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MINI-REVIEW

Neural plasticity in developing and adult olfactory pathways – focus on the human olfactory bulb

C. Huart[1,2] · Ph Rombaux[1,2] · T. Hummel[3]

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Abstract
The topic of human adult neural plasticity and neurogenesis is of great interest for medical and scientific community, but it is also largely debated. In the last years, an increasing interest has been paid to the olfactory system, and particularly to the plasticity of the olfactory bulb (OB). While the molecular/cellular mechanisms underlying OB plasticity remain a matter of debate, measurements of the OB using magnetic resonance imaging clearly indicate that it is a highly plastic structure. In this review, we present results regarding the plasticity of the human adult olfactory system.

Keywords Smell · Anosmia · Nose · Plasticity · Neuroregeneration

Introduction

Among all the particularities of the human olfactory system, the most amazing one is probably its high plasticity. Indeed, olfactory abilities of normal smellers can be improved all life long and even patients with damaged olfactory nerve may expect a spontaneous recovery of their deficit.

The olfactory bulb (OB) is of paramount importance in the processing of olfactory information. This small structure is not only the relay between the peripheral and central nervous olfactory system, but is also processes olfactory information.

Several studies have shown that the OB is a highly plastic structure, the volume of which varies as a function of olfactory sensitivity. Not only the OB volume is decreased in patients with olfactory disorders (Mueller et al. 2005b; Rombaux et al. 2006a; Rombaux et al. 2006b; Yousem et al. 1999; Yousem et al. 1996), but even more interestingly, the OB volume may increase (1) after olfactory training of normosmic patients or (2) during recovery from the olfactory disorder (Gudziol et al. 2009).

✉ T. Hummel
thummel@mail.zih.tu-dresden.de

[1] Department of Otorhinolaryngology, Cliniques universitaires Saint-Luc, Brussels, Belgium

[2] Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium

[3] Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany

The mechanisms of this plasticity are not clearly understood. It has been hypothesized that, similarly to animals, the human olfactory system benefits from continuous neurogenesis throughout adult life. Although adult neurogenesis has been intensely studied in animals, it received comparatively little attention in humans. Because the brains and olfactory systems of humans and animals differ simple extrapolation of animals study to humans probably misrepresents the reality.

Based on human research findings, the aim of the present review is to summarize current research on the OB, as a structure exhibiting astonishing plasticity.

Anatomy and physiology

From the olfactory epithelium to the olfactory bulb

The olfactory epithelium is located in the upper part of the nasal fossa, in an area named the olfactory cleft. It is covered by a mucus layer, secreted by the Bowman's glands, and contains the olfactory receptor neurons (ORNs), surrounded by the supporting and the basal cells.

ORNs are bipolar cells, with (1) their body located in the olfactory epithelium (OE); (2) a dendritic extension directed toward the olfactory cleft and carrying on its surface several cilia on which are located olfactory receptors; and (3) an axon directed toward the OB.

Odorants reaching the olfactory cleft are probably carried through the mucus layer by olfactory binding proteins and bind to olfactory receptors, giving rise to the olfactory transduction. In 1991, Axel and Buck (Buck and Axel 1991), made the amazing discovery of a family of approximately 1000 genes that code for an equivalent number of olfactory receptors, corresponding to the largest family of genes in the mammalian genome (Zhang et al. 2011), highlighting the importance of the sense of smell in mammals. However, the number of functional genes is lower; and in humans, there are only about 350 functional genes (Crasto et al. 2002). Importantly, each ORN expresses only one type of odorant receptor and each receptor is specialized for a certain number of odors (Buck and Axel 1991).

Following olfactory transduction, depolarization of an ORN gives rise to action potentials that propagate through its axons. These axons combine to form olfactory nerves and pass through the cribriform plate of the ethmoid bone to directly project to the ipsilateral OB.

The OB

The OB is a twin ovoid structure, located in the anterior cranial fossa, above the cribriform plate of the ethmoid bone and beneath the frontal lobe.

Within the OB, axons of ORNs synapse with dendritic extension of second order neurons, the mitral and tufted cells, within small spherical structures called glomeruli. Each glomerulus collects axons of ORNs that express the same receptor protein (Mombaerts et al. 1996). A given odorant will activate a typical pattern of olfactory receptors, relayed to specific glomeruli.

The OB encompasses different types of neurons. The neurons conveying afferent olfactory information to olfactory cortex are named the mitral and tufted cells. These neurons have connections with number of interneurons, modulating their activity (e.g. periglomerular, short-axon cells).

The OB has a laminar organization arranged in different concentric circular layers, defined on the basis of cell type and composition (Fig. 1): (1) the olfactory nerve layer; (2) the glomerular layer; (3) the external plexiform layer; (4) the mitral cell layer; (5) the internal plexiform layer and (6) the granule cell layer. The (1) ***olfactory nerve layer*** is made up of axons of the incoming ORNs. The (2) ***glomerular layer*** is composed by glomeruli wherein axons of ORNs synapse with dendrites of mitral, tufted, periglomerular and short-axon cells. It is essentially composed of interneurons with local connections in this layer. The (3) ***external plexiform layer*** consists mainly of tufted cells, interneurons and dendrites of mitral cells. Tufted cells are the most numerous cells of this layer. Within this layer, the synapses between mitral, tufted and granular cells give rise to complex dendritodendritic, feedback or feedforward interactions, aiming to modulate the olfactory output. The (4) ***mitral cell layer*** contains cell bodies of mitral cells. The (5) ***internal plexiform layer*** contains a population of small-axon cells. The (6) ***granule cell layer*** contains soma of granule cells and small-axon cells.

Granule cells are GABAergic interneurons and represent the most numerous cells in the OB (Ennis and Holy 2015). Glutamate is the principal neurotransmitter of ORNs, mitral and tufted cells. However, it is important to note that numerous neurotransmitters (i.e. Dopamine, GABA) are involved in bulbar cell interactions at the level of the glomerulus and within the external plexiform layer (for a review see (Nagayama et al. 2014)).

From the OB to the olfactory cortex

Axons of the mitral and tufted cells coalesce to form the olfactory tract, located at the base of the forebrain. From the OB, bottom-up information is so conveyed to a wide number of brain regions referred to as primary olfactory cortex, encompassing the piriform cortex, the entorhinal cortex, the periamygdaloid cortex and the anterior olfactory nucleus.

Top-down modulation

Importantly, the OB also receives top-down information from higher brain structures (Ennis and Holy 2015). Top-down fibers can be subdivided into two classes: (1) fibers arising from olfactory-related structures and implied in feedback inputs and (2) fibers arising from non-olfactory structures.

The first group's fibers mainly originate from the primary olfactory cortex. Glutamatergic pyramidal neurons arising from the primary olfactory cortex massively target granular cells. Activation of these cells will produce a dendritodendritic inhibition on mitral and tufted cells due to GABA release, modulating the activity of the OB.

The second group fibers, arising from non-olfactory structures, are essential to modulate the activity of the OB, in a context and behavioral state-dependent manner. For that purpose, OB receives inputs from cholinergic, noradrenergic and serotoninergic cells, located in basal forebrain and brainstem structures. Cholinergic fibers enter the bulb from the ipsilateral nucleus of the horizontal limb of the diagonal band, they have a role in odor habituation and discrimination (Linster and Cleland 2002; Wilson et al. 2004). Centrifugal serotoninergic inputs arise from the dorsal and medial raphe nuclei (McLean and Harley 2004; Morizumi et al. 1994; Yuan et al. 2003) and are involved in conditioned olfactory learning. Noradrenergic innervation arises from the locus coeruleus and is involved in early olfactory preferences learning (Ennis and Holy 2015). All these different fibers project diffusely to multiple OB layers, modulating multiple neuronal subtypes (Ennis and Holy 2015).

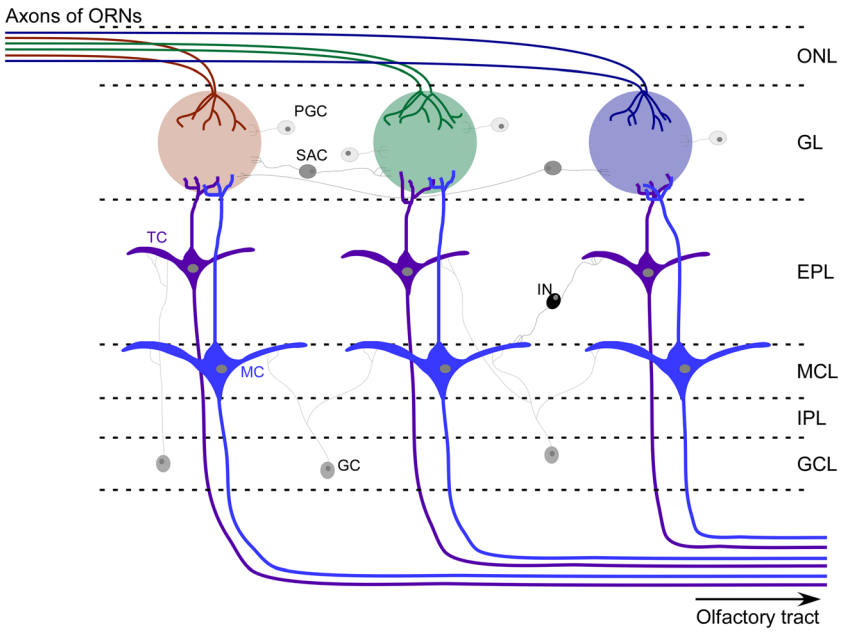

Fig. 1 Basic model of the olfactory bulb organization. The OB has a laminar organization arranged in different concentric circular layers: (1) the olfactory nerve layer (ONL); (2) the glomerular layer (GL); (3) the external plexiform layer (EPL); (4) the mitral cell layer (MCL); (5) the internal plexiform layer (IPL) and (6) the granule cell layer (GCL). (ORN = Olfactory receptor neurons; PGC = periglomerular cells; SAC = short-axon cells; TC = tufted cells; IN = interneurons; MC = mitral cells; GC = granule cells)

In summary, the neuronal activity within the OB is influenced by sensory input from the OE (bottom-up input) and top-down input from higher brain structures. The small size of the OB contrasts with its high complexity: more than a relay conveying olfactory information to central nervous system, the OB processes actively the olfactory information and performs complex neuronal computations similar to those of the primary cortices of other sensory systems (Cleland and Linster 2005).

Cellular substrates supporting adult neurogenesis

Mechanisms of neurogenesis and plasticity have been extensively investigated in animals, particularly in rodents. Even if it is currently acknowledged that adult neurogenesis is very well conserved among mammals, animal and human olfactory system show noticeable differences and simple extrapolation of animal study to humans probably misrepresent the reality (e.g. brain size, cortex expansion, cortical tissue folding, the existence of a secondary olfactory system in animals, the number of olfactory receptors, glomeruli-to-olfactory receptor convergence ratio) (Bergmann et al. 2015; Paredes et al. 2016; Maresh et al. 2008). A recent review (Paredes et al. 2016) discussed current knowledge on adult neurogenesis across several species and proposed that the increase in brain size between these species has significantly influenced the manner in which new born neurons are able to contribute to adult plasticity. Indeed, if young neurons migrating within the rostral migratory stream through the OB have to travel over a short distance in mice brain, this distance is dramatically increased in human brain. This may limit the circuits able to receive new neurons and the duration of neurogenesis through life. This review highlighted one more time the current controversy as to whether the mechanisms of neurogenesis and plasticity described in animals are relevant in humans.

However, studying possible mechanisms of adult neurogenesis is particularly challenging in humans (Bergmann et al. 2015), due to methodological issues. While some studies report evidence in favor of significant adult human neurogenesis within the OB (Lotsch et al. 2013), others do not support its existence (Bergmann et al. 2012). For example, analyzing the transcriptome of adult human OBs, Lötsch et al. reported that a fifth of genes expressed in adult human OBs serve functions of nervous system or neuron development. Although their study doesn't answer the question of the origin of the human neurogenesis, their results support the existence of neurogenesis in the adult human OB (Lotsch et al. 2013). In contrast, measuring the age of human OB neurons, using a ^{14}C dating technique, Bergmann et al. argued that there is "very limited, if any, postnatal neurogenesis in human OB" (Bergmann et al. 2012).

Hence the question of the adult human neurogenesis within the OB and its exact mechanisms remains open. Still, the plasticity of the olfactory system may involve three different mechanisms of continuous neurogenesis occurring (1) at the level of the OE; (2) in the supraventricular zone of the lateral ventricle; and (3) within the OB itself.

OE

It has been demonstrated that the OE contains a population of proliferating progenitor cells, located in its basal layer and the lamina propria. These stem cells have the ability to produce ORNs, as well as their ensheathing and supporting cells. Hence, through that mechanism, the OE would be continuously reconstituted and ORNs would regenerate throughout life

(Schwob 2002). This regeneration is of importance since the OE is in direct contact with the environment and is particularly exposed to various sources of damage (i.e. toxins, irritants, viruses, trauma).

Based on animal studies, it can be hypothesized that the continuous regeneration of ORNs also implies a continuous synaptogenesis within the OB. Indeed, the incoming axonal projections of ORNs continuously form new synapse with dendrites of mitral / tufted cells, at the glomerular level (Lledo and Gheusi 2003).

Supraventricular zone of the lateral ventricle

In adult rodents and in monkeys, several studies have shown that neural stem cells residing in the walls of the lateral ventricle give rise to neuroblasts (Kornack and Rakic 2001; Lois et al. 1996; Ming and Song 2011). Neuroblasts form a migratory chain, following the rostral migratory stream (RMS) and migrate towards the OB where they differentiate into olfactory interneurons throughout adult life (Alvarez-Buylla et al. 2008; Doetsch et al. 1999). These new neurons are thought to be implicated in complex processes, such as olfactory memory formation, odor discrimination and social interactions (Carlen et al. 2002; Lazarini and Lledo 2011).

In humans, the prerequisite of a similar mechanisms would thus be (1) the existence of a RMS; and (2) the presence of migrating neuroblasts.

Evidences of human rostral migratory stream

Similarly to animals, a RMS has been described in fetal human brain, from the lateral ventricle SVZ to the olfactory tract and OB; as well as the presence of neuroblasts forming migratory chains (Sanai et al. 2011; Wang et al. 2011a). In human infant, many proliferating cells are observed in the SVZ. In contrast, the number of proliferating and migrating neuroblasts strongly declines after birth. Only a few migrating neuroblasts and limited proliferation in the SVZ and RMS could be observed at 6 to 8 months of age, with cells being mostly vanished by the age of 2 years (Sanai et al. 2011).

In the adult human brain, Curtis et al. (Curtis et al. 2007) have described a ventral extension of the lateral ventricle suggesting the presence of a RMS, where the SVZ remains an active proliferative region. They proposed that neuroblasts migrate through the OB via this so-called olfactory ventricle (Curtis et al. 2007). Nevertheless, the existence of a human RMS with an open ventricular structure and the presence of migratory neuroblasts in adults are still controversial. Although the olfactory ventricle seems to exist in the fetal human brain (Guerrero-Cazares et al. 2011), other studies (Sanai et al. 2011; Wang et al. 2011a) didn't support the idea of a persistent ventricular lumen connecting the lateral ventricle to the OB in adult humans as well as in postnatal infants.

The question of possible OB ventricle has also been addressed using MRI. Smitka et al. (Smitka et al. 2009) showed that 59% of healthy human subjects had a central lucency in the OB, interpreted as an OB ventricle. By contrast, autopsy results identified an OB ventricle in only 7% of cadavers. They explained this discrepancy between MRI and histopathology by postmortem resorption of cerebrospinal fluid from OB ventricles. However, a later study did not verify this finding, since they found such a structure in only 5.5% (Burmeister et al. 2011a). More recently, an in vitro study on human cadavers investigated OB using a high resolution MRI at 3 T and MR microscopy at 9.4 T. This study indicated that 58.9% of images in T2 had a central hyperintensity, similar to the results of Smitka et al. (Smitka et al. 2009). Nevertheless, it appeared from microscopy that this was not an OB ventricle but that is was due to the lamination pattern of the OB (Burmeister et al. 2012). Pozzati et al. (Pozzati et al. 2014) recently described a case report of a patient with olfactory neuroblastoma where MRI were able to show the existence of an olfactory ventricle. Hence, the debate regarding the existence of an olfactory ventricle remains open. Probably this structure exists in a small percentage of human adults. However, its functional significance is unknown.

Evidences of migrating neuroblasts in humans

Another key question regarding the possible existence of neurogenesis within the SVZ of the lateral ventricle is whether neuroblasts are able to migrate towards the OB.

Examining adult human brains, Sanai et al. (Sanai et al. 2004) found no evidence of chains of migrating neuroblasts in the SVZ or in the pathway to the OB. In contrast, they identified a ribbon of SVZ astrocytes lining the lateral ventricles and behaving as neural stem cells. However, their potential role and the question as to whether they give rise to neuroblast that migrate to the OB were unanswered (Curtis et al. 2007; Sanai et al. 2004). Later, other studies described the presence of very few migrating neuroblasts in the SVZ and the RMS pathway (Sanai et al. 2011; Wang et al. 2011a). Wang et al. (Wang et al. 2011a) found neuroblasts in the anterior ventral SVZ and in the RMS. These neuroblasts appeared singly or in pairs, without forming chains; and few appeared to be actively proliferating. They thus suggested that generation of neuroblasts from neural stem and progenitor cells occur in the SVZ of the adult human brain. However, they did not find any neuroblasts within the OB. Their possible explanation is that neuroblasts actively control the formation and maintenance of their own migratory route (Kaneko et al. 2010). Consequently, it is probably impossible for neuroblasts to establish a long and complex migratory route from the SVZ to the OB.

In summary, it seems that adult human brain SVZ maintains the ability to produce neuroblasts; and a smaller and

morphologically different RMS-like pathway seems to exist in adult human brain (Curtis et al. 2007; Sanai et al. 2011; Sanai et al. 2004; Wang et al. 2011a). However, the existence of migrating neuroblasts and whether they are able to reach the OB remains questionable.

Intrinsic bulbar plasticity

In addition to the mechanisms aforementioned, some studies suggest the presence of progenitor cells directly within the OB itself (Gritti et al. 2002; Pagano et al. 2000). Such neural stem cells have been isolated from adults rodents OB (Gritti et al. 2002) and adult patients OB (Pagano et al. 2000).

Moreover, in mice, recent evidences suggest a new form of structural remodeling of adult-born OB neurons, based on the activity-dependent relocation of mature spines of granule cells towards the dendrites of active mitral cells. This mechanism would allow a more rapid adjustment of neuronal network in response to quick and persistent changes in sensory inputs. This mechanism is able to explain quick behavioral changes induced by odor exposure since spine relocation occurs within a few minutes. It seems to be perfectly adapted to rapid changes in odor environment, unlike synaptogenesis, which need some weeks (Breton-Provencher et al. 2016; for a review see Hardy and Saghatelyan 2017). However, no data are currently available regarding the existence of this mechanism in humans.

Taken together, these studies suggest that the adult OB benefits from a continuous neurogenesis. However, in humans the exact mechanism(s) remain(s) unknown and the debate about a possible ongoing OB neurogenesis is still open. We must also note that in addition to the mechanisms described above, animal studies have shown that different mechanisms may exist. For example, top-down projections from noradrenergic neurons located in locus coeruleus would be involved in learning-related plasticity phenomenon (Ennis and Holy 2015). Although there is currently no data to confirm this hypothesis, we cannot exclude that similar mechanisms exist in humans.

Macroscopic evidence of human OB plasticity – MRI findings

Although results of studies investigating the cellular mechanisms of OB plasticity in adult humans are still controversial, studies assessing macroscopically the OB using magnetic resonance imaging are clear: the OB is a highly plastic structure! In the following section, we will describe the results of these different studies, as evidence of OB plasticity in humans.

OB volume as measure of OB function in humans–technical details

MRI is the imaging modality of choice in order to measure OB volume (Fig. 2). Standard protocol usually includes 2-mm-thick T2-weighted images in Fast Spin Echo (FSE) mode in the coronal plane, which is the best technique for anatomical olfactory tract overview, detection of parenchymal lesions and OB volumetry. OB measurement is usually performed using a 1.5 T magnet MRI, or better 3 T.

When evaluating patients suffering from olfactory disorders, whole brain coverage remains mandatory for detecting parenchymal lesions/processes. Hence, fluid-attenuated inversion recovery (FLAIR) sequence and hemosiderin-sensitive gradient echo T2* sequences covering the whole brain are usually performed to detect post-contusion gliotic changes (on FLAIR images) and post-traumatic hemosiderin deposits (on GRE-T2* images) (Duprez and Rombaux 2010).

Volumetric measurement of the OB is typically done using planimetric manual contouring. All frontal slices (without interslice gap) of the FSE T2-weighted sequence are browsed from anterior to posterior (Duprez and Rombaux 2010).

The first image in which the OB becomes clearly recognizable is considered to be the first slice through the OB. The OB cross-sectional area, calculated in mm^2, is delineated using an electronic cursor. The surfaces on all slices are summed and the total surface is multiplied by the thickness of the slices (usually 2-mm) to give a volume in mm^3. The posterior end of the OB is defined as a sudden decrease in the diameter of the OB, meaning that the OB ends with the olfactory tract (Rombaux et al. 2009).

Buschhüter et al. *(Buschhuter* et al. 2008*)* have proposed normative data of OB volume based on data of 125 patients. They proposed that people <45 years should have a minimum OB volume of 58 mm^3; and people >45 years should have a minimum OB volume of 46 mm^3.

The reliability and reproducibility of OB volumetry have been demonstrated by several authors (Yousem et al. 1997; Mueller et al. 2005b; Burmeister et al. 2011b; Gudziol et al. 2009). Notably, this method has a good intraobserver (interclass coefficient of correlation greater than 0.7) and interobserver reliability (interclass coefficient of correlation greater than 0,8). Also, it shows a good accuracy, as proven by Yousem et al. (1997) who compared the true volume of phantoms structures to MRI-measured volumes and found a mean measurement error of 7.3%. Moreover, comparing repeated MRI of normosmic subjects, performed at a 3 months interval; Gudziol et al. found no significant difference between the two measurements (average difference ± standard deviation: left OB: 1.22± 0.58; right OB: 0.64± 0.64) (Gudziol et al. 2009). These results suggest that MRI is indeed a non-invasive and reliable tool to assess OB volume and to study OB plasticity.

However, this technique has also some limitations. First of all, the true accuracy of volumetric measurements cannot be

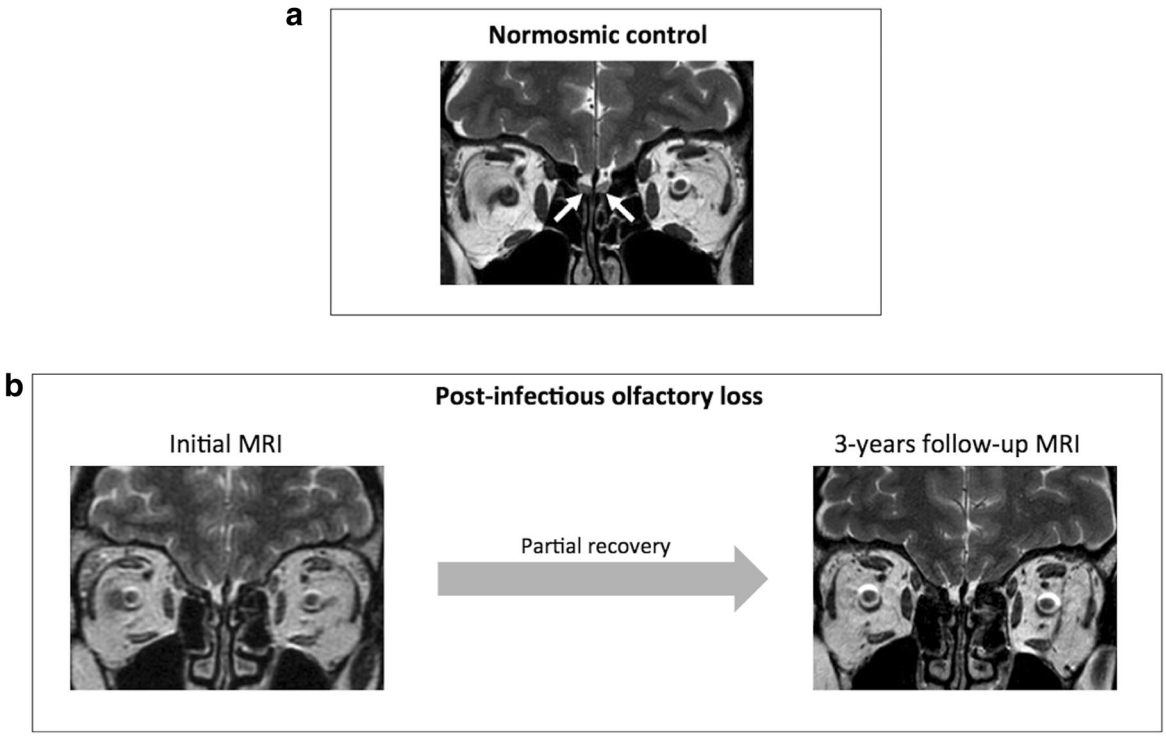

Fig. 2 Coronal T2-weighted magnetic resonance images. **A**. Normal olfactory bulbs (white arrows). **B**. MRI images of a patient suffering from post infectious olfactory loss, with decreased olfactory bulbs volume. Left: Initial MRI performed at the time of the diagnosis. At that time, psychophysical evaluation revealed anosmia (TDI score = 12 (Hummel et al. 2007)). Olfactory bulbs are hypoplastic and hardly visible. Right: Follow-up MRI performed in the same patient 3 years later. Patient had partial recovery and was in the range of hyposmia (TDI score = 24 (Hummel et al. 2007). Recovery was associated with an increase in olfactory bulb volume

addressed because of lack of direct anatomic correlations. Second, the occurrence of artifacts must be considered. Third, a learning curve is needed to correctly assess the OB volume (Burmeister et al. 2011b). Fourth, like every volumetric measurement technique, OB volumetry is subject to potential error. This is even more true as we are dealing with small volumes. Including or excluding even a single slice may significantly impact on the measure. Establishing the posterior terminus of the OB is probably the most problematic aspect of morphometry since this boundary is ill defined. This might explain some differences in the measurement of OB volumes obtained by different authors (Buschhuter et al. 2008; Duprez and Rombaux 2010; Yousem et al. 1998).

OB in healthy subjects

The OB volume is intimately correlated to olfactory function, independently of age. Using the Sniffin' Sticks test, Buschhüter et al. demonstrated that OB volume correlated significantly with overall olfactory function; but also with specific olfactory functions, namely odor thresholds and odor identification (Buschhuter et al. 2008).

In healthy subjects it has been demonstrated that OB volume varies as a function of sex, with men having a larger OB volume as compared to women.

Age has also an impact on OB volume. OB volumes decrease significantly with advancing age (Buschhuter et al. 2008; Yousem et al. 1998), in parallel with the olfactory function. As with other senses the olfactory function decreases over time and it has been described in numerous previous studies that there is a strong decrease in olfactory function above the age of 55 years (Buschhuter et al. 2008; Hummel et al. 2007; Murphy et al. 2002). Several mechanisms have been proposed to explain this age-related olfactory dysfunction:

- At a peripheral level, changes in mucociliary movement, mucus composition, submucosal blood flow, or epithelial thickness might disturb the transport of the odorant to the receptor (Rawson 2006). At the level of the neuroepithelium it is assumed that the regeneration of ORNs decreases with age (Conley et al. 2003; Naessen 1971). Moreover, studies have described a decreased extent of the OE (Paik et al. 1992) and a decreased density and complexity of adrenergic innervation within the lamina propria of the OE (Chen et al. 1993).
- At the level of the OB, post mortem studies have shown that the number of mitral cells continuously decreases with age, as well as the number of glomeruli, the glomerular layer thickness and the mitral cell size and concentration (Bhatnagar et al. 1987). The number of mitral cells and

glomeruli declines steadily with age at an approximate rate of 10% per decade (Meisami et al. 1998). Moreover, 86% of normal aged subjects have neurofibrillary tangles in the OB, and one third of them show amyloid deposition in the OB (Kovacs et al. 1999). It has also been described that aging is associated with structural abnormalities of the OB. For example, olfactory nerve fibers invade deep to the glomerular layer of the OB forming ectopic glomeruli. These misrouted olfactory fibers and ectopic glomeruli might alter the normal synaptic organization and hence olfactory processing (Hoogland et al. 2003; Kovacs et al. 1999).

- At a more central level, brain damage due to chronic ischemia or systemic disorders might also be proposed as a potential cause of age-related olfactory disorder. It was also shown that normal aging is associated with the presence of neurofibrillary tangles and senile plaques in the brain and abundant tau pathology is present in almost one third of non-demented older people (Attems et al. 2005).

Interestingly, Hummel et al. reported that there is a differential change of olfactory functions with aging. Indeed, olfactory thresholds decrease more strongly with age as compared to odor discrimination and odor identification (Hummel et al. 2002; Hummel et al. 2007). Since threshold measurements best reflect the function of the peripheral olfactory system than other olfactory tests (Jones-Gotman and Zatorre 1988; Moberg et al. 1997), this finding may indicate that age-related change of olfactory function is, at least in part, due to damage of the OE (Hummel et al. 2007). Nevertheless, it is important to keep in mind that age-related decrease of olfactory function might also be a consequence of side effects of drugs, onset of neurodegenerative diseases etc.

The vast majority of studies evaluating OB volume in healthy volunteers do not provide any follow up data. Nevertheless, these data are probably the most interesting ones to assess possible plasticity phenomena. Recently, Negoias et al. (Negoias et al. 2017) did so in a study assessing changes in OB volume after exposure to odors, so called "olfactory training". They found that olfactory training of normosmic healthy subjects induces a significant increase of OB volume. Even more interestingly, in this study, the authors found that lateralized olfactory training lead to a significant increase of OB volume for both trained and untrained nostril. The fact that OB volume on the untrained side was significantly increased suggests that, not only bottom-up, but also top-down influences (discussed later) are involved in OB volume modulation.

OB in patients

The study of patients with olfactory disorders has offered some important insights to the question of the plasticity of the human OB. It has been demonstrated that decreased olfactory function is associated with decreased OB volume in patients suffering from a wide range of pathologies including: post-traumatic olfactory disorder (Rombaux et al. 2006b; Yousem et al. 1999; Yousem et al. 1996), post-infectious olfactory disorder (Mueller et al. 2005b; Rombaux et al. 2006a) (Fig. 2), sino-nasal related olfactory disorders (Rombaux et al. 2008), idiopathic olfactory loss (Rombaux et al. 2010b), neurodegenerative diseases (Mueller et al. 2005a; Thomann et al. 2009; Wang et al. 2011b), acute depression (Negoias et al. 2010; Rottstadt et al. 2018), post total laryngectomy patients (Veyseller et al. 2011)). More interestingly, follow-up studies revealed that the recovery of olfactory function is associated with an increase in OB volume suggesting that the OB is a highly plastic structure (Gudziol et al. 2009). From these studies in patients, it also appeared that OBs are influenced by both peripheral (bottom-up effect) and central nervous system information (top-down effect).

Bottom-up modulation

The bottom-up modulation refers to fact that the peripheral input influences the OB. Studies in favor of bottom-up modulation are numerous.

The main argument of these studies is that OB volume is decreased secondary to missing input, either following postinfectious olfactory loss (Mueller et al. 2005b; Rombaux et al. 2006a) (Fig. 2), head trauma (Rombaux et al. 2006b; Yousem et al. 1999; Yousem et al. 1996), sinonasal inflammation (Rombaux et al. 2008), total laryngectomy (Veyseller et al. 2011), or unilateral nasal obstruction (Altundag et al. 2014; Askar et al. 2015).

A second argument is that follow up of these patients showed that changes in odor threshold correlated significantly with changes in OB volume (Gudziol et al. 2009; Haehner et al. 2008) (Fig. 2), with patients improving olfactory function also exhibiting an increase of OB volume. Because odor threshold is more closely related to peripheral olfactory function (Moberg et al. 1997) in comparison to odor identification or odor discrimination, this suggests that OB function is related to peripheral input rather than central input. In this vein a study showed that side differences in OB volume correlated to respective differences in odor threshold and odor discrimination, suggesting that OB volume may be dependent on lateralized influences from peripheral input (Hummel et al. 2013a).

Finally, it has been shown that the migration of nasally administrated Thallium-201, a radioisotope shown to migrate to the OB after nasal administration in rodents, was reduced in patients suffering from post infectious olfactory loss, post traumatic olfactory loss and chronic rhinosinusitis, as compared to healthy controls, suggesting a decreased connectivity in patients. Moreover, the migration of Thallium-201 to the OB was correlated with odor threshold as well as with OB volume (Shiga et al. 2013).

Altogether, these results suggest that OB volume is regulated, at least partly, by centripetal influences, involving sensory input from the OE. This hypothesis is corroborated by animal studies, which showed that sensory deprivation leads to a decreased OB volume (Benson et al. 1984; Cummings and Brunjes 1997; von Gudden 1870).

Top-down modulation

Nevertheless, it is also obvious that top-down processes are involved in OB plasticity. Indeed, patients suffering from temporal lobe epilepsy (Hummel et al. 2013b), depression (Negoias et al. 2010; Rottstadt et al. 2018), schizophrenia (Nguyen et al. 2011; Turetsky et al. 2000), Alzheimer's disease (Thomann et al. 2009), or multiple sclerosis (Goktas et al. 2010; Tanik et al. 2015; Yaldizli et al. 2016) exhibit significantly reduced OB volumes, as compared to healthy controls.

In particular, patients suffering from acute major depression showed a inverse correlation between OB volume and depression scores (Negoias et al. 2010). Similarly, depressive adults with a history of childhood maltreatment exhibit smaller OB volumes compared to depressive adults without history of childhood maltreatment. Possible explanations could be that major stress during childhood development disturbs neurogenesis (Croy et al. 2013). In animal studies, it has been shown that mice exposed to stress have reduced neurogenesis at the level of the SVZ (Mineur et al. 2007). Hence, it can be speculated that results observed in depressive humans might be due to a reduced neurogenesis, resulting in reduced OB volume due to centrifugal influences.

An additional argument in favor of top-down control over the OB came from a study in early blind subjects. This study showed that early blind subjects exhibited superior olfactory abilities and significantly higher OB volume as compared to controls, suggesting that OB plasticity is involved in the compensatory mechanisms between visual deprivation and enhanced olfactory perception (Rombaux et al. 2010a). However, regarding their olfactory function, a recent meta-analysis from Sorokowska et al. (Sorokowska et al. 2018) found that blind people do not have superior abilities compared to the sighted. This discrepancy may be explained by the fact that Rombaux et al. investigated OB volume in early blind subjects, whereas the meta-analysis included heterogenous blind population. Moreover, it is possible that blind people do not perform better on relatively simple olfactory tasks, whereas they could outperform sighted controls using complex or environmental-related olfactory tasks.

In light of these studies, we may reasonably hypothesize that the human OB receives both top-down and bottom-up influences. This hypothesis might be supported by studies in rodents, which have shown that both top-down and bottom-up pathways regulate OB activity which itself regulates the recruitment of new neurons. This adult neurogenesis is also directly sensitive to olfactory experience (i.e., sensory deprivation) and to behavioral state (i.e., learning) (Lazarini and Lledo 2011). However, the specific functional role of top-down and bottom-up projections in humans as well as the interaction between them and their influence on neurogenesis is yet unclear.

Although it is obvious from MRI studies that OB is a highly plastic structures, the underlying cellular or synaptic basis remain largely unanswered. As reported above, aging is associated with a reduction of olfactory function and parallel OB volume reduction. Post-mortem studies have shown that aging is associated with reduction in the thickness of all bulb layers and in the number of glomeruli (Bhatnagar et al. 1987; Samaulhaq and Lone 2008). Considering the fact that glomeruli occupy a significant portion of the olfactory bulb, some authors have proposed that the loss of glomeruli would reduce the global OB volume with advancing age (Samaulhaq and Lone 2008). Moreover, correlation between olfactory function and OB volume in patients with olfactory loss suggests that OB volume is related to the input from olfactory epithelium (Haehner et al. 2008) and consequent synaptogenesis between ORNs and mitral cells at the level of the glomerulus. However, the question whether the reverse is also true, that is when the olfactory function and OB volume increase, remains unexplored in humans.

Finally, we can speculate based on animal studies that OB interneurons are also potential candidates to explain dynamic changes of OB volume. Indeed, interneurons are continuously replaced by adult-born interneurons. If the morphology of mitral cell dendrites is relatively stable over time (Mizrahi 2003); interneurons seem to be more dynamic and show activity-dependent plasticity (Mizrahi 2007; Breton-Provencher et al. 2016). It is thus likely that interneurons play more important roles for functional plasticity of OB circuitry.

Conclusions

Despite its small size compared to the neocortex, the OB is a functionally complex structure that plays a central role in the transmission and processing of olfactory information. One of its fascinating features is its apparent plasticity. Although animal studies agree on the mechanisms of OB plasticity and adult neurogenesis, results of human studies are more controversial. However, based on both basic and clinical research findings, we may reasonably propose that human adult OB is indeed a highly plastic structure, subject to the influence of both bottom-up and top-down processes and possibly benefiting from continuous adult neurogenesis. The exact mechanisms of plasticity and neurogenesis are still unclear, and the debates they generate definitely constitute a hot topic in the scientific community. Answering these questions will be major challenge for the future.

References

Altundag A, Salihoglu M, Tekeli H, Saglam M, Cayonu M, Hummel T (2014) Lateralized differences in olfactory function and olfactory bulb volume relate to nasal septum deviation. J Craniofac Surg 25: 359–362. https://doi.org/10.1097/SCS.0000000000000617

Alvarez-Buylla A, Kohwi M, Nguyen TM, Merkle FT (2008) The heterogeneity of adult neural stem cells and the emerging complexity of their niche. Cold Spring Harb Symp Quant Biol 73:357–365. https://doi.org/10.1101/sqb.2008.73.019

Askar SM et al (2015) Ipsilateral reduced olfactory bulb volume in patients with unilateral nasal obstruction. Otolaryngolo Head Neck Surg 152:959–963. https://doi.org/10.1177/0194599815573196

Attems J, Lintner F, Jellinger KA (2005) Olfactory involvement in aging and Alzheimer's disease: an autopsy study. J Alzheimers Dis 7:149–157 discussion 173-180

Benson TE, Ryugo DK, Hinds JW (1984) Effects of sensory deprivation on the developing mouse olfactory system: a light and electron microscopic, morphometric analysis. J Neurosci 4:638–653

Bergmann O et al (2012) The age of olfactory bulb neurons in humans. Neuron 74:634–639. https://doi.org/10.1016/j.neuron.2012.03.030

Bergmann O, Spalding KL, Frisen J (2015) Adult Neurogenesis in Humans. Cold Spring Harb Perspect Biol 7:a018994. https://doi.org/10.1101/cshperspect.a018994

Bhatnagar KP, Kennedy RC, Baron G, Greenberg RA (1987) Number of mitral cells and the bulb volume in the aging human olfactory bulb: a quantitative morphological study. Anat Rec 218:73–87. https://doi.org/10.1002/ar.1092180112

Breton-Provencher V, Bakhshetyan K, Hardy D, Bamman RR, Cavarretta F, Snapyan M, Côté D, Migliore M, Saghatelyan A (2016) Principal cell activity induces spine relocation of adult-born internuerons in the olfactory bulb. Nat Commun 7:12659

Buck L, Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65:175–187

Burmeister HP, Bitter T, Baltzer PA, Dietzel M, Guntinas-Lichius O, Gudziol H, Kaiser WA (2011a) Olfactory bulb ventricles as a frequent finding–a myth or reality? Evaluation using high resolution 3 tesla magnetic resonance imaging. Neuroscience 172:547–553. https://doi.org/10.1016/j.neuroscience.2010.10.068

Burmeister HP, Baltzer PA, Mölstein C, Bitter T, Gudziol H, Dietzel M, Guntinas-Lichius O, Kaiser WA (2011b) Reproducibility and repaetability of volumetric measurements for olfactory bulb volumetry: which method is appropriate? An update using 3 Tesla MRI. Acad Radiol 18(7):842–849. https://doi.org/10.1016/j.arca.2011.02.018

Burmeister HP et al (2012) Imaging of lamination patterns of the adult human olfactory bulb and tract: in vitro comparison of standard- and high-resolution 3T MRI, and MR microscopy at 9.4 T. NeuroImage 60:1662–1670. https://doi.org/10.1016/j.neuroimage.2012.01.101

Buschhuter D, Smitka M, Puschmann S, Gerber JC, Witt M, Abolmaali ND, Hummel T (2008) Correlation between olfactory bulb volume and olfactory function. NeuroImage 42:498–502. https://doi.org/10.1016/j.neuroimage.2008.05.004

Carlen M, Cassidy RM, Brismar H, Smith GA, Enquist LW, Frisen J (2002) Functional integration of adult-born neurons. Current Biol 12:606–608

Chen Y, Getchell TV, Sparks DL, Getchell ML (1993) Patterns of adrenergic and peptidergic innervation in human olfactory mucosa: age-related trends. J Comp Neurol 334:104–116. https://doi.org/10.1002/cne.903340109

Cleland TA, Linster C (2005) Computation in the olfactory system. Chem Senses 30:801–813. https://doi.org/10.1093/chemse/bji072

Conley DB, Robinson AM, Shinners MJ, Kern RC (2003) Age-related olfactory dysfunction: cellular and molecular characterization in the rat. Am J Rhinol 17:169–175

Crasto C, Marenco L, Miller P, Shepherd G (2002) Olfactory receptor database: A metadata-driven automated population from sources of gene and protein sequences. Nucleic Acids Res:354–360

Croy I, Negoias S, Symmank A, Schellong J, Joraschky P, Hummel T (2013) Reduced olfactory bulb volume in adults with a history of childhood maltreatment. Chem Senses 38:679–684. https://doi.org/10.1093/chemse/bjt037

Cummings DM, Brunjes PC (1997) The effects of variable periods of functional deprivation on olfactory bulb development in rats. Exp Neurol 148:360–366. https://doi.org/10.1006/exnr.1997.6660

Curtis MA et al (2007) Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science 315:1243–1249. https://doi.org/10.1126/science.1136281

Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A (1999) Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell 97:703–716

Duprez TP, Rombaux P (2010) Imaging the olfactory tract (cranial nerve #1). Eur J Radiol 74:288–298. https://doi.org/10.1016/j.ejrad.2009.05.065

Ennis M, Holy TE (2015) Anatomy and neurobiology of the Main and accessory olfactory bulbs. In: Doty RL (ed) Handbook of olfaction and gustation. John Wiley & Sons, pp 157-182

Goktas O, Cao Van H, Fleiner F, Lacroix JS, Landis BN (2010) Chemosensory function in Wegener's granulomatosis: a preliminary report. Eur Arch Otorhinolaryngol 267:1089–1093. https://doi.org/10.1007/s00405-009-1184-4

Gritti A, Bonfanti L, Doetsch F, Caille I, Alvarez-Buylla A, Lim DA, Galli R, Verdugo JMG, Herrera DG, Vescovi AL (2002) Multipotent neural stem cells reside into the rostral extension and olfactory bulb of adult rodents. J Neurosci 22:437–445

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. https://doi.org/10.1093/brain/awp243

Guerrero-Cazares H, Gonzalez-Perez O, Soriano-Navarro M, Zamora-Berridi G, Garcia-Verdugo JM, Quinones-Hinojosa A (2011) Cytoarchitecture of the lateral ganglionic eminence and rostral extension of the lateral ventricle in the human fetal brain. J Comp Neurol 519:1165–1180. https://doi.org/10.1002/cne.22566

Haehner A, Rodewald A, Gerber JC, Hummel T (2008) Correlation of olfactory function with changes in the volume of the human olfactory bulb. Arch of Otolaryngol Head Neck Surg 134:621–624. https://doi.org/10.1001/archotol.134.6.621

Hardy D, Saghatelyan A (2017) Different forms of structural plasticity in the adult olfactory bulb. Neurogenesis 4(1):e1301850. https://doi.org/10.1080/23262133.2017.1301850

Hoogland PV, van den Berg R, Huisman E (2003) Misrouted olfactory fibres and ectopic olfactory glomeruli in normal humans and in Parkinson and Alzheimer patients. Neuropathol Appl Neurobiol 29:303–311

Hummel T, Heilmann S, Murphy C (2002) Age-related changes of chemosensory function. In: Rouby C, Schaal B, Dubois D, Gervais R, Holley A (eds) Olfaction, taste, and cognition. Cambridge University Press, New York, pp 441–456

Hummel T, Kobal G, Gudziol H, Mackay-Sim A (2007) Normative data for the "Sniffin' sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol 264:237–243. https://doi.org/10.1007/s00405-006-0173-0

Hummel T, Haehner A, Hummel C, Croy I, Iannilli E (2013a) Lateralized differences in olfactory bulb volume relate to lateralized differences

in olfactory function. Neuroscience 237:51–55. https://doi.org/10.1016/j.neuroscience.2013.01.044

Hummel T et al (2013b) Olfactory bulb volume in patients with temporal lobe epilepsy. J Neurology 260:1004–1008. https://doi.org/10.1007/s00415-012-6741-x

Jones-Gotman M, Zatorre RJ (1988) Olfactory identification deficits in patients with focal cerebral excision. Neuropsychologia 26:387–400

Kaneko N et al (2010) New neurons clear the path of astrocytic processes for their rapid migration in the adult brain. Neuron 67:213–223. https://doi.org/10.1016/j.neuron.2010.06.018

Kornack DR, Rakic P (2001) The generation, migration, and differentiation of olfactory neurons in the adult primate brain. Proc Natl Acad Sci U S A 98:4752–4757. https://doi.org/10.1073/pnas.081074998

Kovacs T, Cairns NJ, Lantos PL (1999) Beta-amyloid deposition and neurofibrillary tangle formation in the olfactory bulb in ageing and Alzheimer's disease. Neuropathol Appl Neurobiol 25:481–491

Lazarini F, Lledo PM (2011) Is adult neurogenesis essential for olfaction? Trends Neurosci 34:20–30. https://doi.org/10.1016/j.tins.2010.09.006

Linster C, Cleland TA (2002) Cholinergic modulation of sensory representations in the olfactory bulb Neural networks : the official. J Int Neural Network Society 15:709–717

Lledo PM, Gheusi G (2003) Olfactory processing in a changing brain. Neuroreport 14:1655–1663. https://doi.org/10.1097/01.wnr.0000092070.64779.76

Lois C, Garcia-Verdugo JM, Alvarez-Buylla A (1996) Chain migration of neuronal precursors. Science 271:978–981

Lotsch J et al (2013) Functional genomics suggest neurogenesis in the adult human olfactory bulb. Brain Struct Funct. https://doi.org/10.1007/s00429-013-0618-3

Maresh A, Rodriguez GD, Whitman MC, Greer, CA (2008) Principles of glomerular organization in the human olfactory bulb – implications for odor processing Plos One 9;3(7):e2640 doi:https://doi.org/10.1371/journal.pone.0002640

McLean JH, Harley CW (2004) Olfactory learning in the rat pup: a model that may permit visualization of a mammalian memory trace. Neuroreport 15:1691–1697

Meisami E, Mikhail L, Baim D, Bhatnagar KP (1998) Human olfactory bulb: aging of glomeruli and mitral cells and a search for the accessory olfactory bulb. Ann N Y Acad Sci 855:708–715

Mineur YS, Belzung C, Crusio WE (2007) Functional implications of decreases in neurogenesis following chronic mild stress in mice. Neuroscience 150:251–259. https://doi.org/10.1016/j.neuroscience.2007.09.045

Ming GL, Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70:687–702. https://doi.org/10.1016/j.neuron.2011.05.001

Mizrahi A (2003) Dendritic stability in the adult olfactory bulb. Nat Neurosci 6(11):1201–1207

Mizrahi A (2007) Dendritic development and plasticity of adult-born neurons in the mouse olfactory bulb. Nat Neurosci 10(4):444–452

Moberg PJ, Doty RL, Mahr RN, Mesholam RI, Arnold SE, Turetsky BI, Gur RE (1997) Olfactory identification in elderly schizophrenia and Alzheimer's disease. Neurobiol Aging 18:163–167

Mombaerts P, Wang F, Dulac C, Chao SK, Nemes A, Mendelsohn M, Edmondson J, Axel R (1996) Visualizing an olfactory sensory map. Cell 87:675–686

Morizumi T, Tsukatani H, Miwa T (1994) Olfactory disturbance induced by deafferentation of serotoninergic fibers in the olfactory bulb. Neuroscience 61:733–738

Mueller A, Abolmaali ND, Hakimi AR, Gloeckler T, Herting B, Reichmann H, Hummel T (2005a) Olfactory bulb volumes in patients with idiopathic Parkinson's disease a pilot study. J Neural Transm (Vienna) 112:1363–1370. https://doi.org/10.1007/s00702-005-0280-x

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

Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM (2002) Prevalence of olfactory impairment in older adults. JAMA 288:2307–2312

Naessen R (1971) An enquiry on the morphological characteristics and possible changes with age in the olfactory region of man. Acta Otolaryngol 71:49–62

Nagayama S, Homma R, Imamura F (2014) Neuronal organization of olfactory bulb circuits. Front Neural Circuits 3(8):98. https://doi.org/10.3389/fncir.2014.00098

Negoias S, Croy I, Gerber J, Puschmann S, Petrowski K, Joraschky P, Hummel T (2010) Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression. Neuroscience 169:415–421. https://doi.org/10.1016/j.neuroscience.2010.05.012

Negoias S, Pietsch K, Hummel T (2017) Changes in olfactory bulb volume following lateralized olfactory training. Brain Imaging Behav 11:998–1005. https://doi.org/10.1007/s11682-016-9567-9

Nguyen AD, Pelavin PE, Shenton ME, Chilakamarri P, McCarley RW, Nestor PG, Levitt JJ (2011) Olfactory sulcal depth and olfactory bulb volume in patients with schizophrenia: an MRI study. Brain Imaging Behav 5:252–261. https://doi.org/10.1007/s11682-011-9129-0

Pagano SF et al (2000) Isolation and characterization of neural stem cells from the adult human olfactory bulb. Stem Cells 18:295–300. https://doi.org/10.1634/stemcells.18-4-295

Paik SI, Lehman MN, Seiden AM, Duncan HJ, Smith DV (1992) Human olfactory biopsy. The influence of age and receptor distribution. Arc Otolaryngol Head Neck Surge 118:731–738

Paredes MF, Sorrells SF, Garcia-Verdugo JM, Alvarez-Buylla A (2016) Brain size and limits to adult neurogenesis. J Comp Neurol 524:646–664. https://doi.org/10.1002/cne.23896

Pozzati E, Martinoni M, Marucci G, Bacci A (2014) Olfactory neuroblastoma and olfactory ventricle. A case report. Neuroradiol J 27:452–455. https://doi.org/10.15274/NRJ-2014-10060

Rawson NE (2006) Olfactory loss in aging. Sci Aging knowledge Environ 2006(pe6). https://doi.org/10.1126/sageke.2006.5.pe6

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. https://doi.org/10.1097/01.MLG.0000195291.36641.1E

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. https://doi.org/10.1097/01.mlg.0000217533.60311.e7

Rombaux P, Potier H, Bertrand B, Duprez T, Hummel T (2008) Olfactory bulb volume in patients with sinonasal disease. Am J Rhinol 22:598–601. https://doi.org/10.2500/ajr.2008.22.3237

Rombaux P, Grandin C, Duprez T (2009) How to measure olfactory bulb volume and olfactory sulcus depth? B-Ent 5(Suppl 13):53–60

Rombaux P, Huart C, De Volder AG, Cuevas I, Renier L, Duprez T, Grandin C (2010a) Increased olfactory bulb volume and olfactory function in early blind subjects. Neuroreport 21:1069–1073. https://doi.org/10.1097/WNR.0b013e32833fcb8a

Rombaux P, Potier H, Markessis E, Duprez T, Hummel T (2010b) Olfactory bulb volume and depth of olfactory sulcus in patients with idiopathic olfactory loss. Eur Arch Otorhinolaryngol 267:1551–1556. https://doi.org/10.1007/s00405-010-1230-2

Rottstadt F et al (2018) Reduced olfactory bulb volume in depression-a structural moderator analysis. Hum Brain Mapp 39:2573–2582. https://doi.org/10.1002/hbm.24024

Samaulhaq MT, Lone KP (2008) Age and gender related differences in olfactory bulb glomeruli in human. Biomedica 24:12–17

Sanai N et al (2004) Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature 427:740–744. https://doi.org/10.1038/nature02301

Sanai N et al (2011) Corridors of migrating neurons in the human brain and their decline during infancy. Nature 478:382–386. https://doi.org/10.1038/nature10487

Schwob JE (2002) Neural regeneration and the peripheral olfactory system. Anat Rec 269:33–49

Shiga H et al (2013) Assessment of olfactory nerve by SPECT-MRI image with nasal thallium-201 administration in patients with olfactory impairments in comparison to healthy volunteers. PloS One 8: e57671. https://doi.org/10.1371/journal.pone.0057671

Smitka M et al (2009) Olfactory bulb ventricles as a frequent finding in magnetic resonance imaging studies of the olfactory system. Neuroscience 162:482–485. https://doi.org/10.1016/j.neuroscience.2009.04.058

Sorokowska A, Sorokowski P, Karwowski M, Larsson M, Hummel T (2018) Olfactory perception and blindness: a systematic review and meta-analysis. Psychol Res. https://doi.org/10.1007/s00426-018-1035-2

Tanik N, Serin HI, Celikbilek A, Inan LE, Gundogdu F (2015) Olfactory bulb and olfactory sulcus depths are associated with disease duration and attack frequency in multiple sclerosis patients. J Neuro Sci 358: 304–307. https://doi.org/10.1016/j.jns.2015.09.016

Thomann PA, Dos Santos V, Toro P, Schonknecht P, Essig M, Schroder J (2009) Reduced olfactory bulb and tract volume in early Alzheimer's disease–a MRI study. Neurobiol Aging 30:838–841. https://doi.org/10.1016/j.neurobiolaging.2007.08.001

Turetsky BI, Moberg PJ, Yousem DM, Doty RL, Arnold SE, Gur RE (2000) Reduced olfactory bulb volume in patients with schizophrenia. Am J Psychiatry 157:828–830. https://doi.org/10.1176/appi.ajp.157.5.828

Veyseller B, Aksoy F, Yildirim YS, Bayraktar FG, Gurbuz D, Savas Y, Ozturan O (2011) Reduced olfactory bulb volume in total laryngectomy patients: a magnetic resonance imaging study. Rhinology 49: 112–116. https://doi.org/10.4193/Rhino10.001

von Gudden B (1870) Experimentaluntersuchungen ueber das periphere und zentrale. Nervensystem Archiv f Psychiatrie u Nervenkrankheiten 2:693–723

Wang C et al (2011a) Identification and characterization of neuroblasts in the subventricular zone and rostral migratory stream of the adult human brain. Cell Res 21:1534–1550. https://doi.org/10.1038/cr.2011.83

Wang J, You H, Liu JF, Ni DF, Zhang ZX, Guan J (2011b) Association of olfactory bulb volume and olfactory sulcus depth with olfactory function in patients with Parkinson disease. AJNR Am J Neuroradiol 32:677–681. https://doi.org/10.3174/ajnr.A2350

Wilson DA, Fletcher ML, Sullivan RM (2004) Acetylcholine and olfactory perceptual learning. Learn Mem 11:28–34

Yaldizli O et al (2016) The association between olfactory bulb volume, cognitive dysfunction, physical disability and depression in multiple sclerosis. Eur J Neurol 23:510–519. https://doi.org/10.1111/ene.12891

Yousem DM, Geckle RJ, Bilker WB, McKeown DA, Doty RL (1996) Posttraumatic olfactory dynfunction: MR and clinical evaluation. AJNR 17:1171–1179

Yousem DM, Geckle RJ, Doty RL, Bulker WB (1997) Reproducibility and reliability of volumetric measurements of olfactory eloquent structures. Acad Radiol 4(4):264–269

Yousem DM, Geckle RJ, Bilker WB, Doty RL (1998) Olfactory bulb and tract and temporal lobe volumes. Normative data across decades. Ann N Y Acad Sci 855:546–555

Yousem DM, Geckle RJ, Bilker WB, Kroger H, Doty RL (1999) Posttraumatic smell loss: Relationship of psychophysical tests and volumes of the olfactory bulbs and tracts and the temporal lobes. Acad Radiol 6:264–272

Yuan Q, Harley CW, McLean JH (2003) Mitral cell a1 and 5-HT2A receptor colocalization and cAMP coregulation: a new model of norepinephrine-induced learning in the olfactory bulb. Learn Mem 10:5–15

Zhang K, Yu C, Zhang Y, Wu X, Zhu C, Chan P, Li K (2011) Voxel-based analysis of diffusion tensor indices in the brain in patients with Parkinson's disease. Eur J Radiol 77:269–273. https://doi.org/10.1016/j.ejrad.2009.07.032