REVIEW

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Olfactory bulb volume in the clinical assessment of olfactory dysfunction*

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SUMMARY

The olfactory bulb collects the sensory afferents of the olfactory receptor cells located in the olfactory neuroepithelium. The olfactory bulb ends with the olfactory tract and is closely related to the olfactory sulcus of the frontal lobe. Many studies demonstrated that olfactory bulb volume assessed with magnetic resonance imaging is related to the olfactory function both in normal and pathological conditions. It has been shown that olfactory bulb volume changes with the degree of olfactory dysfunction, that it decreases with the duration of the olfactory loss and that patients with qualitative disorder such as parosmia have smaller olfactory bulbs than patients without parosmia.

In this review, we will discuss the actual knowledge regarding olfactory bulb function, practical ways to measure olfactory bulb volume and olfactory sulcus depth, and report systematic observations regarding these measurements related to various causes of olfactory dysfunction, e.g. infection of the upper respiratory tract, head trauma, or neurodegenerative disease.

Measurement of olfactory bulb volume may provide valuable information for patients with olfactory dysfunction.

Key words: smell, olfaction, magnetic resonance imaging, olfactory bulb volume, olfactory sulcus depth

INTRODUCTION

The olfactory bulb (OB) plays a central role in the processing of olfactory information. It receives input from sensory neurons located in the olfactory epithelium responding to odours. OB are paired, of oval shape that occupy the most anterior portion of the skull base. In animals, one of the most pronounced effects of olfactory deprivation is the reduction of olfactory bulb size [1,2]. This is probably due to the decreased activity of OB neurons and also to a negative effect on cholinergic centrifugal systems [3]. In contrast, behaviour such as olfactory training may have a positive impact on neurogenesis, migration and replacement of interneurons in the OB indicating plasticity [4]. Moreover, olfactory conditioning during early postnatal period temporally stimulates neurogenesis in the OB in rats, suggesting that stimulation in early life is of importance for the normal development of the OB [5]. There is some evidence that OB volume is related to olfactory dysfunction in humans [6] and OB volume has been correlated to results from psychophysical or electrophysiological testing [7]. On the other hand, relation with olfactory function and OB volume in healthy subjects also suggests that a close relationship exists between structure and function [8]. In this review, we will discuss the actual knowledge regarding OB function, volumetry using magnetic resonance imaging, and the clinical evaluation of OB volume related to various causes of olfactory dysfunction [9].

OLFACTORY BULB

The OB receives olfactory information from olfactory receptor neurons located in the olfactory neuroepithelium. It has a laminar organization arranged in circular layers. Glial cells (called olfactory ensheating cells) surround axon bundles on their way to the OB. Axons then form spherical structures (called olfactory glomeruli) where they synapse with mitral cells. Axons from olfactory receptor neurons also synapse with dendrites of intrinsic cells (periglomerular and tufted cells). Between the glomerular layer and the mitral cell layer, the so-called "external plexiform layer" is found. Myelinated axons from the mitral cells run to the internal plexiform layer. Finally, the granule cell layer is constituted by granule cells, the dendrites of which end in the external plexiform layer or within the granule cell layer. This organization serves as a unique coding system in the OB, with each glomerulus receiving converging projections from numerous olfactory receptor neurons expressing the same receptor [10]. Centripetal information then projects to structures with glutamate as principal neurotransmitter. Centrifugal informations are also represented in the OB with GABA and acetylcholine as principal neurotransmitters.

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The OB is one of the few brain structures receiving a supply of newly generated cells throughout adult life. In addition, the OB maintains continuing synaptogenesis throughout life, which probably contributes to the plasticity of the sense of smell. Neuronal precursors are generated from stem cells in the subventricular zone lining the lateral ventricles. The OB appears to be continuously populated by new granular and periglomerular cells [11]. Progenitor cells are transferred to the OB via the rostral migratory stream, invade the glomerular and granule cell layers and become periglomerular and granule cells. This mechanism explains why processes of cell death and cell regeneration coexist in the OB, resulting in continual remodeling of local synaptic connections. It has been shown that this ventriculo-olfactory neurogenic system is of primary importance and that human neuroblasts migrate to the OB via a lateral ventricular extension, starting at the subventricular zone [12,13].

The OB ends with the olfactory tract, which runs at the skull base and terminates in three different projections; the internal, medial and external projections the connections of which terminate in the primary olfactory cortex. Primary olfactory cortex includes the anterior olfactory nucleus (in humans integrated in OB and olfactory tract), the piriform cortex, the periamygdaloid cortex, the amygdala, the entorhinal cortex and its tubercle. Therefore, the OB is viewed as a center of great complexity, containing associative connections at several levels with a sensory centripetal circuit of informations as well as a centrifugal one.

OLFACTORY BULB; MRI ASSESSMENT

The OB has received much attention since routine MRI tools allow the clinician to measure its volume. However, routine clinical imaging of the brain and of the skull base does not usually show the entire olfactory apparatus. MRI sequences may differ in plane resolution and voxel size explaining why certain imaging sequences are not useful for olfactory imaging. Volumetric measurement of the right and left OB usually is performed by manual segmentation of the coronal slices through the OB. Usually, patients for clinical purpose undergo a 1.5 Tesla MRI and most of researchers use the same methodology: the plannimetric contouring method. The OB is located at the skull base, viewed on coronal slices (Figure 1).

Plannimetric contouring of the surface is performed and volume is calculated by multiplying the obtained surface by slice thickness (Figure 2). The OB is an ovoid structure and the anterior part is usually easy to assess. The posterior end of the OB is sometimes difficult to determine and the exact definition of this posterior end probably explains some differences in the measurements obtained by different authors. We propose that the posterior end of the OB would be determined when two successive slice measurements yield the same results revealing that the OB ends with olfactory tract.

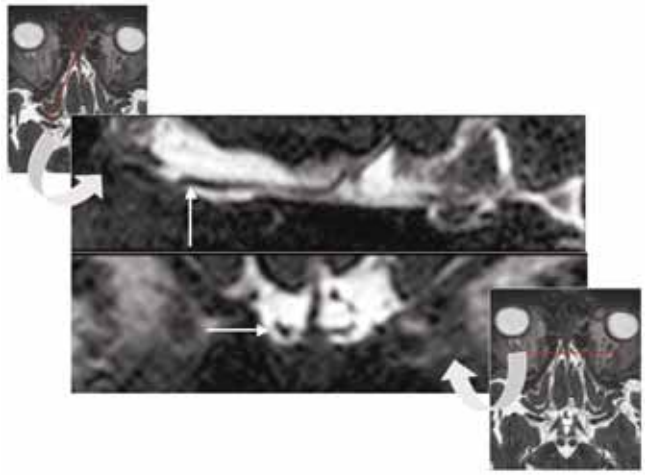

Figure 1. Coronal and sagittal T2 weighted sequence, reconstruction from horizontal plane OB volume (arrow) and olfactory tract.

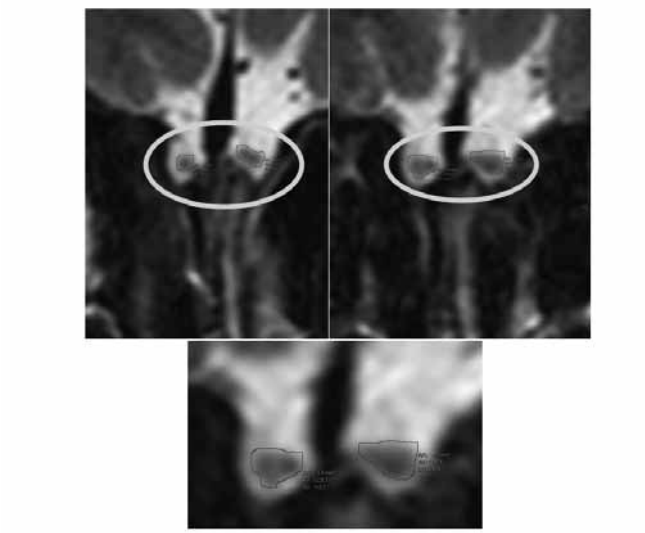

Figure 2. Coronal T2 weighted sequence, OB from normosmic patient. Manual contouring of the OB with surface expressed in mm^2.

As mentioned above, patients are typically examined on a 1.5 Tesla MRI system (Signa Echospeed, GEMS, Milwaukee, WI, USA; or Sonata, Siemens, Erlangen, Germany) using a standardized protocol for OB analysis [6,14,15]. Higher Tesla power MRI are now available. While these systems promise higher resolution their effectiveness in measuring OB volume needs to be proven.

A typical protocol includes: (i) 5-mm-thick standard T2-weighted fast spin-echo images covering the whole brain without interslice gap to rule out any organic brain disorder; (ii) 5mm-thick T2-weighted images gradient-echo images using the Echo-Planar imaging technique (EPI-GRE-T2*) covering the whole brain to rule out the presence of any parenchymal or meningeal post-traumatic hemosiderin deposit; and (iii): 2-mm-thick T1- and 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. OB volumes are calculated by planimetric manual contouring using standard

methods. The contours of the bulb are manually delineated using an electronic cursor. For each slice the surface of the contoured area is computed in mm^2. All surfaces are added and multiplied by two because of the 2-mm slice thickness to obtain a volume in mm^3. Measurements are performed twice by the same observer. When two measurements of the same bulb exhibited a difference of less than 10%, a mean of the two measurements is calculated and included into the database as the definitive volume. When a difference higher than 10% between the two measurements is present, a second observer performs a third measurement. When this third volume shows a difference of less than 10% with one of those made by the first observer, a mean of them is calculated and included into the database as the definitive volume to be used for statistical analyses.

Another way to measure the OB volume is to determine the larger of the left and right OB volumes when the intent is to correlate the OB volume with psychophysical testing of olfactory function tested birhinally. As birhinal tests usually reflect the function of the better side, it seems logical to correlate it to the highest OB volume that could be obtained.

The olfactory sulcus of the frontal lobe is visible above the OB and the olfactory tract. The depth of the OS seems to be dependent on the presence of the OB [16].

The depth of the OS is calculated using a standardized method [6,14-16]. The observer browses the coronal T2-weighted sections from anterior to posterior and selects the first slice on which the eyeball is no more seen. This slice location corresponds to the so-called "plane of the posterior tangent through the eyeballs" (PPTE) which cuts the anterior-mid segment of the OBs. A straight line tangent to the surface of the top of the gyrus rectus and to that of the orbital gyrus is drawn using the electronic cursor. The depth of the olfactory sulcus is measured by drawing a perpendicular line connecting this tangent line to the deepest point of the sulcus. This measurement is of particular interest in patients with congenital anosmia.

Test-retest normative data have been published by pioneers in this field with very satisfactory results [17]. More recently, nomative data adjusted for sex and age have been published giving the following results [8]; for healthy subjects between 19 to 79 years old, the average OB volume is 70 mm^3 (left) and 69 mm^2 (right) for men and 64 mm^2 (left) and 65 mm^3 (right) for women. Between individual variation in OB volume is relatively large, with the volume ranging from 41 mm^3 to 97 mm^3 for right OB and from 37 to 98 mm^3 for left OB. On the contrary, within individual variation (right vs left) is relatively small (Figure 3A).

Typically, OB volume is on average higher in men than in women although women usually exhibited higher olfactory performances than men. The volume of the entire brain that is different between sexes probably explains this fact. OB also decreases with age. This appears to be related to the fact that older subjects have reduced olfactory function and reduced intranasal trigeminal sensitivity. The right OB is usually bigger than the left one. If a normal OB volume is defined as to be above the 10th percentile of the distribution of volumes in the investigated population, the following normative data may be given; 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. Recently, Buschhüter et al. reported a large cohort of healthy subjects for whom OB volumes have been correlated to their olfactory performances assessed with the "Sniffin' Sticks" test [18], one of the most popular tests in Europe to assess olfactory acuity. In this study, a significant correlation was observed between OB volume and odour identification ability independent of age [18].

It should also be noted that variance in the OB shape has been observed in healthy subjects with trifoliated or trifurcated appearance (Figure 3B), some degree of asymmetry or a "kidney" appearance (Figure 3C).

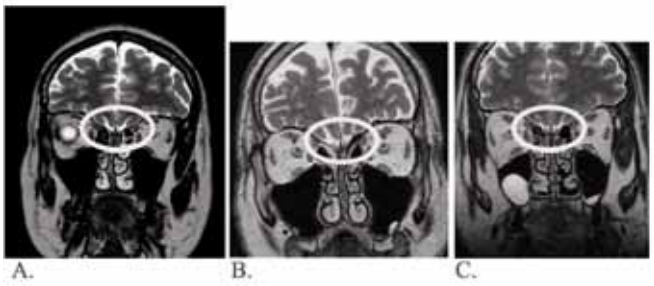

Figure 3. Coronal T2 weighted sequence, OB from normosmic patient (A) OB are paired structure of oval shape. (B) variation; trifoliated or trifurcated appearance. (C) variation; "kidney" appearance.

CLINICAL EVALUATION

OB function is deteriorated when sensory input from periphery is likely to be decreased as in post-infectious olfactory disorder, in post-traumatic olfactory loss, or in olfactory loss due to sinonasal disease. Most of the studies relying on OB volume and OS depth have been performed on a relatively small number of patients and without adequate control groups. However, there is evidence that OB volume is decreased in many clinical circumstances associated with olfactory loss [7,18-20].

Modern assessment of olfactory function includes psychophysical testing, through both orthonasal and retronasal routes, electrophysiological recordings (olfactory and trigeminal event-related potentials) and structural MRI focusing on OB volume and olfactory sulcus depth. OB volume has now been calculated in a number of clinical conditions and correlation between OB volume and olfactory dysfunction has been demonstrated both for qualitative and quantitative disorders (Table 1).

Post-infectious olfactory loss

Patients with post-infectious olfactory loss are typically middle-aged women who observe olfactory disturbances after an acute upper airway respiratory infection. They frequently complain

Table 1. Clinical studies focusing on olfactory bulb volume in different diseases. TDI score; treshold, discrimination, identification scores used in the Snifin' stick test. UPSIT; University of Pennsylvania Smell Identification Test.

References	Disease	n	Olfactory function	Olfactory bulb volume	Remarks
6.	Postinfectious, posttraumatic	31 patients 17 controls	Decreased (TDI score)	Reduced compared to control	Also more reduced for patients with parosmia compared to patients without
14.	Postinfectious	26 patients	Decreased (TDI score)	Higher for hyposmic compared to anosmic	Also more reduced for patients with parosmia compared to patients without
15.	Posttraumatic	25 patients	Decreased (TDI score)	Higher for hyposmic compared to anosmic	Also more reduced when temporal lobe damage were present
22.	Posttraumatic	36 patients	Decreased (UPSIT score)	Reduced	Correlated to olfactory function
23.	Chronic rhinosinusitis	22 patients 16 controls	Normal (TDI score)	Reduced for patients with severe inflammation (CT Scan)	Correlated to sinonasal inflammation at CT scan
29.	Parkinson's disease	11 patients 9 controls	Not determined	No difference between patients and controls	
30.	Alzheimer's disease	21 patients 21 controls	Not determined	Reduced for patients compared to controls	OB volume correlated to Mini Mental State Examination
31.	Schizophrenia	26 patients 22 controls	Slight decrease	Reduced for patients compared to controls	Correlated to olfactory function

of quantitative but also qualitative dysfunction such as parosmia. Until now, no medications has been proved to be effective in controlled studies and spontaneous recovery may be expected in 35% of the cases within the first two years after the infectious event. First evidence that a correlation exists between OB volume and olfactory dysfunction in postinfectious olfactory disorder patients has been demonstrated by Muller et al. [6]. In addition, we conducted a study based on 26 patients where OB volume and OS depth have been correlated to psychophysical olfactory testing (Figure 4) [14]. OB volumes of patients with hyposmia were found to be larger than those of patients with functional anosmia. No difference was found between left and right-sided OB volumes. In addition, left- and right-sided OB volume exhibited significant correlations with the patients' odor identification score.

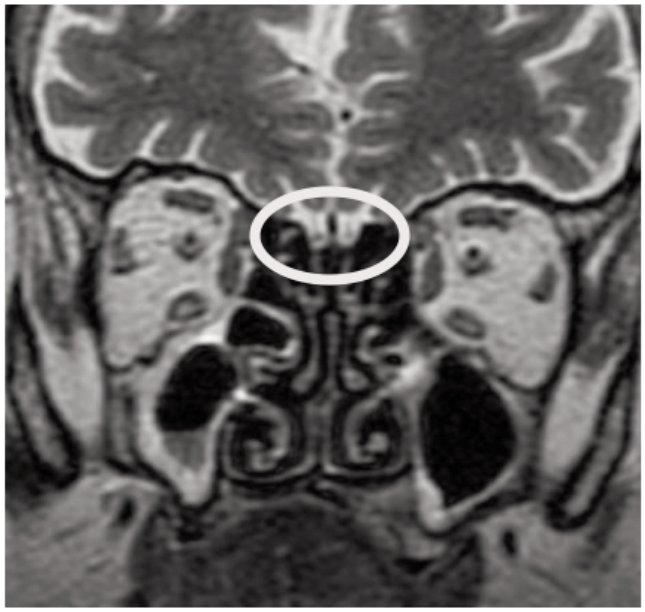

Figure 4. Coronal T2 weighted sequence, OB from patient with postinfectious olfactory loss. Bilaterally decreased volume of the OB.

With regard to depth of the OS, no significant difference was observed between patients with anosmia / hyposmia or between the left and right OS. No significant correlations between OS depth and any measure of olfactory function was observed. There was a negative correlation between OB volumes and duration of the olfactory loss. Finally, patients with parosmia had smaller OB volumes compared to patients without parosmia although the two groups did not differ significantly in terms of measured olfactory sensitivity as obtained with the "Sniffin' Sticks".

Post-traumatic olfactory loss

Current explanations about post-traumatic olfactory disorders include a lesion and/or tearing of the fila olfactoria on their way through the cribriform plate and contusion and/or haemorrhage in the central olfactory pathways such as OB, olfactory tracts, orbitofrontal cortex, frontal lobe (gyrus rectus), or the antero-inferior part of the temporal lobe [21,22].

There is strong evidence about a relation between OB volume and olfactory function (Figure 5A and 5B) [6,15,22]. A total of 25

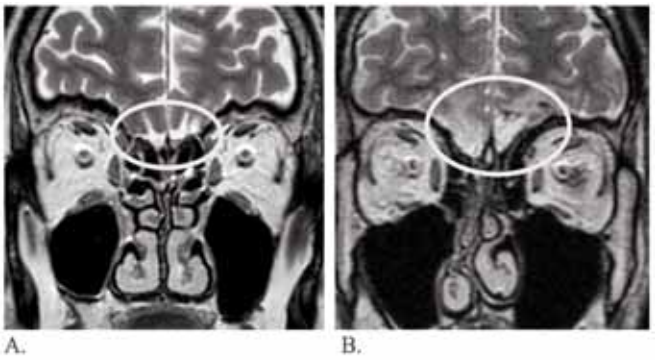

Figure 5. Coronal T2 weighted sequence, OB from patient with post-traumatic olfactory loss. (A) OB volume is decreased with minor cortical damage in the left basofrontal area. (B) OB volume is decreased with major cortical damage in the bilateral basofrontal area.

patients were included in our study. Parosmia was present in seven patients. Orthonasal testing showed that 20 of the patients had anosmia and five were hyposmic. The mean retronasal olfaction score was 9.5 (range 4–15) or 47.5% (range 20–75%) expressed as the percentage of the maximal score of 20. Mean orthonasal function for odour identification was 4.5 (range 1–14) or 29% (range 6–88%) expressed as the percentage of a maximum score of 16. These scores differed significantly indicating that retronasal function was less affected than orthonasal function.

Correlations between orthonasal scores, retronasal olfactory function and OB volume revealed that retronasal odour identification correlated significantly with OB volume while this was not the case for orthonasal odour identification. These analyses suggested that, at least in this study, OB volume is of greater significance in retronasal than in orthonasal function.

Patients with anosmia had significantly smaller OB volumes than those with hyposmia, and patients with parosmia had significantly smaller OB volumes than those without parosmia.

Damage to the frontal lobes was noted in 15 patients (60%); seven of these patients exhibited additional damage of the antero-inferior temporal lobe. There was a clear relation between patients without cortical damage, those with frontal lobes damages, and those with both damages, and retro-olfaction scores and OB volume.

Chronic rhinosinusitis and olfactory dysfunction

Olfactory disturbances in patients with CRS are supposed to appear secondary to inflammatory mediators in the nasal fossa interacting in a negative way with the olfactory neuroepithelium or to the obstruction to the passage of odorant molecules to the olfactory cleft due to polyp formation. Recently, we conducted a study on OB volume in CRS patients who had no polyps at endoscopic evaluation and who had no other possible causes for their smell loss [23]. OB volume was investigated in patients with sinonasal disease and in a control group. There was no significant group difference between patients and controls with regard to OB volume. However, patients with slight to moderate inflammation of the paranasal sinuses had significantly higher OB volume than patients with a higher paranasal sinuses inflammation (expressed with the Lund mackay score originally described for CT Scan evaluation). Even, when controlling for the subjects' age, a significant correlation was present between OB volume and SND score with smaller OB volumes being associated with a higher degree of nasal pathology. This study shows that patients even with marginally decreased olfactory function may have some deprivation in olfactory stimulation leading to a decreased volume of their OB. This emphasizes that OB volume is sensitive even to subtle changes in the olfactory system.

Idiopathic olfactory loss

In patients with idiopathic olfactory loss classical causes of olfactory dysfunction have been ruled out. It is therefore difficult to gather many patients in this category. Recently, we performed a study in patients with idiopathic olfactory loss and were able to demonstrate that OB volumes in idiopathic patients are indeed decreased compared to controls matched for sex and age (Figure 6) [24].

Congenital anosmia

Some patients claim that they never had had any sense of smell. When others causes have been ruled out these patients may be viewed as congenitally anosmic patients. Congenital anosmia may be isolated or associated with hypogonadotropic hypogonadism in the so-called Kallman syndrome. MRI usually demonstrates absence or hypoplasia of the OB and a marked

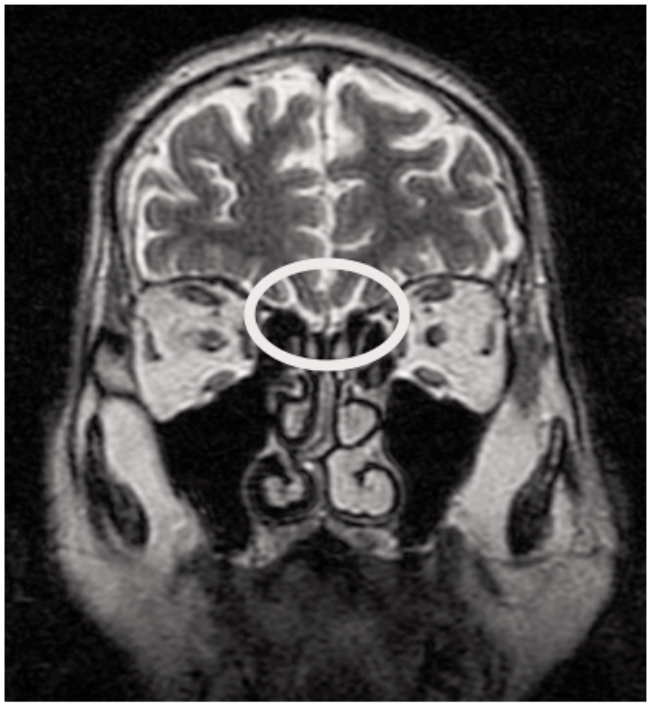

Figure 6. Coronal T2 weighted sequence, OB from patient with idiopathic olfactory loss. OB volume is decreased.

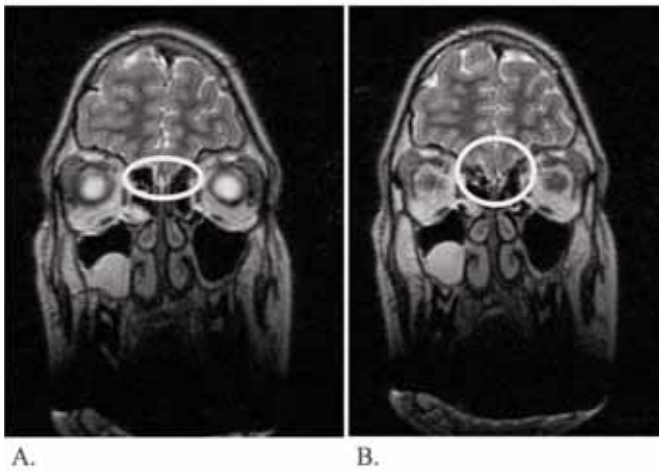

Figure 7. Coronal T2 weighted sequence, MR scan from a patient with congenital anosmia (A) absence of OB structure (B) absence of OS.

flattening or even an absence of any olfactory sulcus (Figure 7) [25-27]. The flattening of the OS appears to be an additional criterion to diagnose congenital anosmia especially when image acquisition has been difficult due to patient's movement.

Neurologic and psychiatric disorders

It is well known that olfactory dysfunction may be present at early stages of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases, in the case of Parkinson's disease actually several years before onset of motor symptoms. However, despite of the strongly decreased olfactory function OB volume patients with idiopathic Parkinson's disease were not decreased compared to controls [28,29]. Thus, it appears that olfactory disorder in Parkinson's disease is not a primary consequence of damage to the olfactory neuroepithelium but rather a consequence of central nervous damage.

In Alzheimer's disease, clinical characteristics include neuronal loss and deposition of neurofibrillary tangles (NFTs) and amyloid plaques in the brain. First, parahippocampal regions are involved, then the medial temporal lobe and structures of the limbic system, then other cortical structures. OB volume has been shown to be decreased in patients with Alzheimer's disease. In this study, OB volume correlated to results from the minimental state examine [30] indicating that dementia was correlated with OB volume.

Finally, in psychotic disorders such as schizophrenia OB volume is also decreased compared to controls [31]. This change is also accompanied by changes at the level of the olfactory epithelium [32].

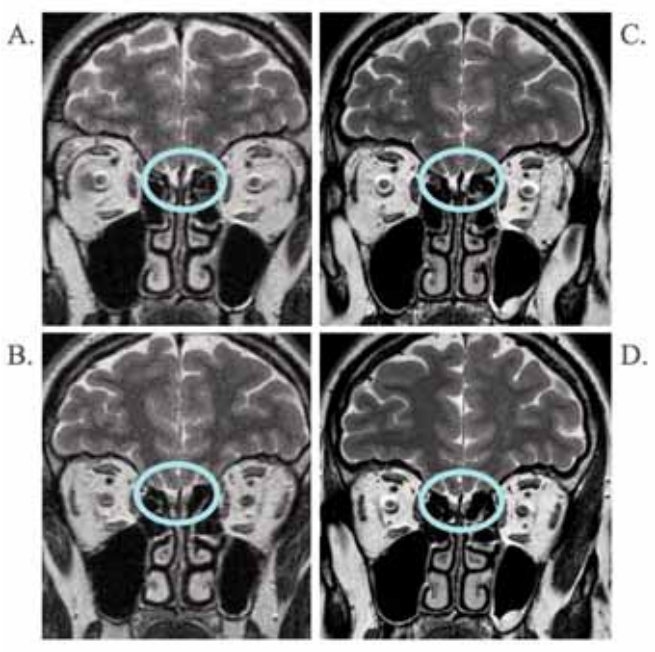

Figure 8. Coronal T2 weighted sequence, OB from patient with post-infectious olfactory loss. (A, B) MR scans at first visit; OB from anterior to posterior plane at the diagnosis, OB volume is decreased (right 37 mm^3 + left 33 mm^3). (C, D) MR scans at second visit 18 months later; OB from anterior to posterior plane with dynamic change in the OB volume (right 44 mm^3 + left 42 mm^3). The patient showed a marked increase both of its olfactory performances and of the OB volume.

OB volume and olfactory event-related potentials

OB volume has been related to electrophysiological recording. Olfactory event-related potentials are recorded in one third of patients with olfactory dysfunction [7]. Patients exhibiting responses are usually hyposmic. It is therefore not surprising that patients with reproducible olfactory event-related potentials have a higher OB volume than patients with no response, supposed to be profoundly affected. In our study [7], OB volumes were significantly different when paired comparisons were performed between control and patients with olfactory dysfunction secondary to nasal polyposis, post-infectious event and post-traumatic event. OB volumes were lowest in subjects with post-traumatic olfactory loss. Patients with nasal polyposis and post-infectious olfactory dysfunction, respectively, also demonstrated lower OB volumes compared to controls.

Dynamic changes in OB volume

As the OB is a highly plastic structure, it might be expected that OB volume changes when partial or total recovery of olfactory function is observed. This relation has been recently published in a cohort of 20 hyposmic patients for whom a correlation between OB volume and odour threshold scores has been demonstrated [33] when studied at two occasions (also demonstrated in one of our patients Figure 8). This longitudinal study emphasizes the idea that the volume of the human OB reflects individual changes in olfactory status.

CONCLUSIONS

OB volume correlates with decreased olfactory sensitivity in many diseases. It seems to be determined by olfactory function with a strong relation to orthonasal and/or retronasal olfactory test scores depending of the cause of the olfactory loss. OB volume also varies with regard to qualitative olfactory dysfunc-

tion such as parosmia and with the duration of the olfactory loss. With time when olfactory sensitivity is increasing, it could also show dynamic changes demonstrating that OB is a highly plastic brain structure. MRI-based measurement of OB volume should be included in the clinical investigation of patients with a major complaint of olfactory loss and would probably help the clinician in counselling of patients waiting for spontaneous recovery of their olfactory function.

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