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GRAY MATTER ALTERATIONS IN PAROSMIA

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Abstract—Parosmia is a common olfactory disorder. In this condition, odors are perceived in a different quality than usual. This distorted olfactory percept is typically reported to be unpleasant. Little is known about the pathophysiology of this phenomenon. Previous studies demonstrated smaller volumes of the olfactory bulbs in patients with parosmia compared to subjects without parosmia. In order to investigate structural brain alterations in areas beyond the olfactory bulb, in the current study voxel-based morphometry was applied. A group of 22 parosmic patients was compared with control subjects matched for age- and sex, who exhibited a similar performance in olfactory tests. Performing a whole brain analysis, we found profound gray matter volume loss in the left anterior insula in parosmic patients. In an additional volume of interest analysis including primary and secondary olfactory areas, we also found volume loss in the right anterior insula, the anterior cingulate cortex, the hippocampus bilaterally, and the left medial orbitofrontal cortex. Many of these areas are critically involved in olfactory quality discrimination and odor memory. The present results indicate that reduced gray matter volume in brain regions supporting odor discrimination and memory is related to disturbed olfactory sensation in parosmia.

Key words: human, olfaction, parosmia, volumetry, magnetic resonance imaging, insula.

Olfactory disorders can be divided in quantitative and qualitative alterations (Holbrook and Leopold, 2006). In quantitative olfactory disorders, hyposmia is characterized by a decreased sensitivity for odors while a complete olfactory loss is designated as anosmia. In qualitative olfactory dysfunctions, phantosmia is an olfactory hallucination resulting in the perception of an odor in the absence of an actual environmental smell. In contrast, parosmia is a distorted smell perception in the presence of an odor. Like in phantosmia, this olfactory percept is described as unpleasant in almost all cases. It is typically reported as a foul, rotten, sewage, or burn smell (Bonfils et al., 2005). Parosmia can occur as an independent symptom, although it typically accompanies quantitative olfactory disorders. While parosmia is sometimes described as a rare disease, this seems to depend on its definition and the population investigated. For example, Nordin et al. reported in one study a prevalence of parosmia of 4% in the general population (Nordin et al., 2007). Other studies on patients with chemosensory and sinonasal diseases found parosmia in 19% (Nordin et al., 1996) or 28% of these cases (Reden et al., 2007).

Causes for parosmia are most often upper respiratory tract infections (Reden et al., 2007). However, also sinonasal diseases, toxic chemical exposure, and head trauma may result in such a state (Bonfils et al., 2005). The underlying physiopathological mechanism of parosmia is not clear. There are two main hypotheses: a peripheral and a central theory. The peripheral theory proposes the inability of abnormal olfactory neurons to form a complete picture of the odorant, while the central theory suggests that integrative centers in the brain form parosmia (Leopold, 2002). Symptoms usually decrease with time. Therefore, parosmia is proposed as an indicator of a changing olfactory system (Deems et al., 1991; Frasnelli et al., 2004; Hummel and Lotsch, 2010).

Very little is known about alterations of the CNS in patients with parosmia. Some studies suggest that parosmic patients exhibit a smaller volume of the olfactory bulb (OB) compared with olfactory impaired patients without parosmia (Mueller et al., 2005; Rombaux et al., 2006). Cortical brain areas beyond the OB have not yet been studied in patients with parosmia although this seems to be highly interesting since affections in these areas could support the “central” theory of parosmia. Therefore, aim of the present study was to evaluate structural changes in brain areas of patients with parosmia compared to control subjects with a similar olfactory performance, but without parosmia. Voxel-based morphometry should be used since this method has already been demonstrated to be appropriate in showing gray matter alterations in quantitative olfactory diseases like anosmia (Bitter et al., 2010b) and hyposmia (Bitter et al., 2010a). The hypothesis was that parosmia would lead to specific changes in primary and secondary olfactory areas. Analogous to the OB volume changes in parosmic subjects we expected mainly volume decreases in these areas.

EXPERIMENTAL PROCEDURES

The study had been approved by the Ethics Committee of the Medical Faculty of the University of Jena. It was performed ac-

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Abbreviations: GM, gray matter; IC, insular cortex; OB, olfactory bulb; OFC, orbitofrontal cortex; TDI score, threshold discrimination identification score; VBM, voxel-based morphometry; VOI, volume of interest; WM, white matter.

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cording to the guidelines of the Declaration of Helsinki (1975). Prior to commencement of the study all participants provided written informed consent.

Subjects

Twenty-two parosmic patients (12 male, 10 female) and sex- and age-matched control subjects without parosmia but with similar olfactory performance were included in the study. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Olfactory function was determined birhinally using the "Sniffin' Sticks" (Kobal et al., 1996) as a combined score based on a test for butanol odor threshold, odor discrimination, and odor identification (TDI score) (Hummel et al., 2007). Thirteen of the subjects had an idiopathic cause, seven a post-infectious, one a post-traumatic and one a drug-related cause of parosmia. Structural brain lesions were exclusion criteria for all participants. None of the patients had additional major neurological or psychiatric deficits with the exception of the olfactory impairment. Mean age of patients in the parosmic group was 53.6±9.3 years. Duration of parosmia ranged from 8 to 74 months (mean 29.0±19.9 months). Patients with parosmia had an average TDI score of 22.2±5.9 points (range 11–32 points). The Mini-Mental Status Examination (MMSE) showed an average value of 29.4±0.8. For each subject a parosmia score was determined (Abolmaali et al., 2008). This score was calculated according to the parosmia frequency (daily occurrence: 1 point, not daily: 0 point), intensity (very intense: 1 point, not very intense: 0 point), and social consequences due to parosmia for example, weight loss or considerable behavioral changes (present: 1 point, not present: 0 point). This score ranged from 0 to 3 points in the investigated group with a mean of 2.23±1.02 points.

The mean age of subjects in the control group was 50.6±9.6 years. In the control group the TDI score was on average 21.6±5.8 points (range 11–34 points). There was no significant difference between both groups in the composite TDI score nor in the single subtests using the non-parametric Mann–Whitney U test for independent samples at significance level $P=0.05$. Most of the control subjects of the present study took part in a previous voxel-based morphometry (VBM) study on hyposmia (Bitter et al., 2010a). In that study they were part of the hyposmic patient group or normosmic control group depending on their olfactory performance. None of the parosmic subjects were included in the former VBM studies.

MRI data acquisition

All MR data were obtained with a 3.0 Tesla scanner (Magnetom TrioTim system, Siemens, Erlangen, Germany) using a standard receiving 12 channel head coil. Following a survey a sagittal aligned 3-D magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence (TR=2300 ms, TE=3.03 ms, TI 900 ms, flip angle=9°, 192 slices, slice thickness 1 mm, matrix 256×256, in-plane voxel size 1 mm×1 mm, total acquisition time 5:20 min) was acquired to obtain high-resolution T1 weighted images of the brain.

Voxel-based morphometry and statistical analysis

Data were processed and examined using the SPM8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), where we applied VBM implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters. Images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and non-linear transformations (warping), within a unified model (Ashburner and Friston, 2005). Subsequently, analyses were performed on the volume of the gray matter (GM) and white matter (WM) segments, which were multiplied by the non-linear components derived from the normalization matrix in order to preserve actual GM and WM values locally (modulated GM and WM volumes). Importantly, the segments were not multiplied by the linear components of the registration in order to account for individual differences in brain orientation, alignment, and size globally. Finally, the modulated volumes were smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM).

In a first analysis, voxel-wise GM and WM volume differences between parosmic patients and controls were examined using independent two-sample *t*-tests at $P<0.001$ (uncorrected) across the whole brain. A spatial extent threshold of 115 voxels was used as calculated from the expected number of voxels per cluster. To avoid possible edge effects between different tissue types, we excluded all voxels with GM or WM values of less than 0.2 (absolute threshold masking). The subject's age, TDI scores, and the individual total brain volume were used as nuisance effects resulting in a removal of all effects from the data that could be explained by these parameters. A second analysis was performed in order to investigate more subtle changes in the primary and secondary olfactory areas (volume of interest, VOI). Here two-sample *t*-tests at a higher threshold $P<0.01$ (uncorrected) were applied using an explicit mask containing primary and secondary olfactory areas according to our a priori hypothesis. This mask was created using the WFU Pickatlas version 3.0.3 (Maldjian et al., 2003). The following implemented Anatomical Automatic Labeling (AAL) regions were used to generate this mask: olfactory, orbitofrontal including rectus, insula, cingulum, hippocampus, parahippocampal, and thalamus.

In order to evaluate effects correlated with the duration of parosmia a full factorial design was applied with factor 1 at two levels ("parosmic subjects", "controls") and factor 2 also at two levels ("parosmia duration <2 years", "parosmia duration >2 years"). The same covariates were applied as in the above described analyses. Therefore, four subgroups were formed—subgroup 1 (parosmic subjects, disease duration <2 years), subgroup 2 (parosmic subjects, disease duration >2 years), subgroup 3 (age-, sex-, and TDI score-matched controls of subgroup 1), and subgroup 4 (age-, sex-, and TDI score-matched controls of subgroup 2). The mean age of subgroup 1 was 54.7±10.0 years, for subgroup 2 51.6±8.1 years, for subgroup 3 50.5±9.6 years, and for subgroup 4 50.6±10.3 years. The mean duration of parosmia was for subgroup 1 15.9±5.3 months and for subgroup 2 52.0±13.6 months. The mean TDI-score for subgroup 1 was 22.0±7.0 points, for subgroup 2 22.5±3.8 points, for subgroup 3 21.9±7.0 points, and for subgroup 4 21.0±3.0 points. Using a t-contrast, subgroup 3 was tested vs. subgroup 1 and subgroup 4 vs. subgroup 2. Consequently, a conjunction analysis was performed allowing the demonstration of regions which were significant in both t-contrasts at $P<0.01$ (uncorrected).

RESULTS

The MR images showed no pathologies in the patient group nor in the group of healthy volunteers. The average total brain volume of the parosmic group was 1392.3±152.6 ccm with a mean gray matter volume of 577.5±71.0 ccm. The control group showed 1371.5±117.8 ccm total brain volume and a mean of 575.5±48.4 ccm gray matter volume.

In the whole brain VBM analysis, significant gray matter loss was observed in the left anterior insular cortex (IC) (Fig. 1, Table 1). In the additional VOI analysis on primary and secondary olfactory areas, significant gray matter volume decrease was demonstrated for the anterior IC bilaterally, the left anterior cingulate cortex (ACC), the left medial orbitofrontal cortex (OFC), the left piriform cortex (PIR), and the hippocampus (HIP) bilaterally (Fig. 2, Table 2).

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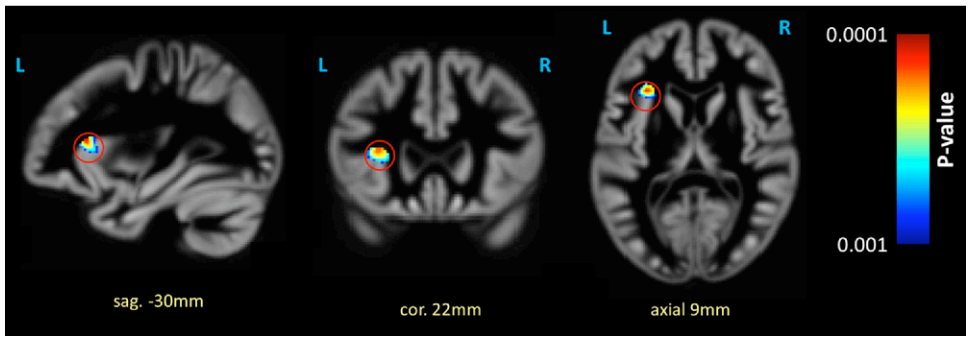

Fig. 1. Gray matter reductions in 22 parosmic patients compared to age-, sex-, and TDI-matched controls—whole brain analysis with a threshold set at $P<0.001$ (uncorrected). A spatial extent threshold of 115 voxels was used. L, left hemisphere; R, right hemisphere.

No volume increases of the gray matter nor alterations of the white matter were found in the analyses.

The conjunction analysis between a group of parosmic subjects with disease duration longer than 2 years and a group of parosmic subjects with disease duration shorter than 2 years revealed a common gray matter loss in the left IC (MNI coordinates: −32, 23, 9; cluster size: 82 voxels; Z score: 2.66). No other clusters exceeded the applied spatial threshold of 10 voxels.

DISCUSSION

The main finding of the present study was the demonstration of a considerable gray matter volume loss in the left anterior IC of parosmic patients. The VOI analysis revealed also an involvement of the right anterior IC. The IC region is a secondary olfactory area which is typically reported to be activated in functional imaging studies on olfaction (Gottfried, 2006). It is considered as an integrative center for multimodal convergence (Shelley and Trimble, 2004). This idea is consistent with the involvement of the IC during various olfactory tasks as demonstrated by functional imaging (Zald and Pardo, 2000) including cross-modal integration of olfactory and trigeminal (Boyle et al., 2007) and olfactory and visual stimuli (Djordjevic et al., 2005). In particular, the anterior part of the IC receives direct input from regions of the olfactory and gustatory cortex and might contribute to limbic interactions to provide hedonic valence to the olfactory percept (Verhagen and Engelen, 2006). With respect to the present results, reduced gray matter volume in the anterior IC could be related to an impaired performance to correctly assess quality of sensory information. Further evidence for this role comes from studies in patients with focal epilepsy. Insular stimulation and electrocorticography during surgery for focal temporal lobe epilepsy revealed numerous visceral sensory and visceral motor functions including gustatory and olfactory sensations (Penfield and Faulk, 1955). In our analysis, we found a predominantly left-sided IC affection. The role of the left anterior IC in odor quality discrimination and in the evaluation of odor properties including its affective component has been demonstrated (Savic et al., 2000; Plailly et al., 2007; Veldhuizen et al., 2010).

In the VOI analysis, gray matter volume loss was also observed in other secondary olfactory areas like the ACC, HIP, and medial OFC. HIP and OFC are, like the anterior IC, involved in odor memory and odor quality discrimination learning (Savic et al., 2000; Martin et al., 2007; Goodrich-Hunsaker et al., 2009). In parosmia, obviously a misinterpretation of actual odors occurs. Therefore, it is consistent that we observed a remarkable remodeling in areas related to the processing of olfactory memories and olfactory discrimination.

The PIR forms the major part of the primary olfactory cortex (Gottfried, 2006). Although we observed only minor volume changes in this area, this result is consistent with the idea that parosmia is reflected by changes in the OB volume (Mueller et al., 2005; Rombaux et al., 2006) and by gray matter volume changes in the primary olfactory cortex and in secondary olfactory areas. OB changes itself were not observed in the present study. This is most probably explained by the limits of VBM and the used MP-RAGE sequence (Bitter et al., 2010b). Volume increases of the gray matter or alterations in the white matter were not found in any of the performed analyses. Nevertheless, subtle changes in these areas may become visible in future studies with higher number of participants.

As stated above, upper respiratory tract infection is the most common cause for parosmia according to the literature. This fact was also observed in our patient collective, where most of the known (and remembered) causes were post-infectious. The link between the expected peripheral

Table 1. Reductions of gray matter in patients with parosmia compared to age-, sex-, and TDI-matched controls—whole brain analysis with a threshold set at $P<0.001$ (uncorrected)

Region	Side	MNI coordinates (mm)			Z-score	Cluster size (voxels)
		x	y	z		
Anterior insular cortex	L	−30	23	12	3.65	210

A spatial extent threshold of 115 voxels was used. All coordinates are given in MNI-space.

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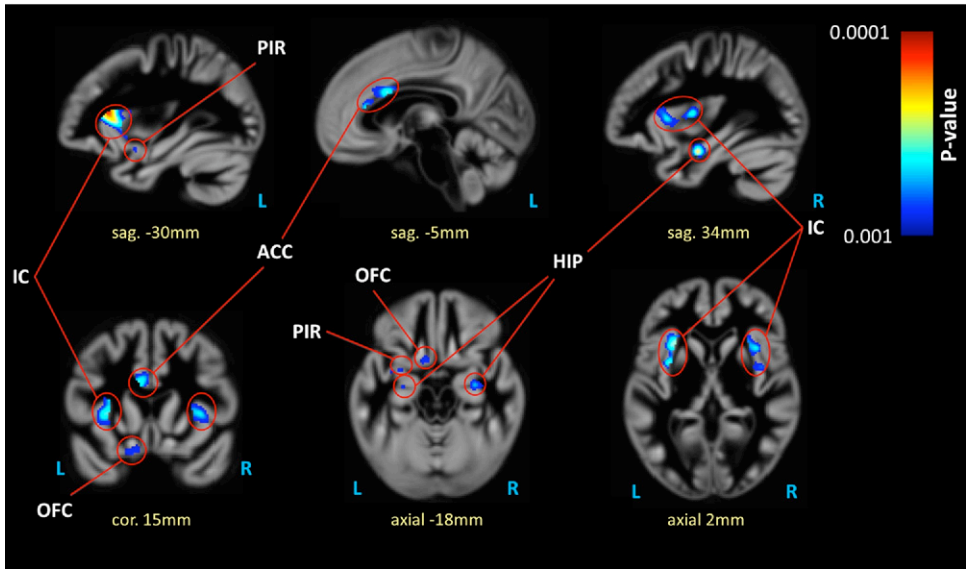

Fig. 2. Gray matter reductions in 22 parosmic patients compared to age-, sex-, and TDI-matched controls—volume of interest analysis for the primary olfactory cortex and secondary olfactory areas with a threshold set at $P<0.01$ (uncorrected). The top row shows three sagittal slices, while in the bottom row one coronal slice and two axial slices are presented. ACC, anterior cingulate cortex; HIP, hippocampus; IC, insular cortex; OFC, orbital frontal cortex; PIR, piriform cortex; L, left hemisphere; R, right hemisphere.

damage at the level of the olfactory epithelium (OE) in post-infectious parosmia (Rombaux et al., 2006) and the observed alterations in the OB and in higher-level olfactory areas is not clear. One might speculate that remodeling in the olfactory system during the recovery period after post-infectious OE damage is disturbed. This could be reflected by a reduction of inhibitory neurons in the olfactory system which might lead to the observed volume decrease. In the present study, we observed a profound laterality of volume changes with a pronounced left hemispheric volume loss. It would be interesting if this laterality can also be observed in the OB volumes of parosmic patients. Unfortunately, until now no study has been published on this question.

All alterations described above had no effect on the total brain volume and the total gray matter volume of the parosmic group. Here no significant difference between the two groups was found. A methodological problem which had to be solved was that parosmia is associated with a different extent of quantitative olfactory disorders. In fact, four of the investigated subjects were functionally anosmic, 15 were hyposmic and three normosmic. In previous VBM studies we could show that quantitative olfactory disorders themselves lead to changes in the cortical gray matter (Bitter et al., 2010a,b). Other studies also showed a connection between olfactory function and gray matter properties: Frasnelli et al. investigated healthy subjects and observed a correlation between olfactory performance and cortical thickness for example, in the right medial OFC, right IC, and areas around the central sulcus (Frasnelli et al., 2010). Pardini et al. showed a relationship between local gray matter volume loss and a normalized olfactory score in patients with corticobasal syndrome for the right insula, the right midfrontal gyrus and bilateral inferior frontal gyrus, and in the frontal variant of frontotemporal dementia for the right midfrontal gyrus (Pardini et al., 2009). In patients with Parkinson's disease a similar correlation was observed for the right piriform cortex and the right amygdala (Wattendorf et al., 2009). Since all of

Table 2. Reductions of gray matter in patients with parosmia compared to age-, sex-, and TDI-matched controls—volume of interest analysis for the primary and secondary olfactory areas with a threshold set at $P<0.01$ (uncorrected)

Region	Side	MNI coordinates (mm)			Z-score	Cluster size (voxels)
		x	y	z		
Anterior insular cortex	L	−30	23	12	3.65	1095
	R	30	21	7	3.00	1004
Anterior cingulate cortex	L	−6	12	25	3.02	546
Hippocampus	R	33	−9	−24	3.21	320
	L	−26	−12	−21	2.51	52
Medial orbitofrontal cortex	L	−12	17	−26	2.57	168
	L	−12	48	−24	3.04	90
Piriform cortex	L	−30	2	−20	2.45	20

All coordinates are given in MNI-space.

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the aforementioned studies showed that olfactory function itself influences cortical gray matter properties, it was necessary in the present investigation to match the control group to the patient group in terms of measured olfactory function (TDI score). Furthermore, we used the TDI score as nuisance effect in the VBM analyses. With this procedure, all remaining effects, which could be possibly explained by olfactory performance, were removed. This strategy allowed focusing solely on brain alterations associated with parosmia.

Taking our results together, in patients with parosmia structural changes have been demonstrated in a putative neuronal network of olfactory memory and olfactory quality discrimination. We speculate that these alterations in olfactory areas involved in odor memory and odor discrimination are crucially related to parosmia. This would be in accordance with the "central", top-down hypothesis of parosmia. However, the present results may also be discussed as a change secondary to an altered olfactory input caused by damage of the OE, a bottom-up hypothesis. In order to find support for the "central theory" in our data, an indirect approach was assessed: If patients who suffer from parosmia since a shorter time exhibit the same alterations in the cerebral gray matter as patients who have parosmia since a longer time, this could be taken as a certain evidence that the observed gray matter alterations do not evolve as a consequence of a peripheral damage but rather are the origin of the parosmia. To assess this hypothesis a conjunction analysis was performed on a group of parosmic subjects with shorter disease duration (mean 15.9±5.3 months) and a group with longer disease duration (mean 52±13.6 months). In this analysis only common volume decreases in both groups are demonstrated. With this approach we could find such a common gray matter volume decrease in the left IC. This result might support the "central hypothesis". Nevertheless, it has to be considered that the investigated subgroups were relatively small and the disease duration of the group with "shorter" duration of parosmia was still quite long. Therefore, further investigations directed towards this issue are needed.

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