BRAIN RESEARCH 1347 (2010) 42–47

available at www.sciencedirect.com

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

# Gray and white matter reduction in hyposmic subjects — A voxel-based morphometry study

Thomas Bitter[a,*], Johanna Brüderle[a], Hilmar Gudziol[a], Hartmut Peter Burmeister[b], Christian Gaser[c], Orlando Guntinas-Lichius[a]

[a]Department of Otorhinolaryngology, Friedrich-Schiller-University, Jena, Germany
[b]Institute of Diagnostic and Interventional Radiology, Friedrich-Schiller-University, Jena, Germany
[c]Department of Psychiatry, Friedrich-Schiller-University, Jena, Germany

ARTICLE INFO

*Article history:*
Accepted 1 June 2010
Available online 8 June 2010

*Keywords:*
Human
Olfaction
Structural plasticity
Laterality
Volumetry
Magnetic resonance imaging

ABSTRACT

The absence of olfactory input causes structural brain remodelling in humans. Mainly, the olfactory bulb and cortical olfactory areas are involved in this process. The aim of our study was to investigate volume changes of the gray and white matter in a group of subjects with an impaired but not complete loss of olfaction (hyposmia). Magnetic resonance images of hyposmic subjects and an age- and sex-matched control group were acquired on a 3 T scanner. Voxel-based morphometry (VBM) was performed using VBM8 toolbox and SPM8 in a Matlab environment. The analysis revealed significant gray matter volume loss in the insular cortex, anterior cingulate cortex, orbitofrontal cortex, cerebellum, fusiform gyrus, precuneus, middle temporal gyrus and piriform cortex. In the VBM white matter analysis areas of volume loss were found underneath the insular cortex, in the cerebellum and middle frontal gyrus. All areas of white matter atrophy were spatially connected to areas of gray matter volume loss except the middle frontal gyrus alterations. No significant gray or white matter volume increases could be observed. The pattern of gray matter alterations was similar to that known from anosmic subjects with a lower extent. To our knowledge, we report here for the first time on white matter volume alterations in patients with olfactory deficit.



## 1. Introduction

Several studies indicated that an impaired sense of olfaction leads to structural changes in the human brain. These changes may involve areas at the level of the olfactory bulb (OB), primary and secondary olfactory brain areas as well as association cortices. In this regard, the OB is well studied: It has been shown that the absence of olfactory afferent input results in a decrease of the OB volu me as observed e.g. in patients with post-viral anosmia (Rombaux et al., 2006a) and post-traumatic anosmia (Mueller et al., 2005; Rombaux et al., 2006b). Interestingly, patients who incorrectly perceive actually present odours (parosmia) have a stronger OB volume reduction compared with olfactory impaired patients without parosmia (Abolmaali et al., 2008).

Cortical brain areas beyond the OB have achieved less attention in the past and only a few studies focussed on these regions. In a previous voxel-based morphometry (VBM) study

* *Corresponding author*. Department of Otorhinolaryngology, Friedrich-Schiller-University, Lessingstrasse 2, D-07740 Jena, Germany. Fax: +49 3641 935 129.
E-mail address: Thomas.Bitter@med.uni-jena.de (T. Bitter).

0006-8993/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2010.06.003

we investigated the gray matter of patients with a complete loss of olfaction (anosmia). In this group of patients we could show a gray matter loss in regions like the piriform cortex (PC) as part of the primary olfactory cortex, in secondary olfactory areas like the anterior insula cortex (IC), anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) and other areas like cerebellum, precuneus (Prec), fusiform gyrus, nucleus accumbens and subcallosal gyrus. Unfortunately, VBM seemed not to be appropriate to demonstrate the assumed changes in the OB volume as mentioned above (Bitter et al., 2010).

Frasnelli et al. studied the correlation of olfactory performance and cortical thickness in healthy subjects using an automated measuring technique. Here, these authors observed a correlation between the olfactory performance of healthy subjects and cortical thickness of distinct structures like the OFC, IC and adjacent cortex, and areas around the central sulcus (Frasnelli et al., 2010).

In the present study we focussed on patients with a reduced but not absent sense of smell. The aim was to evaluate structural changes in brain areas of these hyposmic patients using VBM technique. The hypothesis was to show alterations in similar areas as previously reported for anosmic subjects in a lower degree. Until now, nothing is known about changes in the white matter in patients with an impaired sense of smell. Therefore, the second aim of this study was to evaluate if probable gray matter changes are accompanied by white matter alterations. To our knowledge the present VBM analysis is the first study on changes in the white matter in patients with olfactory disorders.

## 2. Results

The VBM analysis revealed various areas of significant volume loss in the gray matter of the hyposmic group. The largest atrophic area was found in the right hemisphere and included the anterior insular cortex (IC), parts of the adjacent orbitofrontal cortex (OFC) and extended to the right fusiform gyrus, middle temporal gyrus (MTG) and piriform cortex (PC). On the left hemisphere apparent smaller anterior IC atrophy was seen (487 vs. 1722 voxels). A further gray matter volume loss was found in the middle portion of the IC bilaterally (305 voxels each). Cerebellar atrophy was found only on the left side. Further affected areas were located in the gray matter of the anterior cingulate cortex (ACC), the right OFC, the left fusiform gyrus and the precuneus (Prec) bilaterally (Table 1, Fig. 1).

In the VBM white matter analysis two large atrophic areas were found directly below the IC region, bilaterally. Both areas reached the corresponding gray matter atrophy in the middle portion of the IC and extended in inferior direction between IC and thalamus (Table 2, Fig. 2). A left-sided white matter loss of the cerebellum has also been observed. It was spatially connected to the gray matter alterations in the left cerebellum (Fig. 3). Furthermore, two atrophic areas in the middle frontal gyrus on both sides were seen. Here the left hemispheric area was located near the precentral gyrus (Table 2, Fig. 2). In opposite to the other areas no correlation to any of the above described areas of gray matter loss could be observed at the chosen thresholds. No significant gray or white matter volume increases could be observed at a threshold of $p<0.001$.

**Table 1 – Reductions of gray matter in patients with hyposmia compared to healthy controls. The result is thresholded at $p<0.001$ and only clusters exceeding a size of 75 voxels are reported. All coordinates are given in MNI-space.**

| Region | Side | MNI coordinates [mm] | | | Z-score | Cluster size [voxels] |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Anterior insular cortex | R | 36 | 20 | −8 | 4.08 | 1722 |
| Orbitofrontal cortex | | 30 | 15 | −18 | 4.01 | |
| Middle temporal gyrus | | 59 | −6 | −18 | 3.55 | |
| Fusiform gyrus | | 56 | −11 | −30 | 3.45 | |
| Piriform cortex | | 28 | 10 | −19 | 3.37 | |
| Anterior insular cortex | L | −30 | 21 | 1 | 3.82 | 487 |
| Mid-insular cortex | L | −38 | −1 | 7 | 3.97 | 305 |
| Mid-insular cortex | R | 35 | −6 | 10 | 3.51 | 305 |
| Cerebellum | L | −38 | −76 | −21 | 3.92 | 318 |
| | L | −35 | −67 | −36 | 3.79 | 275 |
| Anterior cingulate cortex | R | 3 | 32 | 24 | 3.78 | 281 |
| Orbitofrontal cortex | R | 23 | 50 | −9 | 3.70 | 140 |
| Precuneus | R | 20 | −66 | 43 | 4.03 | 118 |
| Fusiform gyrus | L | −56 | −19 | −29 | 3.43 | 96 |
| Precuneus | L | −14 | −78 | 21 | 3.56 | 91 |

## 3. Discussion

A reduced or absent sensory input results in structural brain reorganization as reported e.g. for the visual (Pan et al., 2007), auditory (Shibata, 2007) or vestibular system (Hufner et al., 2009). After complete olfactory loss such a remodelling is a well known phenomenon at the level of the OB (Mueller et al., 2005) and in distinct areas of the cortical gray matter (Bitter et al., 2010). As expected, in the present study we were not able to detect alterations in the OB. This result can be explained with the limits of VBM analysis using MP-RAGE sequences as discussed elsewhere (Bitter et al., 2010).

In the present study, only patients with an impaired but not complete loss of the sense of smell (hyposmia) were included. Therefore, all subjects of the patient group showed a TDI score between 16 and 25 corresponding to a moderate to severe hyposmia. In the VBM analysis the observed pattern of atrophic gray matter areas in these patients showed similarities but also differences to that known from patients with a complete olfactory loss (anosmia, TDI score$\leq$15) (Bitter et al., 2010). Common gray matter volume decreases were observed in the ACC, IC, OFC, fusiform gyrus, Prec, cerebellum, and PC. The PC is part of the primary olfactory cortex and involved in the early processing of olfactory input (Gottfried, 2006). The large atrophic area on the right hemisphere which included IC, OFC, and fusiform gyrus contained also anterior parts of the PC (Table 1). Compared to the PC gray matter alterations in anosmic subjects it was located more rostral in hyposmic patients. No volume loss in the left PC could be found. This laterality was also described in anosmics where also no left

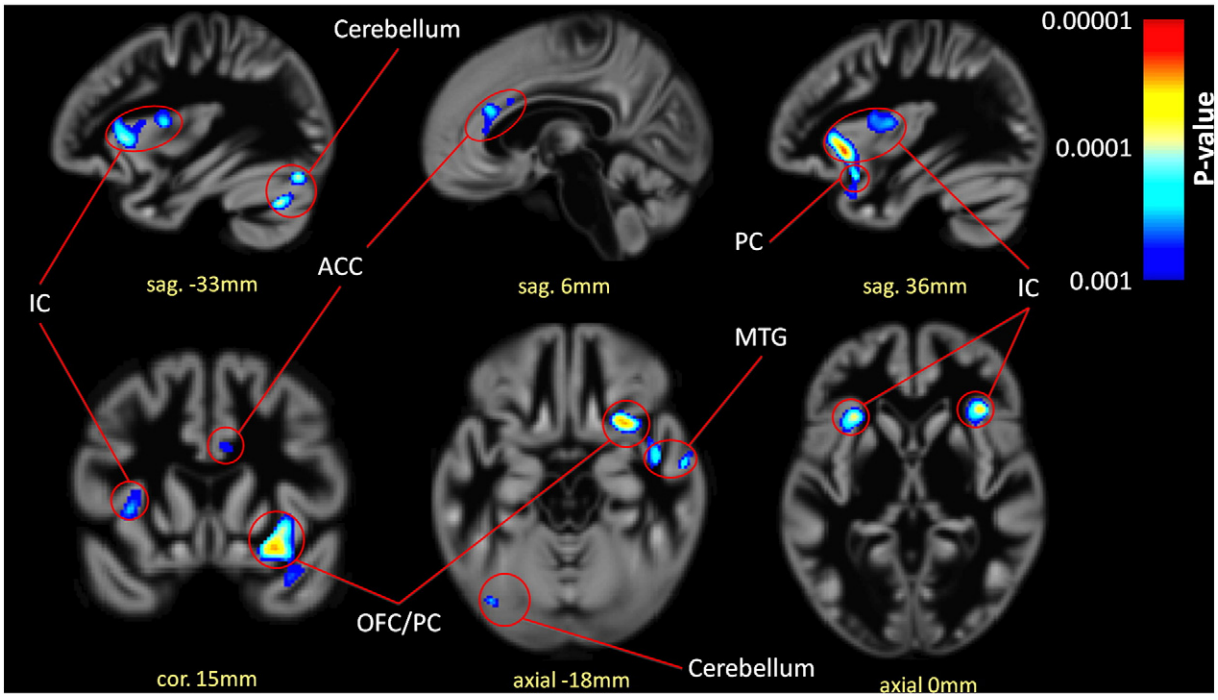


**Fig. 1 – Gray matter reductions in 24 hyposmic patients compared to healthy controls. The VBM result is thresholded at p < 0.001. The top row shows three sagittal slices, while in the bottom row one coronal slice and two axial slices are presented. All coordinates are given in MNI-space. Abbreviations: ACC — anterior cingulate cortex; IC — insular cortex; MTG — middle temporal gyrus; OFC — orbital frontal cortex; PC — piriform cortex; Prec — precuneus.**

hemispheric PC gray matter volume loss could be observed (Bitter et al., 2010). The same was seen in early Parkinson's disease patients where a positive correlation between olfactory performance and gray matter volume was observed exclusively in the right but not in the left PC (Wattendorf et al., 2009). The medial prefrontal cortex (MPC) including ACC was described to be the largest area of gray matter volume loss in anosmics (Bitter et al., 2010). In hyposmics volume loss in this secondary olfactory area was significantly smaller (Fig. 1). Therefore, it can be concluded that the MPC volume is strongly correlated to the olfactory performance. Another support for this conclusion comes from lesion studies where the importance of an intact MPC for odour identification could be clearly demonstrated (Fujiwara et al., 2008). The IC was the region with the most extensive gray matter volume loss. It is part of the secondary olfactory cortex. Two areas were involved — an anterior IC area and a smaller mid-insular region. Generally, the right IC was significantly more affected but also considerable left-sided IC atrophy could be demonstrated (Fig. 1). In contrast to the current study, in anosmic subjects only right-sided IC alterations were described. The reason for this difference is not clear. It may be speculated, that the present study was more sensitive in detection of subtle changes in the left IC due to the larger amount of participating subjects (57 vs. 34). At least, it seems that the IC volume does not correlate in a linear manner with the olfactory input as e.g. assumed for the MPC. In such a case a stronger volume loss in anosmic compared to hyposmic subjects would be expected. The pronounced volume loss in the right IC could be explained with the laterality in olfactory processing at IC level. Support for this assumption comes from several functional imaging studies which showed stronger activity in the right rather than the left IC during olfactory tasks (Bengtsson et al., 2001; Djordjevic et al., 2005; Wang et al., 2005). The OFC is another secondary olfactory area with a plenty of functions in olfactory processing (for review see (Rolls, 2004). Therefore, structural remodelling in this area was expected and also previously reported in anosmic subjects. In the VBM analysis of the gray matter it showed two regions of volume loss in the right hemisphere. One of them reached the right-sided IC atrophic area (Fig. 1). Prec involvement could also be demonstrated in the hyposmic group. This area is known to be connected to olfactory memory (Qureshy et al., 2000). Furthermore, the fusiform gyrus showed bilateral alterations. This region possesses no clear role in olfaction. But its involvement in chemosensory processing could

**Table 2 – Reductions of white matter in patients with hyposmia compared to healthy controls. Thresholds were set at p < 0.001 and an extent of 75 voxels. All coordinates are given in MNI-space. The superscripted numbers refer to the areas given in Figure 2.**

| Region | Side | MNI coordinates [mm] | | | Z-score | Cluster size [voxels] |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Insular cortex–thalamus[1] | R | 36 | −22 | 10 | 3.78 | 1080 |
| Insular cortex–thalamus[2] | L | −30 | −7 | 12 | 3.29 | 332 |
| Middle frontal gyrus[3] | L | −30 | −16 | 43 | 3.76 | 306 |
| Cerebellum[4] | L | −38 | −73 | −35 | 4.08 | 237 |
| Middle frontal gyrus[5] | R | 30 | 5 | 46 | 3.91 | 217 |

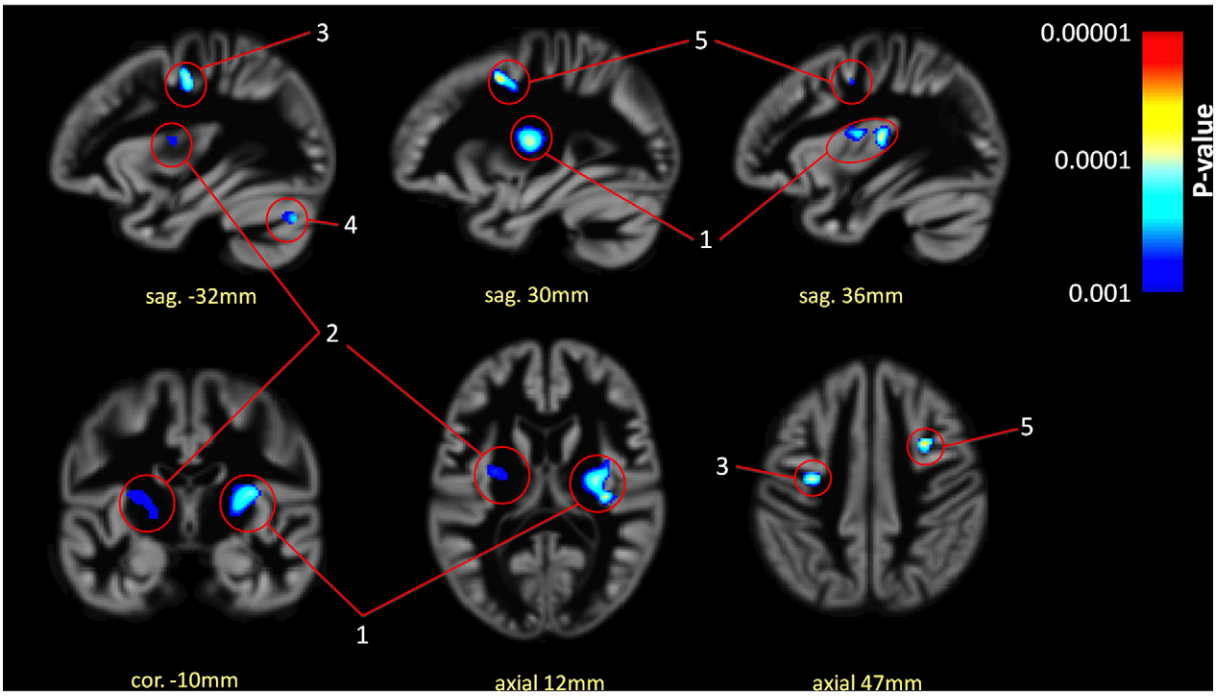


**Fig. 2 – White matter reductions in 24 hyposmic patients compared to healthy controls. The results are thresholded at p < 0.001. All areas are labelled according to Table 2. The top row shows three sagittal slices, while in the bottom row one coronal slice and two axial slices are presented. All coordinates are given in MNI-space.**

be previously demonstrated (Zhou and Chen, 2008). The contribution of the cerebellum in olfactory processing has been repeatedly demonstrated since early functional imaging studies (Sobel et al., 1998). It was assumed that the cerebellum maintains a feedback mechanism that regulates sniff volume in relation to odour concentration. A possible role in cognitive olfactory processing has also been proposed (Qureshy et al., 2000). But details of the cerebellar involvement still have to be elucidated. The MTG was the only region which showed gray matter volume loss in hyposmics but not in anosmics. The significance of MTG

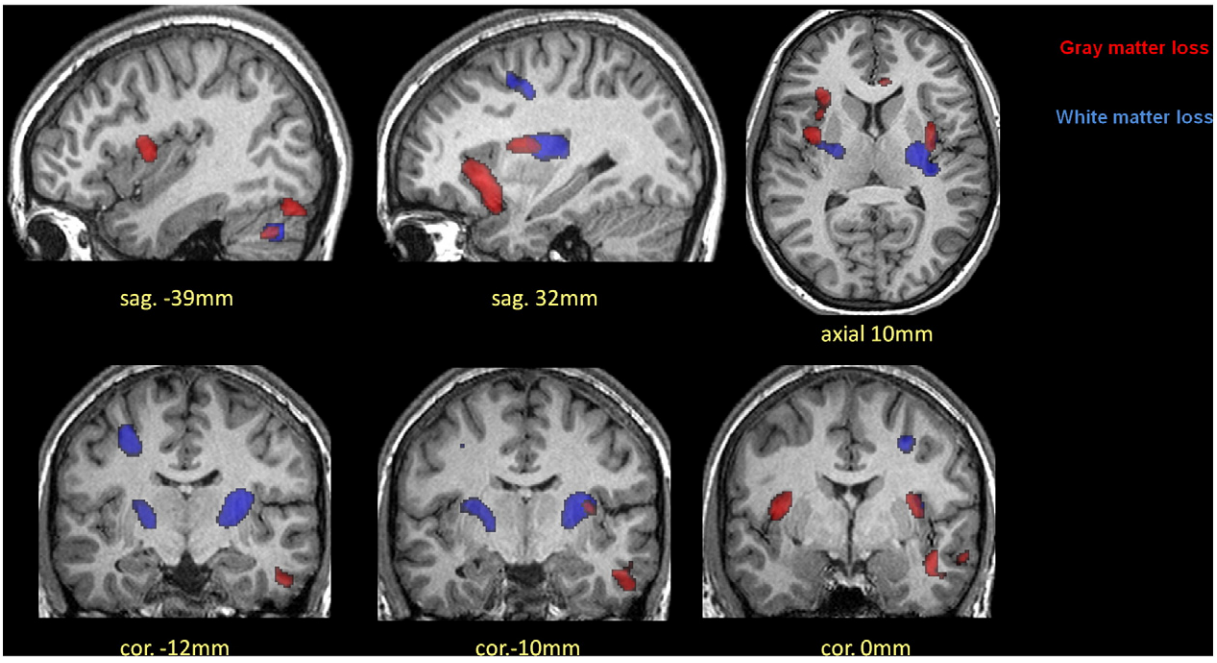


**Fig. 3 – Correlation between gray matter (red) and white matter loss (blue). The gray matter alterations of the IC and cerebellum showed underlying white matter atrophy. The threshold is set for both analyses at p < 0.001. The top row shows two sagittal slices and one axial slice, while in the bottom row three coronal slices are presented. All coordinates are given in MNI-space.**

volume loss is not clear since only a few studies showed an involvement of this area in olfactory tasks (Welge-Lussen et al., 2009).

In functional imaging studies a right-sided dominance in olfactory processing has been often described (Zatorre et al., 1992). In the current VBM study we found the most noticeable volume decrease in the right hemisphere as well. This fact can be seen as further evidence for the right hemispheric dominance in olfaction. This result is in accordance with a study concerning the correlation between gray matter thickness and olfactory performance in healthy subjects without olfactory impairment where also a mainly right hemispheric gray matter thickness decrease was shown (Frasnelli et al., 2010).

White matter changes in olfactory diseases have not been yet addressed. Only one study investigated white matter lesions in patients with multiple sclerosis and their ability for odour identification (Zorzon et al., 2000). Here, inferior frontal lobe and temporal lobe regions were defined as olfactory areas. A significant correlation between lesion load and lower performance in the Cross Cultural Smell Identification Test was seen. In contrast to Zorzon et al., in the present VBM study a user-independent evaluation of the whole white matter without the need of a-priori definition of regions of interest was performed. Furthermore, we studied subjects without additional neurological deficit except the impaired sense of smell. Therefore, besides the higher spatial resolution a higher conclusiveness of our study in regard of white matter volume changes and the correlation to olfactory performance is assumed. The observed white matter alterations showed a spatial relationship to the gray matter alterations in the IC and cerebellum (Fig. 3). No white matter decreases near the primary olfactory cortex could be demonstrated. The detection of alterations in these regions is difficult since these areas have only a limited size. Maybe an increase of the number of investigated subjects would reveal significant volume changes in these regions. Future studies may proof this hypothesis.

Olfactory deficit is known to be one of the first symptoms in neurodegenerative diseases like Alzheimer's or Parkinson's disease (Albers et al., 2006). Here, a central cause of the olfactory impairment can be assumed. To regard this fact in our investigated subjects we performed a VBM analysis on a subgroup of sinunasal hyposmics. In this group a peripheral origin of the olfactory impairment was supposed because of the obvious nasal obstruction due to polyps. This second VBM analysis showed mainly the same atrophic gray and white matter areas as described for the whole group (see additional electronic material). Therefore, we conclude that the observed gray and white matter changes are solely due the reduced olfactory input and not sign of a commencing neurodegenerative disorder which leads to the olfactory impairment. Furthermore it is deduced that different causes of olfactory impairment lead to similar cerebral alterations.

In conclusion, this is the first VBM study on hyposmic subjects. The investigated patient group exhibited a similar atrophic pattern with a lower extent compared to anosmic subjects. Only a few areas known to be atrophic in anosmic subjects could not be demonstrated. For the first time we were able to show structural white matter alterations in an olfactory disease. These areas showed with two exceptions a spatial relation to the observed gray matter atrophic areas.

It is known that volume decrease occurs in the OBs of hyposmic patients. This effect is reversible when the olfactory input is, e.g. post-surgery, enhanced (Gudziol et al., 2009). Therefore, further analyses are necessary to prove if an improved olfactory function (e.g. post-treatment or spontaneous remission) is also followed by an increase of the volume of formerly atrophic areas of cerebral gray and white matter described in this study.

## 4. Experimental procedures

### 4.1. *Subjects*

24 hyposmic patients (58.3% male) and 43 sex- and age-matched control subjects (58.1% male) were included in the study. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The threshold discrimination identification (TDI) score for the hyposmic patients was determined by the Sniffin' Sticks test (Kobal et al., 2000) and ranged from 16.75 to 24.75 (average 20.6±2.6). 16 of the hyposmic subjects had a sinunasal, five a post-infectious and two a post-traumatic anosmia following minor head injury. Structural brain lesions as well as the presence of parosmia and phantosmia were exclusion criteria for all participants. In all cases duration of hyposmia was more than 10 months. Commonly, most subjects were hyposmic for years. All patients had no additional neurological or psychiatric deficits except the impaired sense of smell. The Mini-Mental-State-Examination (MMSE) showed an average value of 28.3±1.5. The age of the patient group ranged from 18 to 55 years with a mean of 43.0±11.4 years.

All control subjects self-estimated their ability of smelling as excellent. The TDI score ranged from 30.0 to 39.5 with an average value of 34.1±2.5. The obtained MRI scans showed no pathology. The age of the volunteers ranged from 22 to 68 years with a mean of 43.0±13.8 years. All participants had given their written consent and the study had been approved by the local ethical committee. The study was performed according to the guidelines of the Declaration of Helsinki 1975.

### 4.2. *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. 3-D magnetization prepared rapid acquisition gradient echo (MP-Rage) sequence (TR=2300 ms, TE=3.03 ms, flip angle=9°, 192 slices, slice thickness 1 mm, matrix 256×256, in-plane voxel size 1 mm×1 mm, and total acquisition time 5:20 min) was acquired to obtain high-resolution T1 weighted images of the brain.

### 4.3. *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 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).

Voxel-wise GM and WM differences between hyposmic 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 or WM values of less than 0.1 (absolute threshold masking). We applied a threshold of $p<0.001$ with an extent of 75 voxels across the whole brain. Age was used as nuisance effect, which means that all effect that can be explained by age was removed from the data.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.brainres.2010.06.003.

## REFERENCES


Abolmaali, N., Gudziol, V., Hummel, T., 2008. Pathology of the olfactory nerve. Neuroimaging Clin. N. Am. 18, 233–242 preceding x.

Albers, M.W., Tabert, M.H., Devanand, D.P., 2006. Olfactory dysfunction as a predictor of neurodegenerative disease. Curr. Neurol. Neurosci. Rep. 6, 379–386.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851.

Bengtsson, S., Berglund, H., Gulyas, B., Cohen, E., Savic, I., 2001. Brain activation during odor perception in males and females. NeuroReport 12, 2027–2033.

Bitter, T., Gudziol, H., Burmeister, H.P., Mentzel, H.J., Guntinas-Lichius, O., Gaser, C., 2010. Anosmia leads to a loss of gray matter in cortical brain areas. Chem. Senses 35, 407–415.

Djordjevic, J., Zatorre, R.J., Petrides, M., Boyle, J.A., Jones-Gotman, M., 2005. Functional neuroimaging of odor imagery Neuroimage 24, 791–801.

Frasnelli, J., Lundstrom, J.N., Boyle, J.A., Djordjevic, J., Zatorre, R.J., Jones-Gotman, M., 2010. Neuroanatomical correlates of olfactory performance. Exp. Brain Res. 201, 1–11.

Fujiwara, E., Schwartz, M.L., Gao, F., Black, S.E., Levine, B., 2008. Ventral frontal cortex functions and quantified MRI in traumatic brain injury. Neuropsychologia 46, 461–474.

Gottfried, J.A., 2006. Smell: central nervous processing. Adv. Otorhinolaryngol. 63, 44–69.

Gudziol, V., Buschhuter, D., Abolmaali, N., Gerber, J., Rombaux, P., Hummel, T., 2009. Increasing olfactory bulb volume due to treatment of chronic rhinosinusitis—a longitudinal study. Brain 132, 3096–3101.

Hufner, K., Stephan, T., Hamilton, D.A., Kalla, R., Glasauer, S., Strupp, M., Brandt, T., 2009. Gray-matter atrophy after chronic complete unilateral vestibular deafferentation. Ann. N. Y. Acad. Sci. 1164, 383–385.

Kobal, G., Klimek, L., Wolfensberger, M., Gudziol, H., Temmel, A., Owen, C.M., Seeber, H., Pauli, E., Hummel, T., 2000. Multicenter investigation of 1, 036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur. Arch. Otorhinolaryngol. 257, 205–211.

Mueller, A., Rodewald, A., Reden, J., Gerber, J., von Kummer, R., Hummel, T., 2005. Reduced olfactory bulb volume in post-traumatic and post-infectious olfactory dysfunction. NeuroReport 16, 475–478.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Pan, W.J., Wu, G., Li, C.X., Lin, F., Sun, J., Lei, H., 2007. Progressive atrophy in the optic pathway and visual cortex of early blind Chinese adults: a voxel-based morphometry magnetic resonance imaging study. Neuroimage 37, 212–220.

Qureshy, A., Kawashima, R., Imran, M.B., Sugiura, M., Goto, R., Okada, K., Inoue, K., Itoh, M., Schormann, T., Zilles, K., Fukuda, H., 2000. Functional mapping of human brain in olfactory processing: a PET study. J. Neurophysiol. 84, 1656–1666.

Rolls, E.T., 2004. The functions of the orbitofrontal cortex. Brain Cogn. 55, 11–29.

Rombaux, P., Mouraux, A., Bertrand, B., Nicolas, G., Duprez, T., Hummel, T., 2006a. Olfactory function and olfactory bulb volume in patients with postinfectious olfactory loss Laryngoscope 116, 436–439.

Rombaux, P., Mouraux, A., Bertrand, B., Nicolas, G., Duprez, T., Hummel, T., 2006b. Retronasal and orthonasal olfactory function in relation to olfactory bulb volume in patients with posttraumatic loss of smell. Laryngoscope 116, 901–905.

Shibata, D.K., 2007. Differences in brain structure in deaf persons on MR imaging studied with voxel-based morphometry. AJNR Am. J. Neuroradiol. 28, 243–249.

Sobel, N., Prabhakaran, V., Hartley, C.A., Desmond, J.E., Zhao, Z., Glover, G.H., Gabrieli, J.D., Sullivan, E.V., 1998. Odorant-induced and sniff-induced activation in the cerebellum of the human. J. Neurosci. 18, 8990–9001.

Wang, J., Eslinger, P.J., Smith, M.B., Yang, Q.X., 2005. Functional magnetic resonance imaging study of human olfaction and normal aging. J. Gerontol. A Biol. Sci. Med. Sci. 60, 510–514.

Wattendorf, E., Welge-Lussen, A., Fiedler, K., Bilecen, D., Wolfensberger, M., Fuhr, P., Hummel, T., Westermann, B., 2009. Olfactory impairment predicts brain atrophy in Parkinson's disease. J. Neurosci. 29, 15410–15413.

Welge-Lussen, A., Wattendorf, E., Schwerdtfeger, U., Fuhr, P., Bilecen, D., Hummel, T., Westermann, B., 2009. Olfactory-induced brain activity in Parkinson's disease relates to the expression of event-related potentials: a functional magnetic resonance imaging study. Neuroscience 162, 537–543.

Zatorre, R.J., Jones-Gotman, M., Evans, A.C., Meyer, E., 1992. Functional localization and lateralization of human olfactory cortex. Nature 360, 339–340.

Zhou, W., Chen, D., 2008. Encoding human sexual chemosensory cues in the orbitofrontal and fusiform cortices. J. Neurosci. 28, 14416–14421.

Zorzon, M., Ukmar, M., Bragadin, L.M., Zanier, F., Antonello, R.M., Cazzato, G., Zivadinov, R., 2000. Olfactory dysfunction and extent of white matter abnormalities in multiple sclerosis: a clinical and MR study. Mult. Scler. 6, 386–390.