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REVIEW ARTICLE

Relation of the volume of the olfactory bulb to psychophysical measures of olfactory function

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Abstract The aim of this review is to investigate whether changes in olfactory bulb volume relate to changes in specific olfactory functions. We studied currently available peer-reviewed articles on the volume of the human olfactory bulb that also included a psychophysical measure of olfactory function. In the present review, we observed a very clear and consistent correlation between general olfactory function and olfactory bulb (OB) volume. We were not able to find a clear relationship between a specific smell component and OB volume, even when analyzing pathologic conditions separately. In some cases, changes were observed for different subtests, but these changes did not significantly correlate with OB volume or had only a borderline correlation. In other cases, we found contradictory data. Several factors may contribute to the difficulties in finding correlations with the different components of smell: (1) the OB volume may be influenced by information from olfactory receptor neurons (bottom-up effect), information from central nervous system (top-down effect) and by direct damage; (2) most pathologic conditions affect more than one area of the olfactory pathway; (3) small sample sizes of hyposmic subjects were used. We believe that it is necessary to do further studies with larger numbers of subjects to answer the currently investigated question.

Keywords Smell · MRI · Olfactory bulb · Odor threshold · Odor discrimination · Odor identification

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Introduction

Prevalence of olfactory dysfunction in the general population can be up to 20 % [1–3]. The most frequent causes of olfactory dysfunction are upper respiratory tract infection (URTI), inflammatory diseases of nose/paranasal sinuses, respiratory dysfunction, and trauma; often, however, a direct cause remains unknown [4, 5]. Frequency of each cause varies according to the population studied. Many studies have shown that there is a relationship between olfactory bulb (OB) volume assessed by MR imaging and olfactory function, in healthy subjects as well as in various pathological conditions [6–8].

Olfactory functions can be divided into at least three different components, namely, (1) perception of odors at the lowest possible concentration (odor threshold), (2) nonverbal distinction of different smells (odor discrimination), and (3) the ability to name or associate an odor (odor identification). Some psychophysical tests assessing olfactory performance include separate subtests for the assessment of each of these components [9] or some of them [10, 11], and others rely on one single component [12]. Previous work has shown that the three subtests tap into different olfactory functions [13, 14].

The aim of this short review is to evaluate whether changes in OB volume are related to a specific component of the sense of smell (threshold, identification, or discrimination).

It is tempting to separate olfactory loss into conductive and sensorineural dysfunction and relate conductive pathology to threshold changes, and sensorineural pathology to identification and discrimination. This should then differently impact in the OB. For example, according to the bottom-up hypothesis, meaning that OB volume is largely dependent on input from the olfactory epithelium [15], OB

volume should be most strongly affected when the periphery is damaged. In contrast, assuming that higher central nervous system (CNS) structure determines OB volume [16], OB volume should be most affected in disorders presumably starting at the level of the CNS, e.g. Parkinson's disease [17]. Fact is, that such differentiations are difficult to maintain, as OB volume seems to be affected in all groups of patients with different causes of olfactory loss.

Nevertheless, we tried to investigate whether OB volume reflects more odor thresholds or odor identification/discrimination.

Olfactory loss in chronic rhinosinusitis (CRS) is believed to be mainly conductive, although the OB could also be involved in the intranasal inflammatory process. In addition, the term "conductive" also does not cover the idea that in CRS inflammation alone produces a striking olfactory loss. However, provided that CRS affects the periphery of the nasal cavity to a higher degree than central-nervous structures, and that odor thresholds reflect peripheral functions to a higher degree than higher cognitive functions, then it can be hypothesized that OB volume changes in CRS are more strongly related to changes in odor threshold compared to changes in odor identification or odor discrimination.

In post-viral olfactory loss, the largest damage appears to be in the olfactory receptor neuron (ORN). Each ORN expresses one type of olfactory receptor (OR). Each "smell" is composed of various molecules, various odors. A certain combination of OR activation conforms an odor. Slight changes in the combination of OR activations may modify the perceived odorous impression [18]. Here, we would like to hypothesize that identification, threshold or both could be affected according to the extent or type of damage produced by viral infection.

In post-trauma olfactory loss, various structures can be affected namely axons of receptor neurons (shearing or "rupture"), OB, or cortex. Lesions of any of these structures could lead to a decrease in olfactory function and change in OB volume by a bottom-up effect, by a direct effect on the OB, or by a top-down effect of the CNS on the OB.

Materials and methods

We studied currently available peer-reviewed articles (until June 2014; English language; review based only on medline/pubmed as the most representative database in medical research) on the volume of the human olfactory bulb that also included a psychophysical measure of olfactory function, namely odor identification, odor discrimination, or odor threshold. We included 17 studies on patients (for a summary see Table 1) plus another three studies on healthy volunteers.

When describing the results, the term correlation will be used if a statistically significant correlation is present. If a correlation is not statistically significant, it will be specified.

Results

Changes in OB volume in patients are mainly related to odor identification and/or odor threshold—also because odor discrimination is rarely investigated. To better understand changes in patients, it is important to study these relationships in healthy subjects of different ages. In the following, results will be discussed for the various investigated groups—healthy subjects and patients with different causes of olfactory loss.

Healthy subjects

In healthy adults, Yousem et al. [19] observed peak olfactory function in the 3rd decade, followed by a plateau until the 7th decade, finally decreasing in the 7–8th decade. Olfactory bulb and tract (OBT) volume peaked in the 4th decade and decreased in the 7–8th decade paralleling olfactory function. Olfactory function was measured with the University of Pennsylvania Smell Identification Test (UPSIT [11]). Buschhüter et al. [6] also studied healthy adults (age range: 19–79 years) and observed that OB volume decreased with increasing age. Psychophysical testing was done with the Sniffin' Sticks [9] comprising of three subtests for odor threshold (T), odor discrimination (D), and odor identification (I). OB volume correlated with overall olfactory function expressed in TDI score. Normative data were given for OB volume according to age and sex. Correlations with specific subtests did not produce a clear picture. When studying children and adolescents, Hummel et al. [7] observed that OB volume increased from age 1 to 17 years. Olfactory function was assessed in children 6-year-old and over, and an increase in overall olfactory function (expressed as TDI score) was observed from age 6 to 17 years. There was a clear correlation between specific olfactory functions (odor identification, odor discrimination, and odor threshold) and OB volume.

Patients

In patients with post-trauma olfactory loss, Yousem et al. [20] observed a decrease in OB volume and olfactory function, but no correlation between smell tests and OB volume. In a further study with a larger number of hyposmic patients, Yousem et al. [21] found that OB volume

Table 1 Summary of studies on olfactory bulb volume in patients and specific olfactory functions

STUDY	MRI field strength; manufacturer	CAUSE	SUBJECTs	PSYCHOPHYSICAL METHOD	OB VOL.	GLOBAL OLFACTORY FUNCTION	T	OI	D	RI	CORRELATION
Yousem et al 1996	1.5T; General Electrics	Post-traumatic	25 patients, 8 control	UPSIT + D + T + odor memory	↓	↓ °	↓ °	↓ °	↓ °		
Yousem et al 1999	1.5T; General Electrics	Post-traumatic	36 patients, 24 controls	UPSIT + T + odor memory	↓	↓	↓ •	↓			Left OB with: total **OI** r= 0.438, p= 0.12; left **OI** r=0.424, p= 0.13; right **OI** r=0.355, p= 0.46; Right OB with left **OI** r= 0.355, p= 0.046
Mueller et al 2005	1.5 T; Siemens	Post-traumatic & Post-URTI	31 patients, 17 control	Sniffin' Sticks'	↓	↓	↓	↓	↓		**TDI** r_{39}= 0.53, p< 0.001; **T** r_{39}= 0.55, p<0.001; **D** r_{39}= 0.34, p= 0.028; **I** r_{39}= 0.44, p 0.004. ^^^
Rombaux et al 2006	1.5T; General Electrics	Post – traumatic	25 patients	Sniffin' Sticks' + RI	↓	↓	↓	↓ °	–	↓	**T** r_{25} = 0.46, p = 0.021; **RI** r_{25} = 0.53, p = 0.007 **OI** r_{25} = 0.37, p = 0.07
Rombaux et al 2006	1.5T; General Electrics	Post-URTI	26 patients	Sniffin' Sticks'	↓	↓	–	↓	–		left OB r_{23} = 0.52, p = 0.008; right OB r_{23} = 0.47, p = 0.019
Haehner et al 2008	1.5 T; Siemens	Post-URTI & Post - traumatic	20 patients	Sniffin' Sticks'	↑		↑	–	–		r_{13} = 0.82, p = 0.001
Rombaux et al 2012	3T; Philips	Post-URTI & Post - traumatic	60 patients	Sniffin' Sticks'	↑	↑	↑	↑	↑	↑	**TDI** r_{60}= 0.40, p= 0.002; **RI** r_{60}= 0.46, p=0.002 °°
Goektas et al 2009	1.5T; Siemens	Post-URTI & Post- trauma & idiopathic	24 patients	Sniffin' Sticks' + OEP	↓	↓ °					r = 0.58
Gudziol et al 2009	1.5 T; Siemens	CRS with NP	19 patients, 18 controls	Sniffin' Sticks'	↑	↑	↑	–	–		r= 0.60, p= 0.002; r= 0.49, p= 0.03
Brodoehl et al 2012	3T; Siemens	IPD	16 patients, 16 controls	Sniffin' Sticks'	↓	↓					Combined OB volume r = 0.52, p = 0.04; left OB volume r = 0.51 p = 0.04, right OB volume r = 0.49, p = 0.05].
Turetsky et al 2000	1.5T; General Electrics	Schizophrenia	26 patients, 22 controls	UPSIT + T	↓		°°°	°°°			**T** r= 0.03, N= 26, p= 0.14 °
Turetsky et al 2003	1.5-T; General Electrics	Schizophrenia & relatives	11 patients, 19 relatives, 22 controls	UPSIT + T	↓		↓ °				
Hummel et al 2013	1.5T; Siemens	TLE	20 patients, 20 controls	Sniffin' Sticks'	↓	↓	↓ °	↓			Left OB vol. with: **OI** r_{28} = 0.43, p = 0.024; **T** r_{28} = 0.31, p = 0.11. Right OB vol. with: **OI** r_{28} = 0.42, p = 0.027; **T** r_{28} = 0.26, p = 0.18
Podlesek et at 2012	1.5T; Siemens	INPH	17 patients, 24 controls	Sniffin' Sticks'	↓	↓ °	↓ °	↓ °	↓ °		

correlated with orthonasal odor identification whereas Rombaux et al. [22] observed a significant correlation between OB volume and odor threshold (T) and retronasal odor identification (RI). Orthonasal odor identification was greatly affected in the population studied by Rombaux et al. [16], but it exhibited no significant correlation with OB volume. There was also a relation between the degree of cortical damage and retronasal odor identification. Retronasal olfactory function was most compromised in patients in the frontotemporal group (damage to the frontal and anteroinferior temporal lobes) and least affected in patients without cortical lesions (the without group).

Table 1 continued

STUDY	MRI field strength; manufacturer	CAUSE	SUBJECTs	PSYCHOPHYSICAL METHOD	OB VOL.	GLOBAL OLFACTORY FUNCTION	T	OI	D	RI	CORRELATION
Schriever et al 2013	1.5T; Siemens	Smokers	21 smokers, 59 controls	Sniffin' Sticks'	↓	–	–	–			
Negoias et al 2010	1.5T; Siemens	AMD	21 patients, 21 controls	Sniffin' Sticks'	↓		↓ °°°°	–	–		Left: r_{39}= 0.37, p= 0.02 Right: r_{39}= 0.19, p= 0.26
Croy et al 2013	1.5T; Siemens	CM	17 patients with CM, 10 without CM	Sniffin' Sticks'	↓	↓	↓ °°°°	↓ °			**T** with OB left: r= 0.41, p= 0.08; OB right r= 0.22; OB best r= 0.34. **OI** r= 0.17; **D** r= -0.02

OB VOL olfactory bulb volume, *T* odor threshold, *OI* orthonasal odor identification, *D* odor discrimination, *RI* retronasal odor identification, *OEP* olfactory event-related potentials, *CRS* chronic rhinosinusitis, *NP* nasal polyps, *IPD* idiopathic Parkinson's disease, *TLE* temporal lobe epilepsy, *INPH* idiopathic normal pressure hydrocephalus, *AMD* acute major depression, *CM* childhood maltreatment, *Down arrow* decrease volume/results, *Up arrow* increase volume/result, "–" no change in result

(°) Decreased but did not correlate with OB volume or had a borderline correlation

(°°) Larger initial OB volumes related to higher olfactory improvement, changes were shown in ALL subtests. Correlations were observed between OB volume and baseline TDI score and baseline RI

(°°°) Does not give the results of the psychophysical evaluation

(°°°°) Significant correlation between LEFT OB and LEFT T

(°°°°°) A trend for correlation between odor threshold and LEFT OB, but not right or best OB

(^^^) Corrected for age

Patients in the frontal group (with frontal lobe lesions) had measures of retronasal olfactory function that lay between the other two groups. A relationship between degree of cortical damage and OB volume was also observed. OB volumes were smallest in the fronto-temporal group, largest in patients without cortical damage, and medium sized in the frontal group.

When analyzing post-URTI ($N = 22$) and post-trauma ($N = 9$) patients, Mueller et al. [23] observed significant correlations between OB volumes and the TDI score expressing overall olfactory function. In addition, olfactory bulb volume was found to correlate significantly with each component of the sense of smell namely odor thresholds, odor discrimination, and odor identification. When controlling for the influence of age, partial correlations were still significant.

On the other hand, when analyzing post-URTI patients, Rombaux et al. [24] observed that OB volume correlated with identification, and not with threshold or discrimination. However, in a longitudinal study of patients with post-URTI and post-trauma olfactory loss, Haehner et al. [25] observed that in initially hyposmic patients, changes in OB volume correlated with changes in odor threshold.

Rombaux et al. [26], when evaluating patients with post-URTI and post-trauma olfactory loss, observed a correlation between baseline TDI score (overall olfactory function) and initial OB volume, as well as correlation between baseline retronasal odor identification and initial OB volume. Initial OB volume proved to be a useful prognostic tool, as larger initial OB volumes related to higher olfactory improvement. Changes in olfactory function were observed in all subtests (odor threshold, odor discrimination, and odor identification) as well as in retronasal odor identification.

Goektas et al. [27] studied 24 patients with post-URTI ($N = 1$), post-trauma ($N = 5$) and idiopathic ($N = 9$) olfactory loss. A significant correlation was found between electrophysiological measures of olfactory function (amplitudes of olfactory event-related potentials) and OB volume; but no correlation was identified for psychophysical olfactory evaluation (TDI score) and OB volume.

In patients with chronic rhinosinusitis, an increase in OB volume was observed after treatment, which correlated significantly with an increase in odor threshold [15].

In several studies, when comparing patients with and without parosmia, OB volume was smaller in patients with parosmia, without differing olfactory function [22–24].

Olfactory loss is also a common symptom of many neurological and psychiatric diseases. Various neurodegenerative diseases are believed to have olfactory dysfunction as an early symptom [28]. The affected areas and mechanisms differ from one to the other and, in some cases, are not clear.

In Parkinson's disease (PD), in a recent study by Brodoehl et al. [29], a significant difference was observed in OB volume between PD patients and healthy controls. Left OB was significantly reduced in PD patients. They also demonstrated a significant correlation between olfactory function (composite TDI score) and OB volume in PD patients. Similar results were observed in a recent study by Chen et al. [30] who found significantly smaller OB volume in PD patients compared to controls. The grey matter of olfactory associated brain areas was also significantly reduced in PD patients. Olfactory function was not assessed. This is contrary to the results by Mueller et al. [17, 25] who reported no differences between the OB volumes of PD patients and controls. In this study, neither left-sided, nor right-sided, nor ''best'' OB volumes correlated significantly with overall olfactory function.

In Alzheimers disease, however, Thomann et al. [31, 32] observed reduced OB volume in patients compared to controls, and reduced OB volume in mild cognitive impairment compared with controls. Unfortunately olfactory function was not assessed.

When studying patients with Schizophrenia, Turetsky et al. [33] observed a 23 % reduction in OB volume in patients compared to healthy controls. In the control group, there was a strong association between OB volume and threshold; such association was not seen in the patient group. OB volume was unrelated to olfactory identification.

In a study comparing Schizophrenia patients, healthy first-degree family members and healthy controls, Turetsky et al. [34] observed reduced OB volume in patients and first-degree relatives. Olfactory threshold decreased only in patients. Olfactory identification did not decrease in patients and first-degree relatives. No correlation was observed between OB volume and olfactory function.

In a study on patients with temporal lobe epilepsy [16] patients were found to have reduced OB volume and reduced odor identification and odor threshold, compared to controls. OB volume correlated with odor identification, not with odor threshold.

Patients with idiopathic normal pressure hydrocephalous have lower olfactory function compared to healthy controls ($p < 0.04$). They also exhibited smaller OB volume ($p < 0.02$) [35].

When evaluating patients with acute major depression, a significant correlation was seen between the left OB and left threshold. Correlation between right OB volume and right threshold was not significant [36].

When evaluating patients treated for depression, comparing patients with a history of childhood maltreatment with patients without history of childhood maltreatment, Croy et al. [37] found significantly reduced odor thresholds and odor identification. OB volume was also significantly reduced in patients with history of childhood maltreatment. A trend was found for the correlation between the olfactory threshold and the left OB volume, but not for the right or the best OB volume. There was no significant correlation between the OB volume and olfactory discrimination or identification.

Smokers were seen to have olfactory function similar to non-smokers, but OB volume was significantly smaller in smokers [38]. Smoking could affect neurogenesis that occurs in the OB, this way reducing OB volume before affecting olfactory function.

Discussion

The OB is the first relay station in the olfactory pathway and is a highly plastic structure. Changes in OB volume occur in healthy subjects during their lifetime, with an increase during childhood and adolescence and a decrease towards 7 and 8th decade of life. Fluctuations in OB volume are related to changes in olfactory function.

OB volume is influenced by information from ORN (bottom-up effect) and by CNS structures (top-down effect). Direct damage to the OB can also affect its volume and function, for example in trauma, infections, and neurodegenerative diseases. Furthermore, factors such as stress and toxins are reflected in a reduced olfactory bulb volume, as was seen in acute major depression [36] and smokers [38]. The effect seems to be more pronounced if stress occurs in early childhood [38].

In the present review, we observed a very clear and consistent correlation between olfactory function and OB volume. A study comparing smokers to non-smokers was one notable exception [36], probably due to OB volume changes in smokers preceding changes in olfactory function.

We were not able to find a clear relationship between a specific smell component and OB volume, even when analyzing pathologic conditions separately. In some cases, changes were observed for different subtests, but these changes did not correlate with OB volume [38] or had only a borderline correlation [20, 33, 34, 38]. In other cases, we found contradictory data, for example in post-viral olfactory loss, Rombaux et al. [24] observed that change in OB volume correlated with a change in orthonasal odor identification while Haehner et al. [25] observed that OB volume change correlated with odor threshold. Other authors found that OB volume changes correlated with all the components of the sense of smell [23, 26]. In addition, in post-trauma olfactory loss, correlations between OB volume and specific components of the sense of smell were not clear.

These inconsistent results may be due to the type of olfactory test used, sample size, and age distribution which

varied between these investigations. It may also be due to different MRI acquisition techniques used in different studies that might have contributed to inconsistencies of results. Further, several factors in olfactory processing may contribute to the difficulties in finding correlations with the different components of smell: (1) the OB is influenced by information from ORN (bottom-up effect), information from CNS (top-down effect) and by direct "affection" and (2) most pathologic conditions affect more than one area of the olfactory pathway; (3) small sample sizes of hyposmic subjects were used.

In conclusion, we believe that it is necessary to do further studies with larger numbers of subjects to answer the currently investigated question. Multicenter studies would be useful to reach meaningful numbers of participants.

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