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LATERALIZED DIFFERENCES IN OLFACTORY BULB VOLUME RELATE TO LATERALIZED DIFFERENCES IN OLFACTORY FUNCTION

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Abstract—The present study aimed to investigate whether side differences in olfactory bulb (OB) volume correlate to respective differences in olfactory function. In a total of 164 healthy volunteers volumetric measures of the OBs were performed plus lateralized measurements of odor thresholds and odor discrimination. Side differences were defined as 10% difference between the left and right OB. In 39 cases volumes on the right side were larger than on the left side, whereas in 29 cases it was the other way around. Subjects with larger right-sided OB volumes were found to be more sensitive to odorous stimulation of the right as compared to the left nostril in terms of odor thresholds and odor detection; higher sensitivity of the left nostrils (decreased odor threshold) was observed in individuals with larger OB volumes on the left side. These data appear to suggest that OB volume may be partly dependent on lateralized influences on the olfactory system, reflecting its lateralized organization.

Key words: lateralization, olfaction, smell, olfactory bulb.

INTRODUCTION

Clinically, during the last years the interest to study the olfactory bulb (OB) has grown. This interest stems from the idea that olfactory function is reflected in the volume of the OB (Yousem et al., 1997; Mueller et al., 2005b). This idea has gained momentum because high-resolution magnetic resonance (MR) scans of the head have become part of the routine investigation of patients. While in the 1980s, OB volume estimation was based upon highly laborious and complicated cell counts from bioptic material (Bhatnagar et al., 1987), more recently, the elegant method of MR-based OB volumetry (Yousem et al., 1997) has opened a wide field for studies of OB volumes in various clinical and experimental contexts. Thus, the size of the OB has been studied in patients with post-traumatic chemosensory deficits (Yousem et al., 1996b, 1999), post-infectious olfactory deficits (Mueller et al., 2005b; Rombaux et al., 2006), sinunasal disease (Gudziol et al., 2009a), congenital anosmia (Yousem et al., 1996a; Abolmaali et al., 2002), neurodegenerative disorders (Mueller et al., 2005a; Thomann et al., 2009; Wang et al., 2011) psychiatric diseases (Turetsky et al., 2003; Negoias et al., 2010; Nguyen et al., 2011), multiple sclerosis (Goektas et al., 2011) or total laryngectomy (Veyseller et al., 2011), as well as in subjects with a normal sense of smell (Yousem et al., 1998; Buschhüter et al., 2008; Rombaux et al., 2010).

The aim of the present study was to investigate whether differences in size between the left and right olfactory bulbs are correlated with differences in function. Such differences occur in approximately 20% of the general population (Gudziol et al., 2007; Welge-Lüssen et al., 2010) whereby the significance of differences in olfactory tests was based on empirical studies in patients (Gudziol et al., 2006). Clinically, they have been reported to be an early indicator of future olfactory loss (Gudziol et al., 2009b).

EXPERIMENTAL PROCEDURES

Data were taken from two previously published studies (for details of these studies please see Buschhüter et al., 2008; Hummel et al., 2011). The study design was approved by the University of Dresden Medical Faculty Ethics Review Board (EK239112006 and EK252112006). All investigations were performed in accordance with the Declaration of Helsinki on Biomedical Studies involving Human Subjects (WMA, 1997). Data from 164 individuals (82 male and 82 female subjects), aged 6–79 years (mean ± standard deviation (SD) = 29.8 ± 18.7 years), were included. None of the subjects had reported olfactory dysfunction. All participants had received volumetric magnetic resonance imaging (MRI) scans of the entire brain and detailed lateralized olfactory tests. In addition, extensive reviews of their clinical histories permitted the exclusion of subjects suffering from potential causes of olfactory dysfunction.

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, 3-AFC) and odor identification (4-AFC). For odor presentation,

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Abbreviations: AFC, alternative forced choice; MRI, magnetic resonance imaging; OB, olfactory bulb; PEA, phenyl ethyl alcohol; SD, standard deviation.

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the pen's cap was removed by the experimenter for approximately 3 s and the tip of the pen was placed ca. 1–2 cm in front of one nostril while the other nostril was sealed by nearly odorless self-adhesive tape (Microfoam; 3-M, Neuss, Germany).

Odor thresholds were determined for phenyl ethyl alcohol (PEA, a rose-like odor) diluted in propylene glycol, with altogether 16 numbered dilutions, number 1 representing the strongest, and number 16 the weakest odor. The dilution series started from a stock solution of 4% PEA in propylene glycol; this was diluted in a ratio of 1 volume PEA to 2 volumes of propylene glycol. Odors were presented in triplets of pens, one pen among each triplet containing diluted PEA and two containing only propylene glycol, serving as blanks. The interval between presentations of individual pens of a triplet was approximately 3 s; the entire procedure for any triplet required roughly 20 s. Employing a 3-AFC paradigm, subjects had to identify the smelling pen among each triplet. Subjects were blindfolded with a sleeping mask to prevent visual identification of the odor-containing pens. Thresholds were determined using a single staircase technique: two successive correct identifications of the pen containing the odor or one incorrect response 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; Ehrenstein and Ehrenstein, 1999). Odor thresholds were determined as the average dilution of the last four staircase reversals.

Assessment of odor thresholds for both nostrils was followed by correspondingly lateralized tests of odor discrimination (Hummel et al., 1997), where 16 triplets of pens containing altogether 32 odorants were presented, with two pens per triplet containing the same and the third one containing a different, that is, the target odorant. The subjects' task was to identify the sample with a different smell out of any triplet. To prevent visual detection of the target pen, subjects were again blindfolded. Subjects were allowed to sample any odor only once. Presentation of triplets was separated by at least 30 s to prevent olfactory desensitization. The discrimination scores were the counts of correctly identified pens.

In a final step, a test of odor identification (compare Doty et al., 1984) was performed in a non-lateralized fashion, but birhinally. Odor identification was assessed by means of 16 common odors, again presented by means of pens. Using a 4-AFC paradigm, identification of individual odors was performed from a list of four verbal descriptors each. Each pen was presented by the experimenter, with intervals of at least 30 s. Subjects were free to sample the odors as often as necessary to make a decision. The test score was a sum score of the correctly identified odors.

MRI

All examinations were performed on a 1.5-Tesla magnetic resonance imaging system (Sonata; Siemens, Erlangen, Germany) using a circularly polarized 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 a T2-weighted turbo spin-echo 2D-sequence in the coronal plane covering the anterior and middle segments of the base of the skull (TR 4.8 s, TE 152 ms, slice thickness 2 mm, matrix 256 × 256, number of slices 30, averages 2, in-plane resolution of 0.4 × 0.4 mm). The coronal sequence was the most sensitive for detecting OBs, which have been identified between the posterior margin of the eyeballs and the anterior parts of the temporal lobes so as to clearly distinguish olfactory bulbs from optic nerves and chiasm.

The relatively high reliability and accuracy of olfactory bulb volume measurements had been demonstrated previously (Yousem et al., 1997; Mueller et al., 2005a,b). The method used provides intraclass coefficients of correlation for repeated measurements by a single observer greater than 0.92 and intraclass coefficients of correlation for measurements across observers greater than 0.96. Data from a single measurement of one observer were used who was blinded with respect to the olfactory test results; this was only done after it had been established that measurements from this observer were highly correlated to measurements from a different, independent

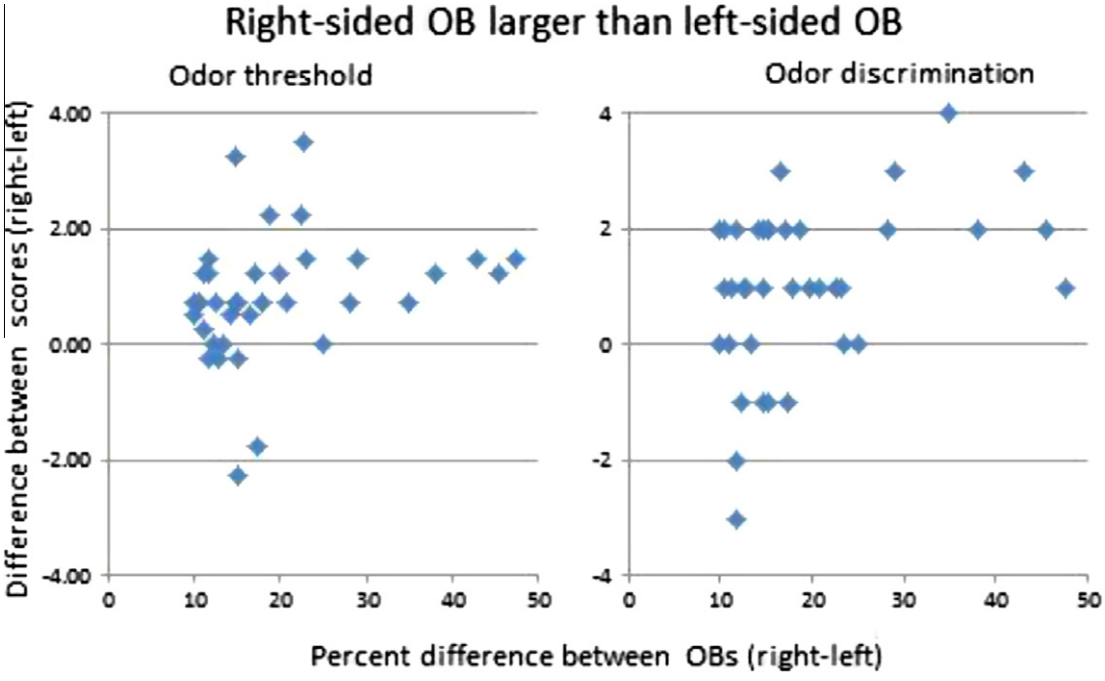

Fig. 1a. Results from analyses where OBs were larger on the right compared to the left side. The *Y*-axes show differences between scores (right-sided scores minus left-sided scores) for odor thresholds (left) and odor discrimination (right), the *X*-axes show percent differences between OBs (right minus left). Please note that some individual data points may sit on each other.