Correlation between olfactory bulb volume and olfactory function

D. Buschhüter a, M. Smitka b, S. Puschmann a, J.C. Gerber c, M. Witt a, d, N.D. Abolmaali e, T. Hummel a,⁎

a Department of Otorhinolaryngology, University of Dresden Medical School, Fetscherstrasse 74, 01307 Dresden, Germany
b Department of Pediatrics, University of Dresden Medical School, Fetscherstrasse 74, 01307 Dresden, Germany
c Department of Neuroradiology, University of Dresden Medical School, Fetscherstrasse 74, 01307 Dresden, Germany
d Department of Anatomy, University of Dresden Medical School, Fetscherstrasse 74, 01307 Dresden, Germany
e Oncoray, University of Dresden Medical School, Fetscherstrasse 74, 01307 Dresden, Germany

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A B S T R A C T

The olfactory bulb (OB) is considered to be the most important relay station in odor processing. Involving 125 randomly selected subjects (58 men, 67 women; age range: 19 to 79 years), the present study aimed to investigate a possible correlation between OB volume and specific olfactory functions including odor threshold, odor discrimination, and odor identification. The history of all participants was taken in great detail to exclude possible causes of smell dysfunction. All participants received an otolaryngological investigation including a volumetric scan of the brain (MRI), lateralized olfactory tests and a screen for cognitive impairment. Volumetric measurements of the right and left OB were performed by manual segmentation of the coronal slices through the OB. Significant correlations between OB volumes in relation to olfactory function were observed, independent of the subjects' age. Additionally, OB volumes decreased with age. In agreement with previous research the present study confirmed the correlation between OB volume and specific olfactory functions. Furthermore, the correlation between OB volume and olfactory function was not mediated by the subjects' age. In conclusion, the present data obtained from a relatively large group of subjects forms the basis for age-related normative values of OB volumes.

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Introduction

The olfactory bulb (OB) is the first relay in the olfactory pathway. Studies in animals show that the OB maintains continuing synaptogenesis such that it remains highly plastic throughout adult life. Accordingly, one of the most outstanding characteristics of olfactory deprivation in animals is the reduction in OB volume due to a decreased number of cells (Cummings et al., 1997; Korol and Brunjes, 1992). The OB also appears to be one of the few brain areas to be populated continuously by new granular and periglomerular neurons (Lledo and Gheusi, 2003). Recently it has been shown also in humans that neuroblasts migrate to the OB via a lateral ventricular extension (Curtis et al., 2007).

Due to the continuous improvement of magnetic resonance imaging (MRI) techniques, MRI-based volumetric analyses offer an ideal instrument to reliably evaluate the OB volume, which seems to be connected to the functional state of the olfactory system. Therefore the size of the OB has been previously studied in patients with post-traumatic chemosensory deficits (Yousem et al., 1996a,b; Yousem et al., 1999), post-infectious olfactory deficits (Mueller et al., 2005a,b; Rombaux et al., 2006), congenital anosmia (Yousem et al., 1996a,b; Abolmaali et al., 2002), neurodegenerative disorders (Yousem et al., 1995; Mueller et al., 2005a,b), and in subjects with a normal sense of smell (Yousem et al., 1998). However, these cross-sectional studies included either only a small control group or even no controls at all. The present study, including a large number of healthy subjects, was performed to compare OB volumes to specific olfactory functions and to provide normative data of the OB volume. These normative data for different decades of life would be necessary to realize the idea of OB volumetry as a tool which may help to assess stage and course of diseases associated with olfactory loss.

Materials and methods

Volunteers and study design

A total of 125 randomly selected individuals (58 men and 67 women), aged 19 to 79 years (mean±standard deviation = 37±17 years), participated in this study. None of them reported...
olfactory dysfunction. The investigations were performed in accordance to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects (World Medical Association, 1997). The study design was approved by the University of Dresden Medical Faculty Ethics Review Board. All subjects provided written informed consent for the study aims and procedures and attended our Smell and Taste Clinic for detailed diagnostic evaluation.

All participants received an otorhinolaryngological investigation including a volumetric Magnetic Resonance Imaging (MRI) scan of the entire brain, and detailed lateralized olfactory tests. In addition, subjects received an extensive review of their clinical histories in order to exclude a possible cause of smell dysfunction. Furthermore, all subjects underwent a mini mental state examination (MMSE) to screen systematically for possible cognitive impairment.

Olfactory testing

Psychophysical testing of olfactory function was performed with the validated “Sniffin’ Sticks” test. Odorants were presented in commercially available felt-tip pens (“Sniffin’ Sticks”, Burghart GmbH, Wedel, Germany; Hummel et al., 1997; Kobal et al., 2000). Olfactory testing comprised three tests, namely tests for odor threshold (testing by means of a single staircase procedure), odor discrimination (3-alternative forced-choice) and odor identification (4-alternative forced-choice). For odor presentation the pen’s cap was removed by the experimenter for approximately 3 s and the tip of the pen was placed approximately 1–2 cm in front of one nostril while the other nostril was closed by a tape.

Instead of liquid dye the tampon of the pens for threshold testing was filled with phenyl ethyl alcohol (PEA, a rose-like odor) diluted in propylene glycol (dilution ratio 1:2, starting from 4%). Odors were presented in a total of 16 triplets of pens, one containing diluted phenyl ethyl alcohol and two containing only propylene glycol serving as blanks. The interval between presentations of individual pens of a triplet was approximately 3 s and presentation of the triplets to a subject occurred every 20 s. Employing a three-alternative, temporal forced-choice paradigm, the subjects had to identify the pen that contained the odorant. Subjects were blindfolded to prevent visual identification of the odor containing pens. Thresholds were determined using a single staircase technique. In the present three-alternative, temporal forced-choice paradigm, two successive correct identifications of the pen containing the odor or one incorrect identification triggered a reversal of the staircase to the next higher or the next lower dilution step, respectively. Seven reversals had to be obtained (Hummel et al., 1997). The odor thresholds were determined as the mean of the last 4 staircase reversals.

Assessment of odor threshold was followed by a test of odor discrimination (Hummel et al., 1997). For odor discrimination 16 triplets of pens were presented, with two containing the same odorant and one containing the target odorant. The subjects’ task was to identify the sample that had a different smell. To prevent visual detection of the target pen, subjects were blindfolded with a sleeping mask. Subjects were only once allowed to sample the odor. Presentation of triplets was separated by at least 30 s. The test result was a sum score of correctly identified pens.

In a final step a test of odor identification (Hummel et al., 1997) was performed to completely assess the subject’s objective function. Odor identification was assessed by means of 16 common odors. Using a multiple forced-choice paradigm, identification of individual odors was performed from a list of four verbal descriptors each. Each odorant was presented by the experimenter and there was an interval of at least 30 s to prevent olfactory desensitization (Hummel et al., 1997). Subjects were

| Table 1 Correlations between investigated parameters (n.s. = not significant) |
|------------------|------------------|------------------|
|                  | Coefficient of correlation | p-value          |
| OB volume (left vs. right) | 0.84             | <0.05            |
| OB volume (left) vs. odor threshold (left) | 0.19             | <0.05            |
| OB volume (right) vs. odor threshold (right) | 0.12             | 0.20, n.s.       |
| OB volume (left) vs. odor identification (left) | 0.39             | <0.05            |
| OB volume (right) vs. odor identification (right) | 0.48             | <0.05            |
| OB volume (left) vs. odor discrimination (left) | 0.17             | 0.07, n.s.       |
| OB volume (right) vs. odor discrimination (left) | 0.07             | 0.48, n.s.       |
| OB volume (left) vs. TDI score | 0.28             | <0.05            |
| OB volume (right) vs. TDI score | 0.20             | <0.05            |
| OB volume (left) vs. age | −0.37            | <0.001           |
| OB volume (right) vs. age | −0.38            | <0.001           |
Results from olfactory testing can be analyzed separately from each other. Overall olfactory function is expressed as the sum of the scores from the 3 individual tests (Wolfensberger et al., 2000).

Magnetic resonance imaging

All examinations were performed at a 1.5-Tesla magnetic resonance imaging system (Sonata Vision; Siemens, Erlangen, Germany) using the cp-head coil. Volumes of the right and left OB were determined using the MRI scans of the brain and a standardized protocol for OB analysis. The protocol included: 1) 5-mm-thick standard T2-weighted fast spin-echo images covering the whole brain without interslice gap to rule out any organic brain disorders; and 2) 2-mm-thick T2-weighted fast spin-echo images without interslice gap in the coronal plane covering the anterior and middle segments of the base of the skull. To additionally investigate the reliability, volumetric measurements of the right and left OB were performed by two independent observers, blinded to the olfactory test results, by manual segmentation of the coronal slices through the OBs using the AMIRA 3D visualization and modeling system (Visage Imaging, Carlsbad, USA). As suggested by Yousem et al. (1998) the sudden change of diameter at the beginning of the olfactory tract was used as the proximal demarcation of the OB. In summary, OB volumes were calculated by planimetric manual contouring (surface in mm²) and all surfaces were added and multiplied by 2 because of the 2-mm slice thickness to obtain a volume in cubic millimeters.

Statistical analysis

All statistics were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). Correlations according to Pearson were computed between volumetric measurements of the OB and functional measurements. In addition, partial correlations controlling for age were performed. The level of significance was set at 0.05.

Results

Interindividual variation in OB volumes was relatively large, ranging from 41 mm³ to 97 mm³ for right OB volumes and from 37 mm³ to 98 mm³ for left OB volumes. Intraindividual variation was relatively small (correlation between left-sided and right-sided OB volumes: \( r_{125} = 0.84, p < 0.05 \); this variation was slightly smaller in women \( r_{67} = 0.88, p < 0.001 \) compared to men \( r_{58} = 0.79, p < 0.001 \). The maximum intraindividual difference between left-sided and right-sided OB volumes was 15 mm³ for women and 32 mm³ for men.

On average, OB volumes of men (left: 70 mm³; right: 69 mm³) were found to be larger than those of women (left: 64 mm³; right: 65 mm³). For both women and men, left and right OB volumes was relatively stable up to the 4th decade of life (women: left: 70 mm³, right: 63 mm³; men: left: 77 mm³, right: 81 mm³) and declined in the 6th and 7th decade, but showed considerable variation within each subject group (Fig. 1).

Olfactory function expressed as the TDI score was slightly higher in men (left: 36.8; right: 35.9) compared to TDI scores of women (left: 34.5; right: 34.2). The mean TDI scores of men and women for both sides peaked in the 4th decade (women: left: 38.1, right: 37.9; men: left: 38.9, right: 39.7) and showed a decline in the 6th and 7th decade (Fig. 1).

One of the most important outcomes of the present study was the demonstration of correlations between special olfactory functions and OB volumes (Table 1). Significant correlations between left-sided OB volumes in relation to left-sided odor thresholds (left: \( r_{125} = 0.19, p < 0.05 \) ) were observed. However correlations between right-sided OB volumes and right-sided odor thresholds missed the criterion of significance (right: \( r_{125} = 0.12, p = 0.20 \)). Furthermore, OB volumes exhibited significant correlations with the subjects’ odor identification abilities (left: \( r_{125} = 0.39; \) right: \( r_{125} = 0.48; p < 0.05 \)) (Fig. 2). However, no significant correlation was found between OB volumes and odor discrimination scores (left: \( r_{125} = 0.17, p = 0.07; \) right: \( r_{125} = 0.07, p = 0.48 \)).

| Summary of results from partial correlations (controlling for age) between OB volume and olfactory function, separately for the left and right side (n.s. = not significant) |
|---|---|---|
| Coefficient of correlation | p-value |
| OB volume (left) vs. odor threshold (left) | 0.08 | 0.40, n.s. |
| OB volume (right) vs. odor threshold (right) | 0.07 | 0.42, n.s. |
| OB volume (left) vs. odor identification (left) | 0.18 | 0.06, n.s. |
| OB volume (right) vs. odor identification (right) | 0.23 | 0.014 |
| OB volume (left) vs. odor discrimination (left) | 0.04 | 0.80, n.s. |
| OB volume (right) vs. odor discrimination (right) | −0.02 | 0.80, n.s. |
OB volumes decreased significantly with advancing age (left: $r_{125}=-0.37$; right: $r_{125}=-0.38$; $p<0.001$). Although men exhibited larger OB volumes than women, on average, the decrease of OB volume with age was similar for both sexes (Fig. 1). Correlations among OB volumes and left- and right-sided TDI scores revealed that OB volumes correlated significantly with TDI scores (left: $r_{125}=0.28$, $p<0.05$; right: $r_{125}=0.20$, $p<0.05$). Furthermore, average OB volumes expressing overall olfactory function (average of left- and right-sided OB) correlated significantly with average TDI scores (average of left- and right-sided TDI scores) ($r_{125}=0.25$, $p<0.05$).

Using “age” as a control variable for partial correlations (Table 2), OB volume did not correlate significantly with odor thresholds (left: $r_{125}=0.08$, $p=0.40$; right: $r_{125}=0.07$, $p=0.42$). However, partial correlations between right-sided OB volumes and right-sided odor identification test results were still significant ($r_{125}=0.23$, $p=0.014$). However, correlations between left-sided OB volumes and left-sided odor identification test results closely missed the criterion of significance ($r_{125}=0.18$, $p=0.06$). No significant correlations were found between OB volumes and odor discrimination when using “age” as a control variable for partial correlations (left: $r_{125}=0.04$; right: $r_{125}=-0.02$; $p=0.80$).

A normal OB volume was defined to be above the 10th percentile of the distribution of volumes within the investigated population (Table 3). Thus, the following normative data arose from: for people <45 years the OB should have a minimum volume of 58 mm$^3$; and for people >45 years the OB should have a minimum volume of 46 mm$^3$. More precisely women <45 years should have a minimum OB volume of 54 mm$^3$ and women >45 years a minimum OB volume of at least 43 mm$^3$. Men <45 years are expected to have a minimum OB volume of 59 mm$^3$ and >45 years a minimum OB volume of 52 mm$^3$.

### Discussion

In agreement with previous research the present study confirmed the correlation between OB volume and olfactory functions. The most salient result from the present study in healthy subjects was that significant correlations between OB volumes and olfactory function were observed independent of age. In addition, the present research provides normative data separately for men, women and different age groups.

As indicated by correlational analyses controlling for age, OB volumes seem to decline parallel to smell function. Such changes have been documented for olfactory loss following post-viral, post-traumatic, and sinusoidal olfactory loss (Yousem et al., 1999; Mueller et al., 2005a,b). In contrast, as shown in former MRI studies, in neurodegenerative disorders, more central diseases of the olfactory system do not significantly affect OB volumes (Yousem et al., 1995). These former data support the idea that olfactory loss in Parkinson's disease is not a primary consequence of damage to the olfactory epithelium but rather results from central-nervous changes (Mueller et al., 2005a,b). In contrast, hypoplasia of the OB has been observed in patients with Alzheimer's disease (Thomann et al., 2007) and schizophrenia (Turetsky et al., 2003).

Results of the present study assumed that OB volumes reflect olfactory functions in humans. Previous MRI-based volumetric measurements of the OB have already demonstrated that OB volume is a gauge of residual olfactory function (Rombaux et al., 2006).

The plasticity of the OB is dependent on two major neurobiological mechanisms. One is the continuous neuronal supply from the subventricular zone (SVZ). Here, neuroblasts migrate along the rostral migratory stream and replace interneurons (periglomerular cells, granular cells) in the OB leaving the major relay neurons, mitral cells, substantially unaffected (Curtis et al., 2007). The second mechanism concerns continuous synaptogenesis that occurs mainly between incoming axonal projections of olfactory receptor neurons and dendrites of mitral/tufted cells at the glomerular level.

In animals, one of the most important effects of olfactory deprivation is the reduction in OB size as a result of hypoplasia (Cummings et al., 1997; Korol and Brunjes, 1992). Bulbar neuroplasticity is related to input from olfactory receptor neurons (Lledo and Gheusi, 2003). Further, a continuous stream of neuroblasts to the OB from the SVZ has been described also in the human CNS (Curtis et al., 2007). By maintaining a constitutive neurogenesis sensitive to environmental influences, this “neuronal recruitment” may in turn lead to a change of OB volume and to an improvement of sensory abilities (Lledo et al., 2004).

In conclusion, the present data obtained in a relatively large group of subjects forms the basis for age-related normative values of OB volumes. These normative data will be helpful in the routine assessment of OB volumes of, for example, patients with neurodegenerative disorders (Mueller et al., 2005a,b), which are associated with olfactory impairment.

### References


Kobal, G., Klimek, L., Wolfensberger, M., et al., 2000. Multicenter investigation of 1,036 patients with neurodegenerative disorders (Mueller et al., 2005a,b). In contrast, hypoplasia of the OB has been observed in patients with Alzheimer's disease (Thomann et al., 2007) and schizophrenia (Turetsky et al., 2003).


