Chemical Senses Advance Access published March 15, 2010

Chem. Senses doi:10.1093/chemse/bjq028

# Anosmia Leads to a Loss of Gray Matter in Cortical Brain Areas

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*Accepted February 12, 2010*

## Abstract

Chronic olfactory disorders, including the complete loss of the sense of smell (anosmia), are common. Using voxel-based morphometry (VBM) in magnetic resonance imaging (MRI), structural changes in the cerebral gray matter (GM) of a group of patients with anosmia compared with a normosmic, healthy control group were evaluated. Patients with anosmia presented a significant decrease of GM volume mainly in the nucleus accumbens with adjacent subcallosal gyrus, in the medial prefrontal cortex (MPC) including the middle and anterior cingulate cortices, and in the dorsolateral prefrontal cortex (dlPFC). These areas are part of the limbic loop of the basal ganglia and except the dlPFC secondary olfactory areas. They also play an important role in many neurological diseases. Furthermore, volume decreases in smaller areas like the piriform cortex, insular cortex, orbitofrontal cortex, hippocampus, parahippocampal gyrus, supramarginal gyrus, and cerebellum could be seen. Longer disease duration was associated with a stronger atrophy in the described areas. No local increases in the GM volume could be observed. A comparison with results of an additionally executed functional MRI study on olfaction in healthy subjects was performed to evaluate the significance of the observed atrophy areas in cerebral olfactory processing. To our knowledge, this is the first study on persisting structural changes in cortical GM volume after complete olfactory loss.

**Key words:** functional magnetic resonance imaging, human, neurodegenerative diseases, olfaction, phenyl ethyl alcohol, structural plasticity, voxel-based morphometry

## Introduction

Chronic olfactory disorders are common. In population-based studies, a prevalence of 19% has been found (Nordin and Bramerson 2008). Causes for the olfactory impairment are in descending order postinfectious olfactory loss, sinunasal diseases, head trauma, toxins/drugs, and congenital olfactory loss (Nordin and Bramerson 2008). Little is known about structural cerebral changes after losing the sense of smell. There have been a few studies focusing on the olfactory bulb (OB) of patients with postviral anosmia (Rombaux et al. 2006a) and posttraumatic anosmia (Mueller et al. 2005; Rombaux et al. 2006b). Using manual segmentation techniques, it could be shown that the absence of olfactory afferent input resulted in a decrease of the OB volume. Furthermore, it was shown that parosmic patients, that is, patients who incorrectly perceive actually present odors, had a stronger OB volume reduction compared with olfactory impaired patients without parosmia (Abolmaali et al. 2008). It was concluded that the OB exhibits a high plasticity depending on the olfactory input. Yousem et al. (1999) also investigated the volume of the manual segmented whole temporal lobes of patients with posttraumatic smell loss. In this study, no separate segmentation of the gray matter (GM) and white matter was performed. As a result, a slight, nonsignificant reduction of bilateral temporal lobe volumes (4%) compared with control subjects was found. This volume loss was discussed to be the result of the reduction of the afferent input to the temporal lobe as well as result of the traumatic damage.

Voxel-based morphometry (VBM) is an elegant, user-independent volumetric method (Ashburner and Friston 2000). With VBM, it became possible to search for volume differences of gray brain matter over the whole brain

without limitation to 1 specific region. Only one study used the VBM technique on olfactory questions so far: using VBM, Garcia-Falgueras et al. (2006) showed sex differences in the volume of the normal olfactory system.

Aim of our study was to evaluate structural changes of human brain areas in patients with anosmia using VBM technique (study 1). Our hypothesis was that we would find structural alterations in areas involved in the processing of olfactory information. A decrease of GM was expected in the OB and the primary olfactory cortex (Rombaux et al. 2006a). In secondary olfactory areas (especially insula, orbitofrontal, and cingulate cortices), we expected areas with volume loss as well as with compensatory hypertrophy as observed in other sensory modalities (Penhune et al. 2003; Noppeney et al. 2005).

Furthermore, a functional magnetic resonance imaging (fMRI) study in healthy subjects was performed (study 2). These experiments were necessary to evaluate the olfactory significance of areas found by the VBM analysis, which were not covered by our hypothesis. A direct comparison between olfactory active brain areas in the fMRI study with the observed structural alterations in anosmics was performed. To our knowledge, the present VBM analysis is the first study on changes of the cortical GM after olfactory loss.

## Materials and methods

All participants of the study parts 1 and 2 had given their written consent, and both studies had been approved by the local ethical committee. The studies were performed according to the guidelines of the Declaration of Helsinki 1975.

### Voxel-based morphometry (study part 1)

#### *Subjects*

Seventeen anosmic patients (6 males and 11 females) and 17 sex- and age-matched control subjects were included in the VBM part of this study. All participants were right handed according to the Edinburgh Handedness Inventory (Oldfield 1971) and showed a normal nasal anatomy as observed by endonasal endoscopy. The threshold discrimination identification (TDI) score for the anosmic patients was determined by the Sniffin' Sticks test (Kobal et al. 2000) and ranged from 4 to 15 (average 10.2 ± 2.7). Eight of the anosmic subjects had an idiopathic, 4 a postinfectious, and 5 a posttraumatic anosmia following minor head injury. A structural brain lesion was an exclusion criterion. All patients had no additional neurological or psychiatric deficits except the loss of the sense of smell. The time since the olfactory loss ranged from 1 to 21 years with an average of 4.15 years. The age of the patient group ranged from 19 to 64 years with a mean of 49.6 ± 13.8 years.

All control subjects self-estimated their ability of smelling as excellent. The average identification score was 14.9 ± 1.3 as evaluated with the 16 Sniffin' Sticks identification task. The obtained MRI scans showed no pathology especially signs of a chronic rhinosinusitis could be excluded. The age of the volunteers ranged from 22 to 65 years with a mean of 40.4 ± 14.9 years.

#### *MRI data acquisition*

All MR data were obtained with a 3.0-T scanner (Magnetom TrioTim System, Siemens) using a standard receiving 12-channel head coil. 3D magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence (repetition time [TR] = 2250 ms, echo time [TE] = 2.94 ms, flip angle = 9°, 192 slices, slice thickness 1 mm, matrix 224 × 256, in-plane voxel size 1 × 1 mm, total acquisition time 5:40 min) was acquired to obtain high-resolution $T_1$-weighted images of the brain. For fMRI analysis, an echo planar imaging (EPI) sequence with 755 whole-head volumes (TR = 3000 ms, TE = 35 ms, 40 slices, flip angle = 90°, slice thickness 3 mm, matrix 64 × 64) additionally to the anatomical $T_1$ scans were obtained.

#### *VBM and statistical analysis*

Data were processed and examined using the SPM5 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), where we applied VBM implemented in the VBM5 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 nonlinear transformations (warping), within a unified model (Ashburner and Friston 2005). Subsequently, analyses were performed on GM segments, which were multiplied by the nonlinear components derived from the normalization matrix in order to preserve actual GM values locally (modulated GM volumes). Importantly, GM 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 GM volumes were smoothed with a Gaussian kernel of 8-mm full width at half maximum (FWHM).

Voxelwise GM differences between anosmic patients and controls were examined using independent sample *t*-tests. In order to avoid possible edge effects between different tissue types, we excluded all voxels with GM values of less than 0.1 (absolute threshold masking). Because we had a strong a priori hypothesis about findings in the OB and primary and secondary olfactory areas, we applied a threshold of $P < 0.01$ across the whole brain. The data were corrected for potential age effects. Age was used as nuisance effect, which means that all effect that can be explained by age was removed from the data.

An additional analysis was performed to investigate the potential effect of disease duration. We used time since olfactory loss to divide the patients into 2 subgroups at a threshold of 2 years. The subgroup with a disease duration

>2 years consisted of 9 patients (7 females and 2 males; mean age 48.5 ± 15.5 years; mean time since olfactory loss 7.5 ± 6.4 years). The second subgroup with a disease duration ≤2 years comprised 8 patients (4 females and 4 males; mean age 50.7 ± 12.9 years; mean time since olfactory loss 1.2 ± 0.35 years). We analyzed the effect of disease duration by modeling the status as a 3-level gradation. Patients with longer disease duration were assigned a value of 1, patients with shorter disease duration a value of 0.5, and control subjects were assigned a value of 0. This model analyzes the increase of volume loss with increasing disease duration. This model assumes that the GM values in patients with shorter disease duration fall between those of the patients with longer disease duration and control subjects. Again, we applied a threshold of $P < 0.01$ across the whole brain.

### Functional MRI (study part 2)

#### *Subjects*

In the fMRI experiments, 20 normosmic, healthy subjects (9 males and 11 females) were investigated. The age of this group ranged from 19 to 71 years with a mean of 40.55 ± 19.8 years. The average TDI score was 33.39 ± 2.54.

#### *MRI data acquisition*

All MR data were obtained as described for study 1. Additionally to the anatomical $T_1$ scans, an EPI sequence with 755 whole-head volumes (TR = 3000 ms, TE = 35 ms, 40 slices, flip angle = 90°, slice thickness 3 mm, matrix 64 × 64) was performed.

#### *fMRI paradigm*

Twenty-five phenyl ethyl alcohol (PEA) stimuli (20% v/v) were presented to the right nostril for 1-s duration using an MRI compliant, computer-controlled, air dilution olfactometer OM4b (Burghart). The total gas flow was 8 L/min at a relative humidity of 80%. All subjects judged the perceived PEA intensity as moderate. Between the olfactory conditions, pseudorandomized resting periods with a mean duration of 85 s were inserted to avoid olfactory habituation. The trial went over 748 scans, which corresponds a total duration of 37 min and 42 s.

#### *fMRI data acquisition and analysis*

The acquired functional images were preprocessed and analyzed with the SPM8 software package (Wellcome Department of Cognitive Neurology, London, UK) running under a Matlab V7.8 environment (Mathworks, Inc.). Preprocessing included realignment, slice timing, coregistration of the high-resolution scans with the functional images, normalization, and spatial smoothing with an 8-mm FWHM isotropic Gaussian kernel. First-level analysis was performed over the whole-brain volume according to the used event-related design. The $P$ values of the subsequent second-level analysis were threshold set at $P < 0.001$.

## Results

No significant volume increases of the gray brain matter was observed when the patient group was compared with the control group at a threshold of $P < 0.01$. On the other hand, there were different significant atrophy areas of the GM as shown in Figure 1. The largest atrophy area was found in the medial prefrontal cortex (MPC) including the anterior cingulate cortex (ACC) and middle cingulate cortex (MCC). This cluster was also significant at a cluster extent threshold of $P < 0.001$, corrected for multiple comparisons using familywise error (FWE). A second area was found in the subcallosal gyrus (SCG) and nucleus accumbens (NAc). Further volume decreases were observed in the dorsolateral prefrontal cortex (dlPFC), cerebellum, and the superior occipital gyrus (SOG). Smaller atrophy areas were seen among others in the piriform cortex (PC), the anterior insular cortex (IC), the orbital frontal cortex (OFC), the supramarginal gyrus (SMG), the precuneus (Prec), the hippocampus, and in the parahippocampal region (Table 1). Patients with a disease duration longer than 2 years showed a stronger atrophy in these areas compared with patients who where anosmic less than 2 years (Figure 3).

To exclude trauma effects even without structural defects by the subgroup of patients with minor head trauma, in a separate analysis, all subjects without posttraumatic anosmia were examined ($n = 12$). Here similar results especially atrophy areas in the MPC and SCG/NAc could be shown.

In the fMRI analysis, bilateral olfactory activation was found in the anterior insula, the rolandic operculum, the dlPFC, the PC, the MPC/ACC, the medial OFC, the MCC, the SMG, Prec, and the cerebellum. Unilateral activations were seen in the right thalamus and left parietal inferior lobule (Table 2).

## Discussion

Cerebral structures involved in the olfactory processing are the OBs, the primary olfactory cortex, and secondary olfactory areas. The olfactory sensory neurons of the nasal olfactory epithelium project their axons in the OB, where first processing of the olfactory input occurs. From there, the efferent information is transferred via the olfactory tract to the primary olfactory cortex, which consists of several distinct areas like the PC, entorhinal cortex (EC), amygdala, anterior olfactory nucleus, and olfactory tubercle (Gottfried 2006; Shepherd 2006). These areas are intimately connected to secondary olfactory centers like the IC, orbitofrontal cortex (OFC), thalamus, hippocampus, and ACC. All mentioned areas, except the IC, are part of the limbic system (Tien et al. 1994). Therefore, the central olfactory system is closely interconnected with limbic structures. Olfaction

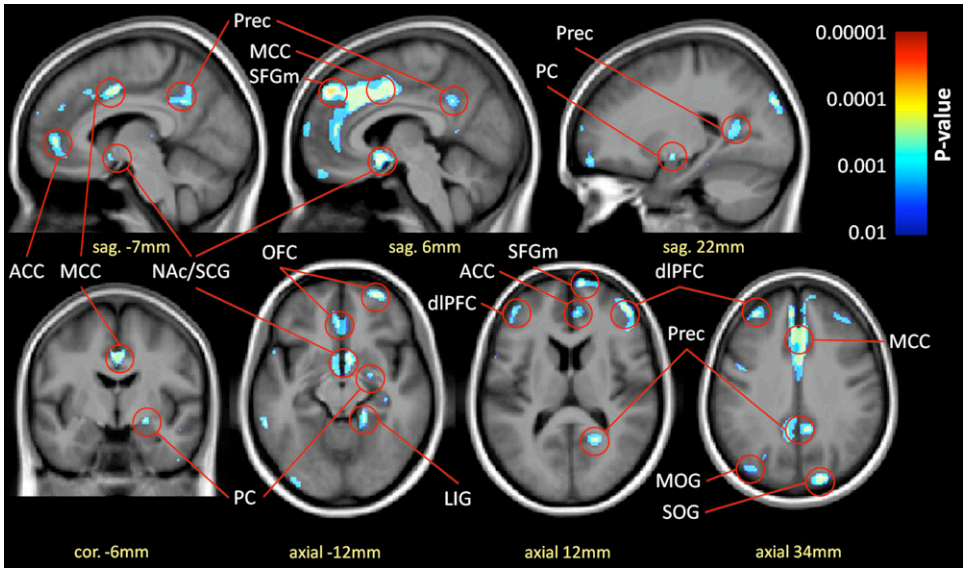


**Figure 1** This image shows the reductions in GM in 17 patients with anosmia compared with 17 healthy controls. The result is thresholded at $P < 0.01$ and overlayed onto the average $T_1$ image of all subjects. The top row shows 3 sagittal slices, whereas in the bottom row, 1 coronal slice and 3 axial slices are presented. All coordinates are given in Montreal Neurological Institute space. SFGm, SFG, medial; MOG, middle occipital gyrus; LIG, lingual gyrus.

is the only human sense that bypasses the thalamus as ''gate to consciousness.'' This means that emotionally evaluation of olfactory information occurs without and before cognitive processing occurs (Cleland and Linster 2003). In the fMRI experiments of our study, many of these primary and secondary olfactory areas could be demonstrated.

The most important result of the VBM analysis was to demonstrate 3 main atrophy areas in anosmics—the MPC including ACC/MCC, the dlPFC, and the SCG/NAc. The MPC was the only area that was even significant at $P < 0.001$ (FWE corrected). A further volume loss could be found in areas known to be involved in olfaction like the right PC as part of the primary olfactory cortex, the right IC, and the right OFC (Gottfried 2006) or areas involved in olfactory memory like dlPFC (Dade et al. 2001), superior temporal gyrus, superior frontal gyrus (SFG), lingual area, inferior parietal lobule, SMG, hippocampus, parahippocampal gyrus, and cerebellum (Cerf-Ducastel and Murphy 2006). Obvious is the right-sided preference of the atrophy in these areas.

In order to evaluate the functional significance of these areas, a direct comparison of the VBM results with the fMRI data was performed (Figure 2). An obvious overlap of the cerebral olfactory activations in healthy subjects and the GM loss in anosmics in the MPC can be seen. This underlines the involvement of this area in olfactory processing. In the dlPFC, the right PC, the right anterior IC, and the right cerebellum, such an overlap could also be measured. In opposite, for the SCG and the NAc, such a correlation has not been observed. Maybe this is due to susceptibility artifacts in the EPI sequences, which complicate the measurement of fMRI signal in these areas near the base of the skull (Du et al. 2007). But, nevertheless, there are other functional imaging studies, which could prove the involvement of these areas in olfaction (Royet et al. 1999; Gottfried et al. 2002).

The NAc is a component of the limbic loop of the basal ganglia. It receives its main projections from the ACC, IC, EC, and OFC, which are all primary or secondary olfactory areas. Closing the circuit, the NAc projects back to these areas via the mediodorsal nucleus of the thalamus and the ventral and dorsal prefrontal cortices (Zahm 2000). In an event-related fMRI study on olfactory associative learning, the NAc was suggested as olfactory reward center (Gottfried et al. 2002). Furthermore, the NAc plays a crucial role in appetite control (Baldo and Kelley 2007) and taste memory formation (Ramirez-Lugo et al. 2007). Therefore, it is reasonable that the loss of olfaction, which also means the loss of the ''taste'' of foods, also implicates the NAc as seen in our study.

Besides the NAc volume loss, a highly significant GM reduction in the MPC including the ACC has been found in this study. The MPC is like the OFC, a division of the prefrontal cortex, and can be subdivided into the infralimbic cortex, prelimbic cortex, and ventral and dorsal ACC (Ongur and Price 2000). As mentioned above, these MPC areas are critically involved in the limbic circuit of the basal ganglia. In addition, especially the ACC is a well-known secondary olfactory area, which is (besides the anterior IC, frontal operculum, and OFC) a key node in the ''flavor network'' (Small and Prescott 2005). Therefore, it is not surprising that an involvement of the MPC in eating disorders could be shown (Uher et al. 2004). Furthermore, Varney et al. (2001) showed in a positron emission tomography (PET) study on patients with posttraumatic anosmia a hypometabolism in the MPC

**Table 1** Reductions in GM in 17 patients with anosmia compared with 17 healthy controls

| Region | Side | MNI coordinates (mm) | | | *Z* score | Cluster size (voxels) |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | |
| MCC/ACC | L | −4 | 2 | 42 | 3.69 | 16663[a] |
| | R | 4 | 6 | 40 | 3.59 | |
| Medial SFG (SFGm) | R | 5 | 48 | 41 | 3.67 | |
| dlPFC | R | 44 | 48 | 11 | 3.14 | 3112[a] |
| | R | 37 | 37 | 37 | 2.76 | 923 |
| | L | −33 | 43 | 36 | 3.18 | 825 |
| | L | −43 | 46 | 9 | 2.86 | 674[a] |
| SOG | R | 15 | −93 | 30 | 3.50 | 1750 |
| NAc/SCG | R | 6 | 9 | −13 | 3.05 | 1667 |
| | L | −4 | 6 | −10 | 2.76 | |
| Cerebellum | R | 47 | −68 | −28 | 3.05 | 1605 |
| | L | −45 | −53 | −42 | 2.48 | 130[a] |
| SFGm | R | 10 | 68 | 10 | 3.15 | 933 |
| SFG | R | 19 | 67 | 12 | 2.50 | |
| | L | −21 | 32 | 38 | 3.09 | 148 |
| Prec | R | 20 | −56 | 12 | 2.85 | 850 |
| | L | −10 | −71 | 59 | 2.58 | 105 |
| SMG | R | 48 | −42 | 23 | 3.33 | 772 |
| | R | 37 | −32 | 40 | 2.64 | 156 |
| Middle occipital gyrus (MOG) | L | −29 | −94 | −5 | 2.83 | 754 |
| | L | −36 | −79 | 33 | 2.65 | 368 |
| | L | −27 | −76 | 28 | 2.63 | 251 |
| Lingual gyrus (LIG) | R | 18 | −39 | −12 | 3.00 | 648 |
| Precentral gyrus | L | −50 | 4 | 31 | 2.71 | 638 |
| Parahippocampal gyrus/fusiform gyrus | R | 33 | −32 | −27 | 2.91 | 453 |
| | R | 35 | −14 | −39 | 2.59 | 200 |
| OFC | R | 7 | 55 | −24 | 2.72 | 347 |
| Middle temporal gyrus | L | −60 | −41 | −13 | 2.95 | 330 |
| | L | −52 | −67 | −3 | 2.52 | 297 |
| Inferior temporal gyrus | L | −52 | −45 | −27 | 2.80 | 280 |
| Hippocampus | R | 36 | −21 | −16 | 2.81 | 213 |
| Superior temporal gyrus | R | 55 | −27 | 0 | 2.67 | 140 |
| Inferior parietal cortex | L | −41 | −61 | 54 | 2.63 | 126 |
| IC | R | 34 | 20 | −6 | 2.52 | 112[a] |
| PC | R | 22 | −7 | −10 | 2.79 | 90[a] |

The result is thresholded at $P < 0.01$, and only clusters exceeding a size of 90 voxels are reported. The cluster in the cingulated cortex (MCC/ACC) was also significant at a cluster extent threshold of $P < 0.001$, corrected for multiple comparisons. All coordinates are given in Montreal Neurological Institute (MNI) space.

[a]Areas that overlap with olfactory active regions in the fMRI part of this study.

**Table 2** Results of the fMRI group analysis

| Region | Side | MNI coordinates (mm) | | | *Z* score | Cluster size (voxels) |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | |
| Insula | R | 38 | 6 | −10 | 5.90 | 3755 |
| dlPFC | | 36 | 38 | 8 | 5.33 | |
| PC | | 24 | 0 | −14 | 4.50 | |
| Rolandic operculum (ROP) | | 52 | −6 | 12 | 4.45 | |
| dlPFC | L | −34 | 34 | 16 | 5.09 | 2588 |
| ROP | | −36 | −8 | 14 | 4.76 | |
| Insula | | −36 | 14 | 0 | 4.59 | |
| PC | | −24 | 0 | −14 | 4.41 | |
| Cerebellum | L | −8 | −82 | −28 | 5.56 | 1244 |
| | R | 22 | −62 | −24 | 3.43 | 14 |
| MPC | M | 2 | 16 | 46 | 4.05 | 159 |
| Medial orbitofrontal cortex (mOFC) | R | 22 | 32 | −14 | 4.66 | 115 |
| | L | −22 | 34 | −14 | 4.64 | 137 |
| Prec | L | −32 | −54 | 6 | 4.46 | 94 |
| | R | 10 | −66 | 42 | 3.65 | 23 |
| SMG | R | 36 | −50 | 38 | 3.96 | 116 |
| | L | −38 | −52 | 40 | 3.48 | 37 |
| MCC | M | 4 | −22 | 28 | 3.52 | 108 |
| Thalamus | R | 8 | −4 | 6 | 3.79 | 56 |
| Parietal inferior lobule (IPL) | L | −58 | −36 | 50 | 3.53 | 47 |

PEA was applied 25 times to the right nostrils to stimulate the olfactory system. Thresholds were set at $P < 0.001$. All coordinates are given in Montreal Neurological Institute (MNI) space.

as well as in the OFC. This hypometabolism could correlate to the GM decrease in the MPC measured by VBM in our study. Interestingly, also activity increases in the visual association cortex were described (Varney et al. 2001).

In the VBM analysis, we also found occipital atrophy areas like the SOG and Prec. Especially, the Prec plays an important role in the recall of episodic memories as well as during olfactory matching (Qureshy et al. 2000). Therefore, the Prec can be added to the above-described other atrophy areas known to be involved in the olfactory memory. This underlines that after olfactory loss, a considerable structural remodeling of the GM in olfactory memory areas occurs. In the fMRI experiments, bilateral Prec activations were also seen, but these were not overlapping in the direct comparison of the fMRI with the VBM data set.

In the analysis of disease duration, we found as expected a correlation between disease duration and extent of the observed GM atrophy (Figure 3). No brain region of the anosmic group showed a compensatory increase of GM. This is in opposite to other sensory modalities like the auditory (Penhune et al. 2003) and visual system (Noppeney et al. 2005) where a sensory impairment also leads to a compensatory volume increase in other areas. But olfaction is a special sense. An olfactory loss, in contrast to the other modalities, is not compensated by the remaining senses. Contrary, it was shown that in patients with a decrease in olfactory performance also a decrease in gustatory function (Gudziol et al. 2007) and trigeminal sensibility (Gudziol et al. 2001) occurs and not, as one could expect, an improved performance.

It is a well-known phenomenon that in patients with olfactory impairment, a volumetric decrease in the OB can be observed (Mueller et al. 2005). Interestingly, this effect seems to be fully reversible when the cause of the olfactory disorder has been diminished, for example, when a surgical intervention in patients with sinunasal anosmia takes place (Gudziol et al. 2009). We could not observe any volumetric changes in the OB by VBM. This might be caused by the poor visualization of the OB in the MP-RAGE sequence and therefore limited segmentation possibilities of this small structure. We aimed in our study on structures beyond the OB, so the

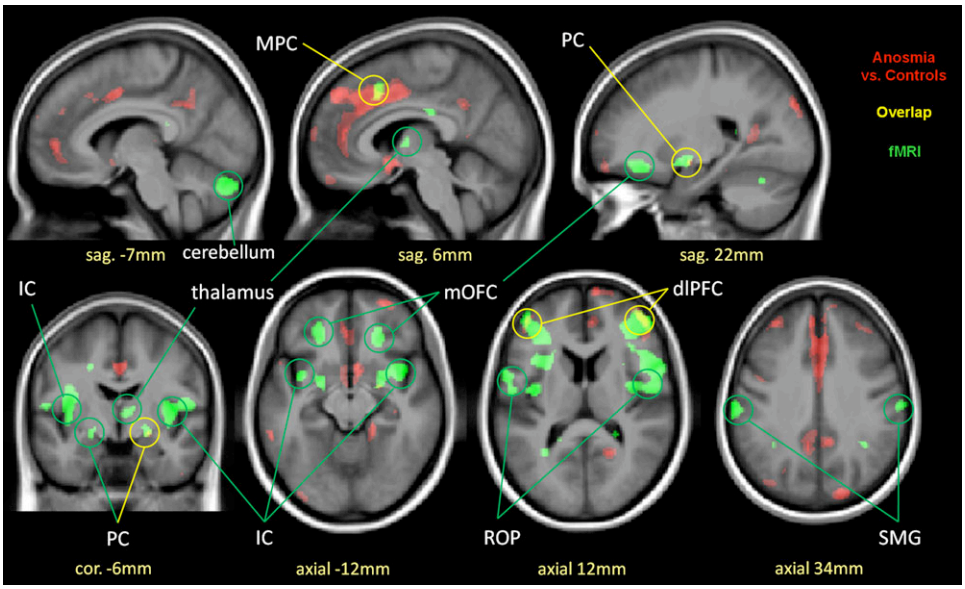


**Figure 2** This image demonstrates the overlap between the reductions in GM in 17 patients with anosmia compared with 17 healthy controls (red colors) and the fMRI result (green colors). A overlap of the cerebral olfactory activations in the fMRI experiments and the GM loss in anosmics could be demonstrated for the MPC, the right PC, and the dlPFC. No such effect could be observed for the NAc/SCG. The VBM results are thresholded at $P < 0.01$, and the fMRI results are thresholded at $P < 0.001$. The top row shows 3 sagittal slices, whereas in the bottom row, 1 coronal slice and 3 axial slices are presented. All coordinates are given in Montreal Neurological Institute space.

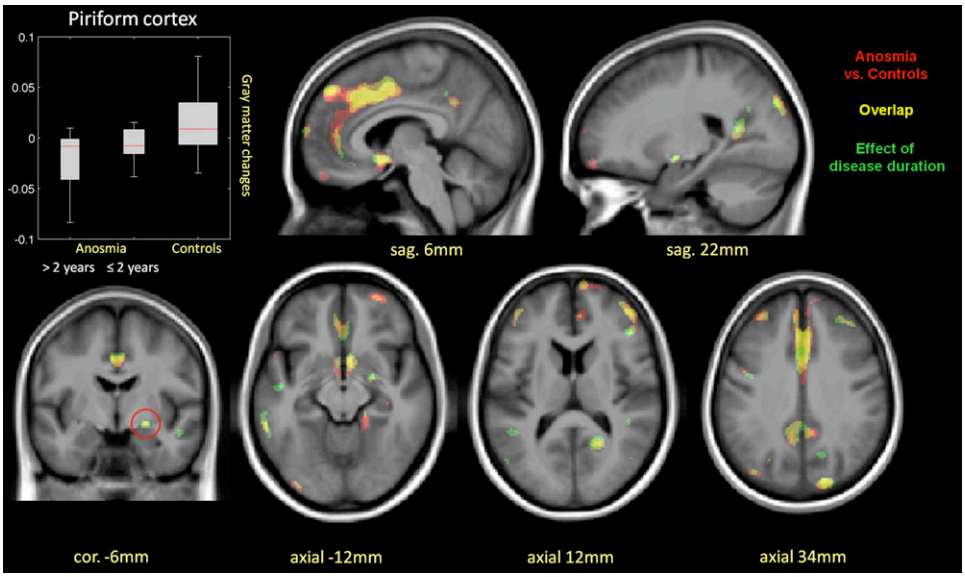


**Figure 3** This figure shows the effect of disease ($P < 0.01$). On the upper left side, a boxplot of patients with disease duration of more than 2 years, less or equal to 2 years, and the control group in the right PC is presented.

MP-RAGE sequence was most suitable. A $T_2$-weighted constructive interference in steady-state sequence would be more appropriate for OB visualization. But if this sequence is also suitable for VBM or only for volumetric studies using manual segmentation has still to be evaluated. Furthermore, a volume reduction in the primary olfactory cortex could only be seen in the right PC. The reason for this unilateral volume loss remains unclear. Maybe an extension of our study in order to achieve a higher number of anosmics in the patient group can finally show subtle changes also in the left PC.

Olfactory impairment is a well-known phenomenon in neurological diseases like major depression, bipolar disorders, multiple sclerosis, schizophrenia, Parkinson's disease (PD), and Alzheimer's disease (AD) (Murphy et al. 2003). It often precedes the onset of other neurological symptoms as observed in AD and PD (Albers et al. 2006). In numerous

volumetric studies, a GM loss in these diseases could be shown. Thereby, areas corresponding to our results were described. For example, in AD atrophy in the GM of the cingulate cortex, the septal region (Callen et al. 2001), the OFC (McEvoy et al. 2009), SFG (Teipel et al. 2005), the MPC, and the Prec (Karas et al. 2007) have been demonstrated. In patients with major depression, a volume reduction of the ACC, dlPFC, and the SCG (Yucel et al. 2008; Koenigs and Grafman 2009) and in patients with PD similar atrophy areas in the ACC and NAc (Summerfield et al. 2005) have been described. ACC atrophy also has been found in schizophrenic patients (Fujiwara et al. 2007) as well as in patients with bipolar disorders (Konarski et al. 2008). The pattern of GM loss observed in these studies is similar to our findings. Therefore, it can be concluded that the loss of the sense of smell results in changes of the cerebral GM according to the changes in patients with various neurological diseases.

In summary, many neurological diseases, especially neurodegenerative diseases like AD and PD, are accompanied with olfactory impairments. This raises the question if the decrease of gray brain matter of the MPC and NAc is part of the neurological disease per se or sign of the concomitant olfactory deficit. We postulate that the olfactory deficit contributes significantly to the, in the literature described, volumetric changes in these diseases. Another possible interpretation is that the cortical atrophy leads itself to the olfactory impairment. To prove this hypothesis, further studies in these patient collectives must be performed to show if there is such a correlation between GM reduction and olfactory impairment.

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