefore, a prospective longitudinal study was performed in patients with CRS and healthy, age- and sex-matched controls.

Patients were diagnosed with CRS with or without nasal polyposis and were consecutively recruited from those awaiting functional endoscopic sinus surgery at the University Hospital Carl Gustav Carus (Otorhinolaryngology Department), TU Dresden. All patients had been diagnosed and undergone initial medical treatment according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (Fokkens et al., 2012). Only patients ≥18 years were included. We excluded patients with neurological (including head injury), psychiatric, or other conditions affecting olfactory function, as well as those who were not available for follow-up testing postoperatively, or those who had contra-indications to MRI scanning. The final patient cohort builds on an initial pilot group of 12 patients (Whitcroft et al., 2018)—who were recruited and scanned under the same protocol, but who did not undergo functional imaging. All patients were assessed for handedness using a modified version of the Edinburgh Handedness Inventory (Oldfield, 1971). Given the pragmatic nature of the patient sample, and because handedness does not appear to affect passive olfactory processing (Lübke et al., 2012), patients who were otherwise clinically eligible were not excluded based on handedness. A convenience sample of control participants (≥18 years) was recruited from the local population, which was age and sex matched with the patient cohort. Only those who were free from sinonasal pathology, as well as neurological (including head injury), psychiatric, and other conditions that affect olfaction were included. As for the patient cohort, only those available for follow-up assessment at 3 months, and those without contraindications to MRI scanning were included. For the cohort of controls undergoing functional imaging, only those who were normosmic at baseline, and with stable olfactory function across the two assessment sessions were included in the final analysis. Again, otherwise eligible controls were not excluded based on handedness. All subjects were asked to refrain from smoking, eating, or drinking (except water) for 1 hr prior to their assessment session.

All patients and controls underwent clinical assessment, psychophysical olfactory testing and neuroimaging during a single session. This was performed at baseline (visit 1), and again at 3 months postoperatively or equivalent for controls (visit 2). Clinical assessment included thorough medical history taking, as well as completion of the validated patient reported outcome measure “SNOT20” (a questionnaire-based measure of CRS-related disease burden adapted and validated for the German population and a common clinical outcome measure when assessing the effect of medical/surgical interventions on CRS (Baumann et al., 2008)). Clinical examination included three-pass rigid nasendoscopy (with findings rated according to the validated Lund–Kennedy scoring system (Lund & Kennedy, 1995)) as well as peak nasal inspiratory flow rate (“PNIF,” a measure of maximal inspiratory flow rate through the nose that has been shown to be reduced in CRS, and which correlates with CRS-related quality of life Kjaergaard et al., 2008; Whitcroft, Andrews, et al., 2017)). The minimum clinically important difference for PNIF is 20 L/min. Psychophysical olfactory testing was performed in accordance with the Position Paper on Olfactory Dysfunction using the “threshold” (T) and “identification” (I) components of the validated “Sniffin’ Sticks” tool (for detailed description of testing procedure, please see ref (Whitcroft, Cuevas, et al., 2017)). Threshold and identification were chosen as previous work has suggested these best represent peripheral and central olfactory function, respectively (Whitcroft, Cuevas, et al., 2017). Given that our cohort included elderly patients, the discrimination component of the “Sniffin’ Sticks” test battery was not undertaken and all testing was performed birhinally, in order to reduce testing time and therefore participant burden. Normosmia was attributed where T ≥ 5.75 and I ≥ 11 (Oleszkiewicz et al., 2019). The minimum clinically important difference for T and I are ≥2.5 points and ≥3 points, respectively (Gudziol et al., 2006). Clinically significant increase in composite T1 score was therefore taken as ≥5.5 points.

2.2 | Functional MRI paradigm

All control participants, and patient 13 onwards underwent functional, in addition to structural imaging. Two odors were used for functional imaging (one per functional run): banana (neat, aroma, Frey+Lau, Henstedt-Ulzburg, Germany) and cis-3-Hexan-1-ol (neat, single molecule with smell of cut grass, Fluka Chemicals, Gillingham, UK). These were shown in pilot work to be iso-intense. During each run, a single odorant was presented birhinally in a block design. During “on” blocks, odors were delivered in 1-s pulses, embedded in 1 L/min clean humidified air, with a 2-s interstimulus interval. During “off” blocks, clean humidified air only was delivered. Odorants were delivered to participants via Teflon® nasal cannulae (4 mm internal diameter) and through use of a computer controlled olfactometer (Sommer et al., 2012). Due to low flow rates (which do not produce perceptible thermo-mechanical trigeminal activation), warming was not required. On blocks were of duration 15 s (6 volumes) and off blocks were of duration 30 s (12 volumes). There were nine on and nine off blocks, totaling 170 volumes (including eight initial dummy volumes). Each participant therefore underwent two functional runs per scanning session, with order of first odor pseudorandomized and counter-balanced across participants. At the end of each functional run, participants were asked to rate odor intensity (0-10, 10 = strongest) and hedonic valence (−5 to +5, +5 = most pleasant). See Figure 1 for schematic diagram of experimental paradigm.

2.3 | Imaging acquisition

Whole brain MRI was performed using a 3-T scanner (Verio, Siemens, Erlangen, Germany) with eight-channel phased-array head coil.
Axial T1-weighted images were acquired using a three-dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence. The following parameters were used: repetition time (TR), 1,890 ms; echo time (TE), 3.24 ms; inversion time (TI), 1,100 ms; field of view (FOV), 280 mm; voxel size, 0.73 × 0.73 × 1 mm; and flip angle, 15° (in total, 176 contiguous slices). Functional data were collected using a 2D GE-EPI sequence, TR 2,500 ms, TE 22 ms, FA 90°, voxel size 3 × 3 × 3 mm.

2.4 Imaging analysis: Voxel-based morphometry

Voxel-based morphometry was performed using the CAT12 toolbox (available from http://dbm.neuro.uni-jena.de/vbm/) implemented in SPM12 (Wellcome Centre of Imaging Neuroscience, UCL, London, UK) and MATLAB (The MathWorks, Natick, MA, USA). T1 images were visually inspected and reoriented as required according to SPM priors, and checked for obvious artifact. These images were then segmented into GM, WM, and cerebrospinal fluid (CSF), using the longitudinal segmentation tool. This process involves an initial intra-subject inverse-consistent spatial realignment with bias correction between the preoperative and postoperative images. In addition to segmentation of images from each time point, a mean image across time points is produced. Estimated spatial normalization parameters were then calculated for the segmented mean image, using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Ashburner & Friston, 2000). The resultant DARTEL deformations are then applied to the segmented images at each time point, prior to their modulation. Images were then smoothed using a Gaussian kernel (FWHM, 8 mm). Automated data quality checks were performed as per the CAT12 toolbox. Significant voxels are reported in relation to the Montreal Neurological Institute (MNI) coordinate space.

Change in GM volume between patients and controls was compared using a flexible factorial model with the between subject factor = group (two levels: patient, control) and the within subject factor = time (two levels: first scan, second scan). An F test for significant group × time interaction was performed, controlling for total intracranial volume [“TIV,” summated GM, WM, and CSF volume (Ashburner & Friston, 2000)], age, sex, and duration of condition. In order to account for inter-individual variability, and in an attempt to separate the effects of changing olfaction from those of surgery, we further compared change in GM volume between patients who had experienced a clinically significant improvement in olfactory function (increase in composite Ti ≥ 5.5 points) with those patients whose scores were worse or unchanged after surgery. Again, this was performed using a flexible factorial model with the between subject factor = group (2 levels: patient_improved, patient_not improved) and the within subject factor = time (2 levels: first scan, second scan). An F test for significant group × time interaction was performed, controlling for TIV, age, sex, and duration of condition. A within group comparison to determine GM volume change after surgery in patients who had clinically improved was also performed using a flexible factorial model, with the between subject factor = subject (one level: patients) and the within subject factor = time (two levels: first scan, second scan), controlling for TIV. T tests for significant increase and decrease in GM volume between visits were performed. An absolute threshold masking value of 0.1 was applied to avoid possible edge effects between different tissue types (Bitter, Gudziol, et al., 2010; Delon-Martin et al., 2013; Han et al., 2017).

Finally, in order to further investigate potential associations between change in psychophysical score and change in GM volume, beta weights were extracted from clusters of significant GM volume change demonstrated during the above within group analysis. As psychophysical scores were not used to identify these clusters, circular analysis was avoided. Extracted beta weight values were used to test for significant correlation between change in GM volume (ΔGM volume = second scan – first scan) and change in psychophysical score (ΔT/I/TI = postoperative score – preoperative score). Results were thresholded using a p value that was Bonferroni corrected for multiple comparisons.

As we were interested in the GM volume within brain regions known to be relevant to olfaction, and have strong a priori hypotheses regarding these olfaction-relevant areas, we performed a region of interest (ROI) analysis, in addition to whole brain analysis. Defined ROIs included bilateral areas of the primary and secondary

**FIGURE 1** Schematic diagram of fMRI paradigm
olfactory cortices as defined by Gottfried (2010) and Fjaeldstad et al. (2017). ROIs from the primary olfactory network included the olfactory cortex (OC), amygdala, and entorhinal cortex. ROIs from the secondary olfactory network included the orbitofrontal cortex (OFC), caudate nucleus, anterior cingulate cortex (ACC), insula, putamen, pallidum, hippocampus (HPC), parahippocampus, thalamus, and temporal poles (TP). ROIs were constructed within the WFU_PickAtlas software (available from: http://fmri.wfubmc.edu/software/pickatlas), based on the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) for all regions except for the entorhinal cortex, which was constructed using Brodmann Areas 28 + 34, based on the Talairach Atlas (Lancaster et al., 2000). We chose to differentiate the entorhinal cortex as an independent ROI from the parahippocampus, as this is anatomically known to receive direct input from the OB and therefore forms part of the primary olfactory network. The OFC ROI was constructed as per Kahnt et al., 2012 and therefore included the bilateral AAL regions of: superior, middle, inferior, and medial orbital gyri as well as the rectal gyri (Kahnt et al., 2012). Volume (bilateral) of the constructed ROI was as follows (mm$^3$): OC 1,920, amygdala 3,668, entorhinal cortex 41,114, OFC 83,787, caudate 15,646, ACC 21,799, insula 29,139, putamen 16,655, pallidum 4,465, hippocampus 14,937, parahippocampus 16,679, thalamus 17,178, and temporal poles 36,456. All whole brain analyses were corrected for multiple comparisons at the family wise error level ($p < 0.05_{FWE}$). For the a priori ROI analysis, small volume corrections were implemented through the "ROI" function in WFU_PickAtlas and results were further corrected for multiple comparisons at the FWE level ($p < 0.05$), or at a more lenient uncorrected threshold of $p < 0.001$, where no or limited results survived correction for multiple comparisons. In order to avoid issues surrounding non-stationarity in voxel-based volumetric analysis (Hayasaka et al., 2004), which means that cluster-based inferences may be inaccurate due to variability in cluster-size distribution depending on local smoothness, we report only voxel-based results.

Images for inclusion in the manuscript were prepared using the Xjview toolbox for SPM (available from: http://www.alivelearn.net/xjview/) and Microsoft PowerPoint.

2.5 Imaging analysis: Cortical thickness

Cortical thickness is the distance between the GM "outer surface" (GM/CSF boundary) and "inner surface" (GM/WM boundary) (Dahnke et al., 2013), and is another morphological neuroimaging technique that has been used as a biomarker for normal development (Sowell et al., 2004), aging (Fjell et al., 2006), and various pathological states (Querbes et al., 2009; Van Haren et al., 2011). CT was analyzed using CAT12, implemented in SPM12. Patient and control T1-weighted images were initially segmented using the surface and thickness estimation writing options. This uses a projection-based thickness approach to determine CT by estimating WM distance, and then projecting the local maxima onto other GM voxels. The latter is done using a neighbor relationship that is defined by the WM distance. The local maxima are therefore equal to the CT. As longitudinal segmentation was performed, as in the VBM pipeline, in addition to segmentation of images from each time point, a mean image across time points was produced. Estimated spatial normalization parameters were calculated for the segmented mean image, and applied to the first and second images. Resultant surface data from both the right and left hemispheres were then smoothed using a 15 mm FWHM kernel.

As for VBM, change in CT was compared between groups (patient vs. control and patients_improved vs. patients_not improved) and within groups (patient_improved) using flexible factorial models. As for the VBM analysis $F$ and $t$ tests were used, with results corrected for sex, age, and duration of condition. All CT analyses were performed at the whole brain level, with results thresholded at $p < 0.05_{FWE}$.

2.6 Imaging analysis: Functional MRI

Functional data were analyzed using SPM12. Anatomical T1-weighted images were inspected and reoriented according to SPM priors during VBM analysis. Functional images were additionally visually inspected for correct orientation according to SPM priors. Pre-processing involved initial realignment and unwarping of functional images followed by segmentation of T1-weighted images according to SPM tissue probability maps. Co-registration of functional and anatomical images was then performed, as well as normalization to MNI space. Finally data were smoothed using an 8 mm FWHM kernel. We then performed a fist level analysis in which the condition "odor baseline" was modeled for each subject, using the canonical HRF. Resultant contrast images were then subjected to a second level random-effects analysis. Second level between and within group analyses were performed using flexible factorial models as for structural analyses. Whole brain analyses were corrected for multiple comparisons at $p < 0.05_{FWE}$. A priori ROI analysis (with small volume correction) was conducted as per structural work, with results thresholded at $p < 0.05_{FWE}$, or a more lenient $p < 0.001_{uncorr}$. As part of an exploratory analysis, we were interested in functional change within a priori ROIs that had demonstrated significant structural results. Accordingly, we additionally performed small volume corrected ROI analysis in these areas using a Bonferroni corrected $p$ value: $p < 0.05/[$number of significant ROI]. As non-stationarity is not an issue in functional analysis, we additionally used cluster-based inference for these lenient thresholds, and only report clusters of $\geq 10$ voxels. Again, results of uncorrected analyses are only reported where either no or limited results survived after correction for multiple comparisons.

2.7 Statistical analysis

Data were analyzed using GraphPad Prism (version 6, GraphPad Software, LaJolla, USA), using parametric or non-parametric tests as
appropriate. Unless specified otherwise, statistical significance was attributed where $p < 0.05$ and data are given as mean (SD) for parametric data or median for non-parametric.

3 | RESULTS

3.1 | Demographics, clinical, and behavioral scores

3.1.1 | Structural cohort (all participants)

T1-weighted images were available from 25 patients and 17 controls. One patient was excluded from further analysis due to cerebral atrophy, leaving 24 in total. There was no significant difference between groups in age (median age patients 47 (range 27–74), controls 44 (range 27–69), $n = 24:17$, $U = 167$, $p = 0.47$) or sex (M:F = 15:9 patients, 11:6 controls, Fisher’s exact test, $p = 0.99$). The mean duration of CRS was 8 years (range 7 months to 57 years). Diagnoses and details of surgery can be found in Table S1. All patients were treated postoperatively with intranasal corticosteroid spray. 

Average threshold (T), identification (I), and composite threshold + identification (TI) scores were statistically significantly higher in the control group than in the patient group at visit 1 and 2. In the patient group, there were statistically significant improvements in T, I, and composite TI scores after surgery: group T and I scores fell below normosmia preoperatively, but improved to normosmic levels postoperatively. Test scores reached clinically significant improvement after surgery in 10 patients for T (≥2.5), 8 patients for I (≥3), and 8 patients for composite TI (≥5.5). PNIF was significantly higher in controls than patients at visit 1 but not visit 2. Within the patient group, there was a statistically significant improvement in mean PNIF after surgery, which reached clinical significance in 15 patients (≥20 L/min). SNOT20 score was significantly higher in patients than controls at visit 1 and visit 2, and there was a statistically significant reduction in SNOT20 score in patients after surgery. Similarly, Lund-Kennedy (LK) score was significantly higher in patients than controls both at visit 1 and visit 2. Within the patient group, there was a statistically significant reduction in LK score after surgery.

Full clinical and behavioral data are shown in Table 1.

3.1.2 | fMRI cohort

Functional data were available for a subset of 12 patients and 12 controls. There was no significant difference in age (mean age patients 50 (12) (range 32–74), controls 45 (14) (range 27–69), $n = 12:12$, $t_{22} = 0.9227$, $p = 0.3662$), or sex (M:F = 8:4 patients, 8:4 controls, Fisher’s exact test, $p > 0.99$) between groups. Mean duration of CRS was 5 years (range 1 to 17). The patient fMRI group T and I scores again fell below normosmia preoperatively but improved to normosmic levels postoperatively. Improvement in psychophysical test score reached clinical significance in five patients for T (≥2.5), four patients for I (≥3), and three patients for composite TI (≥5.5). There were statistically significant improvements in PNIF, SNOT20, and LK scores in the fMRI patient group after surgery. Full clinical and behavioral data can be found in Table 1.

3.2 | Voxel-based morphometry

3.2.1 | Patient versus Controls

For the interaction between group (patients vs. controls) and time (first vs. second scan), two adjacent clusters within the left OFC survived at $p < 0.05_{FWE}$, during a priori ROI analysis. At $p < 0.001_{uncorr}$ significant clusters were also demonstrated within the right entorhinal cortex and right OC (see Table 2). No voxels survived thresholding ($p < 0.05_{FWE}$) at the whole brain level.

3.2.2 | Clinically improved versus not clinically improved patients

Eight patients experienced a clinically significant improvement in composite TI score and seven had scores that were worse or unchanged after surgery. Comparing these groups (patients improved vs. patients not improved), there was a cluster of significant interaction between time and group within the right ACC that survived thresholding at $p < 0.05_{FWE}$ during a priori ROI analysis. At $p < 0.001_{uncorr}$, additional clusters were demonstrated within the right HPC, bilateral OFC, left parahippocampus, and left TP (see Table 3). No voxels survived thresholding at the whole brain level ($p < 0.05_{FWE}$).

3.2.3 | Change in GM volume after surgery—Clinically improved patient group

Within the group of patients with clinically improved composite TI score after surgery, there were areas of both increased and decreased GM volume during a priori ROI analysis. At $p < 0.05_{FWE}$, a cluster of significant increase in GM volume was found within the right HPC. At $p < 0.001_{uncorr}$ there was an additional cluster of increased GM volume within the right parahippocampus, and several clusters of decreased GM volume within the right ACC, bilateral HPC, insula, OFC, and left TP (see Table 4, Figures 2 and 3). No results survived thresholding at the whole brain level ($p < 0.05_{FWE}$).

3.2.4 | Correlation between change in GM volume and change in psychophysical score

Within the subgroup of patients who clinically improved after surgery, there were no correlations between ΔGM volume (from 19 clusters of significant GM change as outlined in Table 4) and Δ psychophysical
**TABLE 1** Clinical and behavioral scores in patients and controls shown as mean (SD) or \( n \) median values for visit 1 and visit 2, in all participants and fMRI subgroup

|                  | Visit 1 |                     | Visit 2 |                     | Visit 2 |                     | Visit 2 |                     | Visit 2 |
|------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|
|                  | Patients | Controls          | Patient versus controls | Patients | Controls          | Patient versus controls | Patients: (visit 1) versus (visit 2) | Patients: (visit 1) versus (visit 2) |
|                  | \( n = 24 \) | \( n = 17 \) |                      | \( n = 24 \) | \( n = 17 \) |                      |                      |                      |
| T                | 4.5\(^a\) | 8.0\(^a\) | \( U = 121.5, p = 0.028 \) | 7.6 (3.6) | 9.6 (2.3) | \( t_{39} = 2.158, p = 0.037 \) | \( W = 170, p = 0.008 \) |
| I                | 10.0\(^b\) | 14.0\(^b\) | \( U = 64, p < 0.0001 \) | 12.0\(^a\) | 15.0\(^a\) | \( U = 105, p = 0.007 \) | \( t_{23} = 3.532, p = 0.002 \) |
| TI               | 13.63\(^a\) | 22.50\(^a\) | \( U = 104.5, p = 0.007 \) | 20.38\(^a\) | 24.00\(^a\) | \( U = 111.5, p = 0.013 \) | \( t_{23} = 3.845, p = 0.001 \) |
| SNOT20           | 34.3 (11.6) | 5.7 (5.2) | \( t_{39} = 9.22, p < 0.0001 \) | 13.5\(^b\) | 4.0\(^b\) | \( U = 106.5, p = 0.009 \) | \( t_{23} = 8.629, p < 0.0001 \) |
| PNIF             | 107.9 (46.0) | 140.9 (43.3) | \( t_{39} = 2.320, p = 0.026 \) | 131.3 (45.8) | 132.6 (45.3) | \( t_{39} = 0.967, p = 0.923 \) | \( t_{23} = 2.759, p = 0.011 \) |
| LK               | 5.5\(^a\) | 0.0\(^a\) | \( U = 29, p < 0.0001 \) | 3.5\(^a\) | 0.0\(^a\) | \( U = 72.5, p < 0.0001 \) | \( W = -144, p = 0.005 \) |

\(^{a}\)Patient group data parametric, hence paired \( t \) test between visits.

**TABLE 2** Voxels of significant interaction between group (patients vs. controls) and time (first vs. second scan) for GM volume during a priori ROI analysis

| ROI            | MNI coordinates | T score | F score |
|----------------|-----------------|---------|---------|
|                 | \( X \) | \( Y \) | \( Z \) |       |
| OFC             | L  | -3  | 36 | -27 | 4.25 | 25.67 |
|                 | L  | -3  | 33 | -27 | 4.17 | 24.59 |
| Entorhinal cortex | R  | 15  | 33 | -26 | 3.43 | 15.81 |
| OC              | R  | 2   | 14 | -8  | 3.25 | 14.09 |

**TABLE 3** Voxels of significant interaction between group (patient_improved vs. patient_not improved) and time (first vs. second scan) for GM volume during a priori ROI analysis

| ROI            | MNI coordinates | T score | F score |
|----------------|-----------------|---------|---------|
|                 | \( X \) | \( Y \) | \( Z \) |       |
| ACC             | R  | 8   | 32 | 24  | 4.24 | 51.49 |
| HPC             | R  | 36  | -14 | -21 | 3.37 | 23.80 |
|                 | L  | -26 | 51 | -4  | 3.71 | 32.13 |
|                 | R  | 2   | 34 | -15 | 3.28 | 22.08 |
|                 | R  | 26  | 57 | -4  | 3.27 | 21.82 |
| Parahippocampus | L  | -22 | -30 | -18 | 3.21 | 20.75 |
|                 | L  | -24 | -28 | -20 | 3.12 | 19.13 |
| TP              | L  | -45 | 15 | -36 | 3.27 | 21.83 |
|                 | L  | -46 | 6  | -12 | 3.16 | 19.9  |
score that were statistically significant at the specified results threshold of \( p < 0.0026 \) [Bonferroni corrected \( p < 0.05/19 \)].

### 3.3 | Cortical thickness

No voxels survived thresholding \( p < 0.05_{\text{FWE}} \) during between (patients vs. controls; patients_improved vs. patients_not_improved) or within group (patients_improved) analyses at the whole brain level.

### 3.4 | Functional MRI

Descriptive statistics for the perceived intensity and hedonic valence of the odors grass and banana in patients and controls are provided in Table 5. Odors were isointense in patient and control groups; functional analysis of the conditions banana and grass was pooled.

No significant group by time interaction was found when comparing change in patient and control functional activity for any odor (grass/banana) during whole brain or ROI analysis, either at \( p < 0.05_{\text{FWE}} \) or \( p < 0.001_{\text{uncorr}} \). As significant structural results were demonstrated in eight ROIs (ACC, entorhinal cortex, HPC, insula, OFC, OC, parahippocampus, and TP), these areas were further interrogated for significant functional interaction with results thresholded at \( p < 0.003125 \) [Bonferroni corrected \( p < 0.05/(8 \times 2_{\text{Right + Left}}) \)]. At this more lenient threshold there was one small area of significant time by group interaction in the right parahippocampus. However, this cluster did not survive correction by the cluster criterion of \( \geq 10 \) voxels.

Within group analysis was not limited to patients who had experienced clinical improvement in composite T1 score after surgery (≥5.5) due to small \( n \) number (\( n = 3 \)). Therefore, within group analysis was performed across all patients in the subgroup (\( n = 12 \)). As we were particularly interested in the functional significance of structural changes demonstrated, we limited our within group \textit{a priori} ROI analysis to the eight regions outlined above. At \( p < 0.003125 \) and \( \geq 10 \) voxels, there were significant increases in functional activity after surgery within the left ACC, bilateral insula, bilateral OFC, and right TP (see Table 6, Figures 2 and 3). The bilateral clusters within the OFC additionally reached significance at \( p < 0.05_{\text{FWE}} \). There were no significant clusters of increased functional activity after surgery that survived thresholding at \( p < 0.05_{\text{FWE}} \) during whole brain analysis.

### 4 | DISCUSSION

#### 4.1 | Key findings

To our knowledge, this is the first prospective study to demonstrate structural as well as functional plasticity of the central olfactory

| Threshold               | ROI                | Side | MNI coordinates | T score |
|-------------------------|--------------------|------|-----------------|---------|
| **Increased GM volume** |                    |      |                 |         |
| \( p < 0.05_{\text{FWE}} \) | HPC                | R    | 34 -15 -20      | 9.43    |
| \( p < 0.001_{\text{uncorr}} \) | Parahippocampus   | R    | 30 -20 -26      | 7.73    |
| **Decreased GM volume** |                    |      |                 |         |
| \( p < 0.001_{\text{uncorr}} \) | ACC                | R    | 6 32 24         | 8.75    |
| \( p < 0.001_{\text{uncorr}} \) | HPC                | L    | -27 -38 -2      | 8.0     |
| \( p < 0.001_{\text{uncorr}} \) | HPC                | R    | -34 -33 -8      | 5.78    |
| \( p < 0.001_{\text{uncorr}} \) | Insula             | R    | 38 16 6         | 7.46    |
| \( p < 0.001_{\text{uncorr}} \) | Insula             | R    | 46 -10 0        | 5.55    |
| \( p < 0.001_{\text{uncorr}} \) | Insula             | R    | 42 -16 -4       | 5.35    |
| \( p < 0.001_{\text{uncorr}} \) | Insula             | L    | -39 0 3         | 5.11    |
| \( p < 0.001_{\text{uncorr}} \) | OFC                | R    | 48 24 -6        | 9.6     |
| \( p < 0.001_{\text{uncorr}} \) | OFC                | R    | 14 39 -4        | 7.71    |
| \( p < 0.001_{\text{uncorr}} \) | OFC                | R    | 52 34 -6        | 6.68    |
| \( p < 0.001_{\text{uncorr}} \) | OFC                | R    | 48 45 -4        | 6.22    |
| \( p < 0.001_{\text{uncorr}} \) | OFC                | L    | -10 44 -6       | 5.68    |
| \( p < 0.001_{\text{uncorr}} \) | OFC                | L    | -26 52 -4       | 5.64    |
| \( p < 0.001_{\text{uncorr}} \) | Midline            | 0    | 45 -14          | 5.1     |
| \( p < 0.001_{\text{uncorr}} \) | Midline            | L    | -2 45 -20       | 5.05    |
| **TP** |                    | L    | -44 16 -18      | 6.56    |
networks, in relation to improved olfactory function. We used four separate approaches to identify a priori regions of interest in which change in GM volume was related to olfactory improvement. 

First, we compared change in GM volume between patients and controls, and demonstrated significant group x time interaction within areas of the primary (OC) and secondary olfactory network (entorhinal cortex, OFC). Second, we compared change in GM volume between patients who had clinically significant improvements
in psychophysical (TI) scores after surgery with those who did not, and found significant group x time interaction within areas of the secondary olfactory network, (ACC, HPC, OFC, parahippocampus, and TP). We also performed a within group analysis in clinically improved patients and demonstrated significant changes in GM volume within areas of the secondary olfactory network (ACC, HPC, OFC, parahippocampus, and TP).
Third, we tested for correlation between ΔGM volume and Δpsychophysical test score in clusters of significant structural change after surgery, although no results survived correction for multiple comparisons. Fourth, we interrogated the regions identified in steps 1–3 for increased functional activity within our fMRI subgroup, and demonstrated increases in BOLD signal after surgery within four regions: ACC, insula, OFC, and TP. Of interest, in patients who had a clinically significant improvement in TI score after surgery, there were significant reductions in GM volume within these four areas. We did not demonstrate any significant alterations in CT after surgery at the given results threshold.

### 4.2 Plasticity of the olfactory networks

The OFC, ACC, and insula are well recognized components of the secondary olfactory network. Accordingly, high probabilities for olfactory activation have been demonstrated in these regions during meta-analysis of functional neuroimaging studies (Seubert, Freiherr, Djordjevic, et al., 2013). More specifically, the OFC is thought to be involved in experience- and affect-dependent odor percept encoding (Anderson et al., 2003; Gottfried et al., 2002; Zou et al., 2016), multi-modal sensory integration (Gottfried & Dolan, 2003), and perceptual decision making (Bowman et al., 2012). The OFC also appears to be required for conscious odor processing: Li and colleagues demonstrated residual autonomic, behavioral, and neuroimaging responses to odors, but lack of conscious olfactory perception in a patient with localized right-sided OFC damage (Li et al., 2010).

The ACC is thought to have a role in hedonic odor processing (Zou et al., 2016), odor recognition memory (Meunier et al., 2014), and a potential role in modulation of olfactory attention (Garcia-Cabezas & Barbas, 2014), while the insula receives olfactory, gustatory, and trigeminal information and is thought to act as a multimodal chemosensory convergence zone (Lundstrom et al., 2011) involved in flavor perception. The temporal poles receive connections from the primary olfactory cortex, OFC, and insula and, although less well established, have been linked to olfaction in functional neuroimaging (Royer et al., 2000) and lesion studies (Jones-Gotman & Zatorre, 1993; Lötisch et al., 2016; Rausch et al., 1977). In particular,

### TABLE 5 Intensity and hedonic ratings of fMRI odors, in patients

|                  | Visit 1      | Visit 2      | Visit 2                  |
|------------------|--------------|--------------|-------------------------|
|                  | Banana       | Grass        | Banana versus grass     | Banana       | Grass        | Banana versus grass |
| Intensity        | 3.5<sup>a</sup> | 2.5<sup>a</sup> | <i>W</i> = −8.0, <i>p</i> = 0.578 | 8.5<sup>a</sup> | 7.5<sup>a</sup> | <i>W</i> = −16.0, <i>p</i> = 0.125 |
| Valence          | 0.50 (1.88)  | 1.083 (2.021) | <i>t</i><sub>11</sub> = 0.8449, <i>p</i> = 0.416 | 1.33 (3.06)  | 0.92 (3.70)  | <i>t</i><sub>11</sub> = 0.2987, <i>p</i> = 0.771 |

<sup>a</sup>And controls, shown as mean (SD) or median values for visit 1 and visit 2.

### TABLE 6 Clusters of significant increase in BOLD signal in patients after surgery

| Threshold         | ROI          | Side | MNI coordinates | T score | k         |
|-------------------|--------------|------|-----------------|---------|-----------|
| <i>p</i> < 0.05<sub>FWE</sub> | OFC          | R    | 40 28           | 5.61    | 2         |
|                   |              | L    | −30 24          | 5.14    | 3         |
| <i>p</i> < 0.00278<sub>FWE</sub> | ACC          | L    | −8 34           | 4.26    | 48        |
|                   |              | R    | 40 26           | 4.52    | 104       |
|                   |              | L    | −34 24          | 4.31    | 240       |
|                   |              | R    | 38 16           | 3.81    | 49        |
|                   |              | R    | 50 0            | 3.32    | 17        |
|                   |              | R    | 40 28           | 5.61    | 42        |
|                   |              | L    | −30 24          | 5.14    | 147       |
|                   |              | R    | 46 12           | 3.42    | 12        |
the temporal poles assign emotional valence to sensory stimuli (Olson et al., 2007) and may be involved in odor memory (Rausch et al., 1977).

Monosynaptic connections between the ACC and primary olfactory cortex (specifically the anterior olfactory nucleus (AON)) have been demonstrated in primates (García-Cabezas & Barbas, 2014). Given that the AON has bilateral feedforward connections with structures of the primary olfactory cortices and feedback connections with the OBs, as well as extensive connections with both the posterior OFC and anterior insula (Carmichael et al., 1994; García-Cabezas & Barbas, 2014; Ghaziri et al., 2017), this emphasizes the potentially important functional link between these structures, and may underlie the pattern of results we demonstrated, where structural and functional plasticity appeared to be most robust within the ACC, insula, and OFC. The functional link between these regions has also been highlighted by time course series in which temporally overlapping activation of these structures occurs (Bowman et al., 2012; Poellinger et al., 2001).

It is of interest that the increased functional activity we demonstrated within the OFC, ACC, and TP was accompanied by areas of decreased, rather than increased GM volume. Previous morphological work has demonstrated significant positive correlation between psychophysical test scores and both GM volume (Seubert, Freiherr, Frasnelli, et al., 2013) and CT (Frasnelli et al., 2010) within the right OFC of healthy participants. Increased GM volume has also been demonstrated within the bilateral OFC of perfumers (considered to be olfactory experts) compared with non-expert controls (Delon-Martin et al., 2013). Similarly, increased GM volume has been demonstrated within the right insula of master sommeliers (considered to be olfactory experts) (Banks et al., 2016), or left insula of “super-smellers” (Wabnegger et al., 2019), compared to controls. Moreover, cross-sectional VBM studies have demonstrated GM volume loss within the OFC, ACC, and insula, in patients with OD. For the OFC, this includes studies assessing patients with OD of mixed cause (Bitter, Bruderle, et al., 2010; Bitter, Gudziol, et al., 2010; Peng et al., 2013), idiopathic OD (Yao et al., 2014), sinonasal OD (Han et al., 2017), post-infectious OD (Yao et al., 2018), and post-traumatic OD (Han et al., 2018); for the insula, OD of mixed cause (Bitter, Bruderle, et al., 2010; Bitter, Gudziol, et al., 2010; Peng et al., 2013), idiopathic OD (Yao et al., 2014), sinonasal OD (Han et al., 2017), and post-traumatic OD (Han et al., 2018); and for the ACC, OD of mixed cause (Bitter, Bruderle, et al., 2010; Bitter, Gudziol, et al., 2010; Peng et al., 2013), idiopathic OD (Yao et al., 2014), and post-traumatic OD (Han et al., 2018). Although lesions of the TP are frequently observed in post-traumatic OD (Han et al., 2018), to our knowledge, no previous cross-sectional studies have reported reduced GM volume or CT of the TP in patient populations.

Taken together, morphometric studies of the OFC, ACC, and insula (less so for the TP) would appear to indicate that increased function is related to increased GM volume or CT. This contrasts with our results, where we demonstrated reduced GM volume in association with increased functional activity. However, as these studies were cross-sectional, insight into this apparent divergence may be afforded from longitudinal work.

Two previous prospective studies have assessed change in GM volume and/or CT after a period of olfactory training (OT), either in patients with post-infectious OD (Gellrich et al., 2017), or in healthy controls (Al Ain et al., 2019), at 12 and 6 weeks, respectively. Gellrich and colleagues demonstrated a small area of increased GM volume within the right OFC during subgroup analysis of patients who had clinically improved after training. In whole group analysis, this OFC cluster was not present—although, similar to the results we demonstrated, there was significantly increased GM volume within the hippocampus and parahippocampus. No GM volume increases were found in the insula, ACC, or TP. Al Ain and colleagues demonstrated increased GM volume within the left OFC and right TP during within group (post-OT–pre-OT) but not between group (group (OT/control) x time interaction) comparisons. Whole brain and region of interest analysis, however, demonstrated no significant correlations between change in GM volume/CT or change in psychophysical test score in this study. Neither Gellrich et al., nor Al Ain et al., reported results of analysis for decreased GM volume/CT.

Comparison of these results with our own is limited by different approaches to analysis, patient populations and, in particular, treatment interventions. Olfactory training has been shown to improve odor identification more than odor threshold (Sorokowska et al., 2016), the latter of which is thought to better represent the peripheral olfactory system (Whitcroft, Cuevas, et al., 2017), which is targeted by functional endoscopic sinus surgery. While the exact mechanisms remain to be elucidated, it is possible that OT improves olfactory function in a mechanistically different way than surgery. One could speculate that sinusonal surgery, by targeting the peripheral olfactory organ and consequently increasing afferent input to the central system, results in a bottom-up process that improves the efficiency of existing networks, unlike OT, which may involve more top-down processes. Increasing the efficiency of existing networks could conceptually involve pruning of redundant synapses (± other unknown cellular changes, e.g., glial) and consequently reduced GM volume. Similar arguments have been made for reduced GM volume and CT in areas such as the OFC and OC in healthy controls, compared to patients with isolated congenital anosmia (Frasnelli et al., 2013). Top-down processes such as OT, or other “learning,” may conversely involve mechanisms such as axonal remodeling, synaptogenesis, or dendritic spine growth (Barnes & Finnerty, 2010; Knafo et al., 2001), neurogenesis ([Bernier et al., 2002; Brann & Firestein, 2014; Huart et al., 2013; Moreno-jiménez et al., 2019; Shapiro et al., 2007] but also see e.g., [Brown et al., 2003]) or glial alterations that result in increased GM volume/CT. Such differences in short-term structural plasticity would theoretically not preclude GM atrophy following prolonged reduced afferent input or other central dysfunction associated with disease states, as seen in cross-sectional patient studies.

However, the relationship between neuroanatomical structure and function is likely complex, and the temporal course of structural changes may be neither linear, nor contemporaneous with functional plasticity. For this reason, it would be of interest to repeat our study.
with an increased number of time points to determine whether an initial reduction in GM volume is followed by a subsequent increase. Moreover, there may be significant inter-individual variability in the nature of structural plasticity. In line with this, a recent study showed that approximately 4% of left-handed women have intact olfactory function in the absence of OBs—structures that were previously considered a prerequisite for olfaction (Weiss et al., 2020). Accordingly, sampling variation may affect results; a limitation of our study was the relatively small sample size, particularly when our cohort was divided for analysis according to improvement in olfactory function.

With these complexities in mind, we would suggest that change in GM volume and/or CT, independent of directionality, may be taken to indicate structural plasticity, where association with change in olfactory function can be demonstrated. Accordingly, our results confirm the role of the OFC, ACC, insula, and TP as neuroanatomical correlates of olfactory function/dysfunction. However, our results require replication, ideally with a larger sample size and prolonged follow-up times.

4.3 | Clinical application

Volumetric assessment of the OBs is frequently used during the clinical investigation of patients with suspected OD. Demonstration of neuroanatomical regions that undergo functionally significant structural plasticity upstream of the OB may add future additional targets for such volumetric assessment. This approach may be of particular use in demonstrating the effect of treatment or disease progression in longitudinal studies. However, more research is needed both on group and individual patient levels.

4.4 | Study limitations

Due to the pragmatic nature of our patient and control samples, we cannot exclude some degree of associated selection bias. However, our first level analysis involved longitudinal paired comparisons within participants, mitigating the effects of any such bias. Furthermore, any selection bias most likely affects both patient and control groups, further mitigating any bias where groups were compared.

Given the observed inter-individual variation in improvement in olfactory function after surgery, and in order to investigate the effects of changing olfaction, we subdivided our patient cohort for part of our analysis into those who had experienced clinically significant improvement with those who did not. Therefore, the participant numbers within our subgroup analyses were small, potentially affecting the statistical significance of our results. Future longitudinal studies should aim for higher initial patient numbers and may wish to focus exclusively on patients with CRS with nasal polyposis, who have been shown to have greater olfactory benefit from functional endoscopic sinus surgery than patients without polyps.

5 | CONCLUSIONS

To our knowledge, this is the first study to demonstrate structural as well as functional plasticity in association with improved olfactory function. In particular, we demonstrated functionally significant structural plasticity within the ACC, insula, OFC, and TP, confirming their role as neuroanatomical correlates of olfactory function and dysfunction.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the Journal of Neuroscience Research, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

ACKNOWLEDGMENTS

We thank Prof Jonathan Gale of the UCL Ear Institute for his continued support to KLW. We thank Dr. Claudia Valder, System Natura, Flintbeck, Germany, for her support in terms of the selection of odors.

ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of the Faculty of Medicine Carl Gustav Carus University Hospital, Technische Universität Dresden, Germany (EK number 56022016), and was conducted in accordance with the Declaration of Helsinki. All patients and controls provided full informed written consent prior to participation.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR CONTRIBUTIONS

All authors 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. Conceptualization, K.L.W., P.A., and T.H.; Methodology, K.L.W., P.A., and T.H.; Formal Analysis, K.L.W.; Investigation, K.L.W. and J.N.; Data Curation, K.L.W. and J.N.; Writing – Original Draft, K.L.W.; Writing – Review & Editing, K.L.W., P.A., and T.H.; Visualization, K.L.W.; Supervision, P.A. and T.H.; Project Administration, T.H.; Funding Acquisition, T.H.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jnr.24897.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.
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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the
Supporting Information section.

Transparent Peer Review Report

Transparent Science Questionnaire for Authors

**TABLE S1** Clinical diagnoses and details of surgery for patient group