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Olfactory Loss and Regain: Lessons for Neuroplasticity

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Abstract

For the visual and auditory senses, an array of studies has reported on neuronal reorganization processes after sensory loss. In contrast to this, neuroplasticity has been investigated only scarcely after loss of the olfactory sense. The present review focuses on the current extent of literature on structural and functional neuroplasticity effects after loss, with a focus on magnetic resonance imaging–based studies. We also include findings on the regain of the olfactory sense, for example after successful olfactory training. Existing studies indicate that widespread structural changes beyond the level of the olfactory bulb occur in the brain after loss of the olfactory sense. Moreover, on a functional level, loss of olfactory input not only entails changes in olfaction-related brain regions but also in the trigeminal system. Existing evidence should be strengthened by future longitudinal studies, a more thorough investigation of the neuronal consequences of congenital anosmia, and the application of state-of-the-art neuroimaging methods, such as connectivity analyses and joint analyses of brain structure and function.

Keywords

anosmia, hyposmia, neuroplasticity, structural and functional changes, voxel-based morphometry, magnetic resonance imaging, smell, olfaction, smell loss

Hyposmia, the reduced ability to perceive odors, and anosmia, the complete loss of olfactory function, are prevalent disorders, with a severe impact on nutritional health and safety (e.g., Temmel and others 2002). About 20% of the general population is affected by olfactory deficits, with a higher prevalence at older ages (Landis and others 2004; Murphy and others 2002). The main causes for deficits in olfactory function include sinunasal disease, head trauma, upper respiratory tract infection, and neurodegenerative diseases (Damm and others 2004; Temmel and others 2002). In rare cases, humans are born without a functional olfactory sense (congenital anosmia). Among patients suffering from olfactory dysfunction, the prevalence of congenital anosmia was reported as approximately 3% (Damm and others 2004; Henkin and Levy 2002; Temmel and others 2002). It is well known that olfactory deficits have a negative impact on quality of life, including an impact on food intake and food enjoyment, interpersonal relations, and also on personal safety, as patients cannot smell fire or spoilt food anymore (e.g., Temmel and others 2002). For a recent review on clinical aspects of anosmia, see Boesveldt and others (2017).

Olfactory loss not only entails social, emotional, and behavioral consequences but also initiates reorganization processes in the brain. However, while such processes have been described in quite some detail for the auditory and visual system, research on neuronal reorganization occurring after loss of the olfactory sense is still scarce. As an example, in other sensory systems, it has been shown that "cross-modal reorganization" occurs after sensory loss—for instance, brain areas that do not process sensory input any longer can take over functions of another sensory system (Frasnelli and others 2011; Merabet and Pascual-Leone 2010). These neural changes are related to compensatory behavioral adjustments in the sensory deprived individuals (Merabet and Pascual-Leone 2010). Whether this is the case for the olfactory sense as well remains to be explored in detail. Which changes occur in olfactory processing regions, on a structural and functional level, when the olfactory sense is lost? In the present review, we will provide a summary of the current state of magnetic resonance imaging (MRI) research on functional and structural brain changes after complete or partial olfactory loss and regain.

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Table 1. The Close Connection between Olfactory and Trigeminal Systems.

Most odors not only stimulate the olfactory but also the trigeminal system, which conveys sensations such as irritation, pain, burning, tingling, itching, tickling, and pressure and temperature sensations (Albrecht and others 2010; Iannilli and others 2007; Lundström and others 2011). Trigeminal substances are detected by nerve endings in the nasal and oral cavities (Lundström and others 2011). The evoked signals are then transferred to the trigeminal nucleus in the brainstem. The olfactory system and the trigeminal sensory system are closely associated with each other and interact with the gustatory sensory system to create a uniform flavor experience (Lundström and others 2011). There is evidence that anosmics and hyposmics are less sensitive for trigeminal stimuli (Frasnelli and Hummel 2007; Gudziol and others 2001). Thus, it is interesting to consider the neuronal consequences of olfactory loss for trigeminal sensations.

Cross-Modal Sensory Reorganization after Olfactory Loss

For the visual and auditory senses, cross-modal consequences have been observed in individuals experiencing sensory loss. For instance, blind individuals were reported to show superior skills in several domains related to other sensory modalities, such as in auditory-pitch discrimination (Gougoux and others 2004) and tactile acuity (Goldreich and Kanics 2003). In line with such behavioral alterations, after sensory loss in the auditory or visual sensory systems, increases in volume in other cerebral sensory areas have been demonstrated (Elbert and others 2002; Merabet and Pascual-Leone 2010). Moreover, there is evidence that sensory brain areas normally responsible for the lost sense (e.g., occipital cortex in blind individuals) take over functions of other sensory systems (for a review of cross-modal neuroplastic changes in blind and deaf individuals, see Merabet and Pascual-Leone 2010).

For the olfactory sense, only few studies investigated to date whether similar processes occur, and whether individuals can compensate for deficits in their olfactory system. Most cross-modal effects of olfactory deficits have been reported in two closely related functions: the gustatory sense and trigeminal perception (see Table 1 for details on trigeminal function). In contrast to the findings on compensatory processes for the visual and auditory senses, it seems that olfactory loss can rather lead to impairment in trigeminal (Frasnelli and others 2010b; Frasnelli and others 2011; Gudziol and others 2001) and gustatory function (Gagnon and others 2014; Gudziol and others 2007; Landis and others 2010, but see also Stinton and others 2010 for a negative finding). In particular regarding gustatory deficits, it is important to consider that due to the large contribution of the olfactory sense to the flavor experience and percept, most individuals suffering from olfactory deficits report gustatory deficits. However, rather than being due to a true impairment of the gustatory sense, this can also reflect a reduced flavor experience caused by impaired retronasal olfactory function. Thus, the use of objective, established tests for assessment of gustatory function is required to investigate this topic.

What could be the reason for the lack of compensatory improvements of other senses after olfactory loss? The three chemical senses (olfaction, gustation, and trigeminal function; see Fig. 1) are tightly connected (Frasnelli and others 2011; Kollndorfer and others 2015c) and there is even evidence that they share central processing areas, such as the insula (Lundström and others 2011) and the orbitofrontal cortex (Frasnelli and others 2011). Moreover, multimodal gustatory, olfactory, and/or trigeminal stimuli activate these brain regions more strongly than their isolated components (Cerf-Ducastel and others 2001; Small and others 1997; Small and Prescott 2005), supporting the notion of a neural network specialized on "flavor processing" (Frasnelli and others 2011; Rudenga and others 2010). Thus, it may be suggested that different to other sensory systems, this tight connection between the olfactory, gustatory, and trigeminal sense might be responsible for a "spreading" of deficits from the olfactory sense to the other chemosensory functions.

Besides the behavioral alterations mentioned above, several studies also investigated changes in peripheral and central physiological responses to trigeminal stimuli after olfactory loss. On a peripheral level (as assessed by negative mucosa potentials (NMP)—electrophysiological responses obtained from the nasal mucosa), persons with acquired anosmia showed increased potentials compared to normosmics (i.e., persons with a normal sense of smell) (Frasnelli and others 2007a). On a central level, however, smaller event-related potentials were observed in anosmics compared to normosmics (Frasnelli and others 2007a). This pattern of results was explained previously by a model of "mixed sensory adaptation/compensation" (Frasnelli and others 2007b; Frasnelli and others 2011). The model assumes that in normal olfactory function, when smelling bimodal odorants (which stimulate both the trigeminal and olfactory system) the peripheral trigeminal system is constantly inhibited by the active olfactory system. On a central level, however, in normosmics trigeminal signals are amplified due to the parallel olfactory and trigeminal stimulation. In olfactory dysfunctions, on the other hand, the inactivity of the olfactory system leads to a released inhibition of the peripheral trigeminal system, reflected by increased peripheral responses to trigeminal stimuli. As the olfactory signal part does not stimulate the system

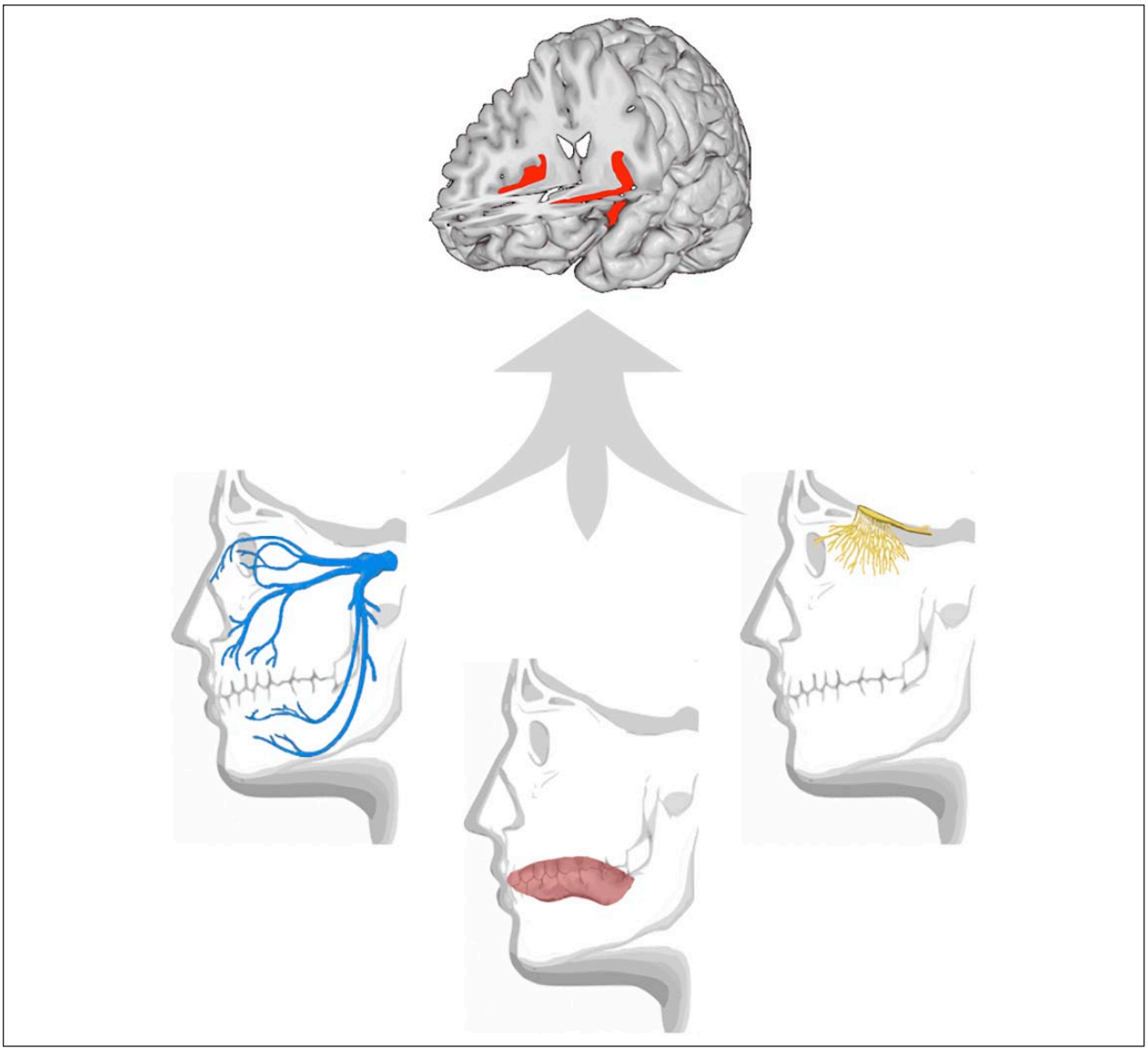

Figure 1. Illustration of the close connection between olfactory, trigeminal, and gustatory functions (from left to right trigeminal nerve [blue], tongue [red], and olfactory bulb and nerve endings [yellow]). Several studies indicate that the insula is involved in the integration of these modalities (Lundström and others 2011; Small and others 2004) (insular cortex depicted in red on a standard MNI template using the "Mango" viewer software [Research Imaging Institute, UTHSCSA]).

anymore, the central signals, on the other hand, are decreased (Frasnelli and Hummel 2007).

Specific Anosmia and the Effects of Olfactory Training

Findings on specific anosmia underline the high degree of plasticity of the olfactory sense. Specific anosmia refers to the impaired ability to perceive specific smells in otherwise fully intact olfactory function. For instance, about half of the adult population was estimated to show a decreased sensitivity for androstenone, a substance with a rather unpleasant, sweaty smell (Amoore and others 1977). Similar findings have been reported for the malty-smelling isobutyraldehyde (Amoore and others 1976) to which 36% of individuals were less sensitive. Of note, while decreased sensitivity for certain substances is common, the number of persons *completely* unable to detect the substances is assumed to be lower. For instance, 2% to 6% of healthy young adults were estimated to be completely unable to detect androstenone (Bremner and others 2003). A recent comprehensive study on more than 1600 individuals revealed that specific anosmia is a highly common phenomenon (Croy and others 2015).

Table 2. Description of Olfactory Training.

During olfactory training, participants receive a set of 4 to 6 odors (for instance prepared in glass jars filled with the odorant soaked in cotton pads). Participants then expose themselves to each odor by taking a deep sniff of the respective odor several times per day over the course of approximately 12 to 56 weeks. Training adherence is often monitored by daily diaries filled out by participants over the training period. Two recent meta-analysis (Pekala and others 2016; Sorokowska and others 2017) reported significant positive effects of olfactory training on smelling abilities (particularly discrimination and identification of odors), though the need of more randomized, controlled studies has been emphasized. Studies suggest that several training features can influence training success: A longer duration of olfactory training (Geißler and others 2014; Konstantinidis and others 2016), a higher number of different training odors used (Altundag and others 2015) and higher concentrations of the used odors (Damm and others 2014) were beneficial for training success, while the molecular weight of the training odors seems to play only a minor role (Poletti and others 2017). Moreover, it was suggested that due to the close connection between the olfactory and trigeminal systems, the use of bimodal odorants (stimulating both systems) might be promising (Poletti and others 2017), though this remains to be elucidated in future studies.

The authors tested 20 odors with 200 participants for each odor and showed that the rate of specific anosmia to these odors varied from 0.5% to 20.4% (Croy and others 2015). Statistical estimations yielded an estimated prevalence of 51.9% of specific anosmia to at least one of the 20 assessed odors (Croy and others 2015).

Intriguingly, already in 1989, Wysocki and others could show that targeted olfactory training can induce the ability to perceive androstenone in subjects previously anosmic to this substance (Wysocki and others 1989); see Table 2 for more details on olfactory training. Croy and others replicated this finding by showing that olfactory training in 25 subjects was strongly effective in reducing their specific anosmia to different substances (Croy and others 2015). The investigators proposed that specific anosmia serves as an adaptive peripheral filter mechanism reducing "olfactory noise" (Croy and others 2015). While there is also evidence for genetic components underlying specific anosmia (e.g., Keller and others 2007; Wysocki and Beauchamp 1984), the increased sensitivity after repeated exposure highlights the way the environment shapes olfactory perception (Croy and others 2015). Which mechanisms might drive the observed improvements in perception ability of different substances? While this question still remains unanswered, it was suggested that olfactory training leads to an increased expression of olfactory receptors or improvements in receptor neurotransmission (Croy and others 2015). Increased amplitudes of olfactory evoked potentials (EOG) and concurrent increases in olfactory event-related potentials (OERP) after repeated exposure with androstenone underline the importance of peripheral plasticity processes (Wang and others 2004). Moreover, olfactory training might also alter the sensitivity to trigeminal compounds present in odors.

In sum, specific anosmia and particularly its reported plasticity after olfactory training are remarkable examples of the flexibility of the olfactory system to adapt according to environmental circumstances. Reports on physiological processes and mechanisms underlying these changes, however, are still lacking and this deserves to be further investigated in future studies. The next sections will outline the current state of literature regarding neuroplastic changes occurring in broader dysfunctions of the olfactory sense, such as hyposmia and complete anosmia.

Structural Reorganization after Olfactory Loss

Olfactory Bulb Volume and Olfactory Function

Most studies concerned with structural changes in the brain after olfactory loss focused on investigation of a single region, the olfactory bulb (OB) (for a review, see Rombaux and others 2009). The OB plays a key role in olfaction, as it is the first neural structure processing odors in the olfactory pathway, receiving direct input from the olfactory receptor neurons of the olfactory epithelium.

A large number of studies has demonstrated positive correlations between OB volume and olfactory function (especially odor sensitivity), both in healthy individuals (Buschhüter and others 2008; Hummel and others 2011; Seubert and others 2013) and in individuals suffering from olfactory deficits (e.g., Mueller and others 2005; Rombaux and others 2006a). Direct group comparisons indicated that patients with olfactory deficits show smaller OB volumes than healthy controls (Mueller and others 2005; Rombaux and others 2010). Moreover, in both postinfectious and posttraumatic olfactory loss, OB volumes of anosmics were found to be smaller than those of hyposmics (Rombaux and others 2006a; Rombaux and others 2006b). Associations between depth of the olfactory sulcus, which is located adjacent to the OB, and olfactory function have been reported as well (Frasnelli and others 2010a; Hummel and others 2003; Hummel and others 2015). Diverse types of nasal obstruction, such as nasal septal deviation, are also associated with reductions in OB volume (e.g., Altundag and others 2014). The potentially causal relation between OB volume and olfactory function is further corroborated by a reported correlation between changes in OB volume

and the duration of olfactory loss (Rombaux and others 2006a). Importantly, it was also demonstrated that improvements in olfactory function due to spontaneous recovery or olfactory training in individuals with olfactory deficits were accompanied by changes in OB volume (Gudziol and others 2009; Haehner and others 2008). Recently, in healthy persons an increase of OB volume after lateralized olfactory training was shown as well (Negoias and others 2016). In this sample of normosmics, however, contrary to the findings in anosmics, a decrease in olfactory sensitivity was observed after training (Negoias and others 2016). This counterintuitive finding could possibly be related to a regression to the mean of the data (see section "Open Questions and Challenges" for a more detailed discussion).

These findings inevitably lead to the question why the OB demonstrates such high sensitivity to olfactory loss. There is evidence that the OB is a highly plastic structure, as synaptic connections in the OB are continuously remodeled due to the constant renewal of receptor neurons at the olfactory neuroepithelium and subsequent synaptogenesis (Huart and others 2013; Lledo and others 2004). Thus, when olfactory input is decreased, such plasticity processes could ultimately lead to a reduction in OB volume. In animal models, it was also shown that neurogenesis occurring at the subventricular zone of the lateral ventricle entails the subsequent migration of neuroblasts toward the OB along the rostral migratory stream. However, whether this occurs in human adults to a significant extent remains debated (Bergmann and others 2012; Curtis and others 2011; Huart and others 2013; Sanai and others 2004; Wang and others 2011).

Interestingly, not only peripheral input but also top-down processes might influence neuroplastic changes of the OB (Huart and others 2013): There is evidence from animal studies that a convergence of sensory ("bottom-up") input with centrifugal ("top-down") inputs occurs in the OB (Kay and Sherman 2007; Mandairon and Linster 2009; McGann 2015). The top-down input drives associative learning-related plasticity processes in the olfactory system (Lazarini and Lledo 2011; McGann 2015). Thus, olfactory experiences might lead to modifications in the OB neural network, which in turn shapes perception and processing of odorants (Mandairon and Linster 2009). In line with these propositions, a recent study conducting a 4-month lateralized olfactory training in healthy humans (Negoias and others 2016) found increases in OB volume after the training for both the trained and untrained nostril. The authors concluded that bottom-up processes cannot be solely responsible for the observed plasticity effects, but central (top-down) mechanisms seem to be involved as well (Negoias and others 2016).

Regarding the predominantly correlative findings on associations between OB volume and olfactory function, it is important to consider the question of causality: Small OB volume might also be a risk factor for olfactory loss (Patterson and others 2015) and more longitudinal studies are required to elucidate this issue further. Moreover, the cause of olfactory deficits might have a direct impact on the OB: In posttraumatic anosmia, the loss of OB volume could also been interpreted as a sign of encephalomalacia caused by the head trauma itself and not as an adaptive reaction of the brain after loss of olfactory input. In postinfectious anosmia, on the other hand, viral agents themselves might penetrate through the cribriform plate and cause damage to the OB (Doty 2008; Rombaux and others 2006a). Furthermore, methodological limitations should be taken into account when interpreting the findings, for example, a possibly confounding role of total brain volume, which is not always considered in the analyses. Of note, OB volume measurements are not entirely objective, as results can differ depending on the observer. However, in most studies at least two observers perform measurements and generally high interrater reliability is reported (e.g., Rombaux and others 2009). Newest findings using functional registration to identify sensory processing structures as recently proposed by Glasser and others (2016) might shed more light on structural alterations of the OB.

Structural Reorganization in Higher Order Areas

Few studies have examined structural differences between individuals suffering from olfactory deficits and normosmics in higher order brain areas. The existing studies applied voxel-based morphometry (VBM), a method that allows uncovering of regional differences in gray and white matter (GM and WM) from MR images. To our knowledge, four VBM studies have been conducted to date that compare anosmics or hyposmics to individuals with a normal sense of smell (see Table 3 for a summary of study characteristics). All of these studies investigated changes in GM/WM volume (i.e., "modulated" analysis). Results indicate that widespread structural reorganization processes occur after olfactory loss (see Fig. 2 and Table 4). More specifically, in olfactory dysfunction decreases in GM were observed compared to normal olfactory function, while no compensatory GM increases were found in anosmics/hyposmics compared to controls. In all four studies, decreases in gray matter were found in anterior cingulate cortex (ACC) and insular cortex. These areas have been consistently reported in functional neuroimaging studies in response to olfactory stimulation (e.g., Albrecht and others 2010; Savic 2002), underlining the close structure-function relation of brain networks (Specht and others 2009). Thus, reorganization processes due to the reduced inflow of olfactory information might

Table 3. Overview of Studies Investigating Changes in Brain Structure after Partial or Total Olfactory Loss.

Study	Sample	Assessment of Olfactory Function	Major Results
Bitter and others (2010b)	17 anosmics (8 idiopathic, 4 postinfectious, 5 posttraumatic), 17 age- and sex-matched controls	Sniffin' Sticks (Hummel and others 1997)	GM volume decreases in anosmics (see Table 4) Correlation of disease duration and extent of GM atrophy
Peng and others (2013)	19 anosmics (1 idiopathic, 13 postinfectious, 4 posttraumatic[a]), 20 age- and sex-matched controls	T&T olfactometer (Takagi 1987)	GM volume decreases in anosmics (see Table 4) WM atrophy mainly spatially near the GM areas with volume loss Patients with disease duration >1 year showed more atrophy than those with disease duration <1 year
Bitter and others (2010a)	24 hyposmics (16 sinunasal, 5 postinfectious, 2 posttraumatic[b]), 43 age-and-sex-matched controls	Sniffin' Sticks (Hummel and others 1997)	GM volume decrease in hyposmics (see Table 4) WM atrophy in areas spatially connected to GM alterations (underneath insular cortex; cerebellum) and in unconnected areas (middle frontal gyrus)
Yao and others (2014)	16 patients with idiopathic olfactory loss, 16 age- and-sex-matched controls	T&T olfactomter (Takagi 1987) and Sniffin' Sticks (Hummel and others 1997)	GM volume decreases in anosmics (see Table 4) (voxel of interest-analysis)

GM = gray matter; WM = white matter.
a. No information about 19th participant in article.
b. No information about the 24th participant in article.

cause the observed GM decrease in these areas. Furthermore, GM decreases in the piriform cortex and the orbitofrontal cortex were present in three of the four studies. As these areas are part of the olfactory cortex, it is plausible to assume that the loss of olfactory input in the patients is responsible for the observed GM deteriorations as well. Moreover, GM decrease in the cerebellum was apparent in three of these four studies. Activations in the cerebellum have been reported in several studies during olfactory stimulation and have been directly associated with sniffing behavior (Albrecht and others 2010; Savic 2002; Sobel and others 1998b). In individuals with olfactory deficits, the olfactory-related cerebellar areas are presumably employed to a lesser extent, which might lead to the reported GM atrophy. Besides these relatively consistent findings, single studies also found GM decreases in other areas, such as the parahippocampal gyrus, and the fusiform gyrus (see Table 4). Further research is necessary to shed more light on the role of these areas with regard to olfaction.

As described above and shown in Figure 2, the findings of the four studies overlap to a considerable extent. However, there are also some discrepancies between the studies' findings. For instance, Peng and others (2013) found more atrophy in right middle temporal gyrus (MTG), while Bitter and others (2010b) found more atrophy in left MTG in anosmics compared to normosmics. These differences might be related to specifics of the studies' samples, such as sample size, differences in disease duration, and cause of anosmia and should be investigated in more detail in the future. A comparison of the study of Bitter and others (2010a) on hyposmics to the findings in anosmics indicates that hyposmics exhibit similar, but spatially more constricted atrophies than anosmics. For instance, volume loss in the medial prefrontal cortex (including ACC) was smaller in hyposmics (Bitter and others 2010a) than in anosmics (Bitter and others 2010b). In a few areas, however, hyposmics showed more volume loss than reported in anosmics. For instance, in hyposmics volume loss in the insular cortex (IC) was present at both hemispheres, while in anosmics, volume loss was present only in the right hemisphere. This finding might also be related to the larger number of subjects and therefore higher power in the hyposmic group study. Higher powered studies might find changes in the insular cortex bilaterally, which is also supported by the bilateral alterations observed by Yao and others (2014) employing a voxel of interest analysis. Furthermore, in hyposmics not only GM but also WM volume loss was reported: WM atrophies were observed

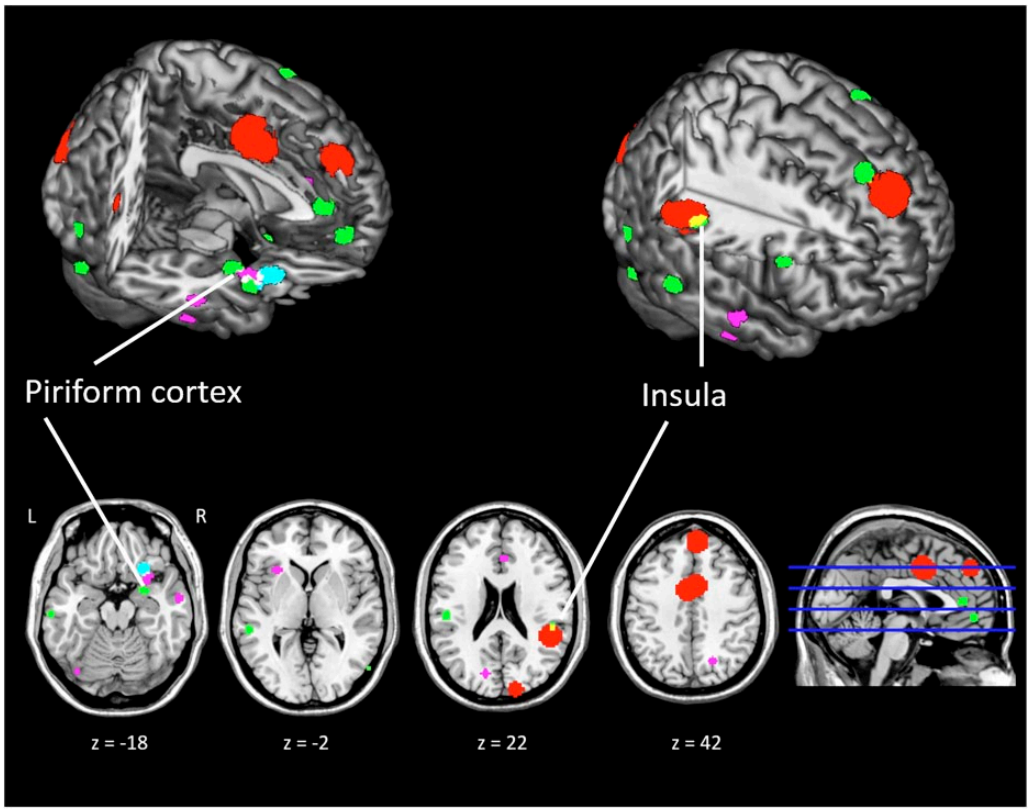

Figure 2. Depiction of GM differences between anosmics/hyposmics and normosmic controls reported in four studies: red (Bitter and others 2010b), violet (Bitter and others 2010a), green (Peng and others 2013), light blue (Yao and others 2014). Overlaps between studies are depicted additively (white and yellow) using MRIcron (https://www.nitrc.org/projects/mricron). Spheres were inserted at the coordinates of the centers of masses of respective GM difference clusters. Sphere radius was calculated so that sphere volume matched reported cluster size. Only clusters with a reported value of $z > 3.29$ ($P < .001$, two-tailed) were included in the figure.

in the cerebellum, middle frontal gyrus and underneath the insular cortex. Most of the WM atrophy areas were located near the areas of GM volume loss.

Summary of Structural Reorganization Processes

In sum, although structural brain changes after olfactory loss are still understudied, the existing studies report consistently on alterations in circumscribed brain areas: Decreases in volume were not only reported in olfactory areas but also in regions with more generalized functions, such as the ACC. Decreases in gray and white matter were also found in patients with hyposmia, supporting the assumption that a lack of sensory information inflow might cause the structural changes. However, in both OB volume assessments and VBM of higher-order brain areas, the question of causality remains: Decreased GM volume in certain areas could also be a risk factor for development of anosmia. Still, reported correlations between atrophies and longer disease duration corroborate the assumption of a causal relation. Although the body of studies yielded at least partially overlapping results, profound differences were observable as well. These might be related to the heterogeneous patient population, as the investigated patients differed regarding a multitude of factors, such as age, cause of anosmia and disease duration. More studies on homogeneous patient groups are needed and systematic comparisons of different patient groups might shed more light on structural alterations after olfactory loss.

Functional Reorganization after Olfactory Loss

Patients with smell loss are by definition not able to perceive olfactory stimuli consciously, rendering it difficult to investigate central processing in response to pure odorants. Therefore, several previous studies (see Table 5 for an overview of study characteristics) stimulated the

Table 4. Areas Exhibiting a Decrease in GM Volume in Anosmic/Hyposmic Individuals Compared to Healthy Controls.

	Bitter and others (2010b)[a]	Bitter and others (2010a) (hyposmics)	Peng and others (2013)	Yao and others (2014)[b]
Anterior cingulate cortex (ACC)	x	x	x	x (VOI)
Insular cortex	x	x	x	x (VOI)
Piriform cortex	x	x		x (VOI)
Orbitofrontal cortex	x	x		x
Cerebellum	x	x	x	
Parahippocampal gyrus	x			x (VOI)
Fusiform gyrus		x	x	
Middle temporal gyrus		x	x	
Hippocampus	x			
Supramarginal gyrus	x			
NCL accumbens with adjacent subcallosal gyrus	x			
Middle cingulate cortex (MCC)	x			
Dorsolateral prefrontal cortex (DLPFC)	x			
Superior temporal gyrus			x	
Supramarginal gyrus			x	
Superior frontal gyrus			x	
Middle frontal gyrus			x	
Middle occipital gyrus			x	
Precuneus		x		

a. When considering these widespread alterations, it is important to take into account that a very liberal criterion for significance ($P < 0.01$ uncorrected) was applied in this study. Applying a cluster-extent threshold correction of $P < 0.001$ (FWE-corrected), only the atrophies in ACC and MCC were significant.

b. In this study, on a whole-brain level only GM volume loss in the right orbitofrontal cortex was found in patients compared to healthy controls at $P < 0.001$ (uncorrected). However, in a voxel of interest (VOI) analysis focusing on primary and secondary olfactory areas, GM decreases in the ACC, insular cortex, parahippocampal cortex and piriform cortex were apparent.

trigeminal system, which is closely connected to the olfactory system (see Table 1).

In a study applying odorless CO_2, anosmics showed lower activation in several areas typically related to processing of somatosensory or irritant stimuli (e.g., somatosensory cortex (SI, SII) and left insula), particularly in right-sided brain areas (side of trigeminal stimulation) (Iannilli and others 2007). In several other regions, on the other hand, anosmics showed higher activation than controls (including parahippocampal and cingulate gyrus, putamen, insular, premotor cortex, middle temporal gyrus), possibly indicating compensatory shifts of activation in anosmics. During presentation of another trigeminal stimulus, menthol, both activation decreases and (possibly compensational) increases in activation were apparent in anosmics as well (Iannilli and others 2011): Anosmics showed less activations than normosmics in the cerebellum, and higher activations than normosmics in the frontal lobe, the dorsolateral prefrontal cortex (DLPFC) and the ACC. There was no effect of stimulus concentration on subjective intensity ratings and brain activation in anosmics, implying that an intact olfactory system might be necessary to enable intensity differentiation of trigeminal stimuli. The reported activation decreases in anosmics in specific brain areas are in line with the model of "mixed sensory adaptation/compensation" (Frasnelli and Hummel 2007; Frasnelli and others 2011; see section "Cross-Modal Sensory Reorganization after Olfactory Loss"), which assumes a decreased central response to trigeminal odorants in anosmics, as the olfactory signal part does not stimulate the system anymore.

While the studies by Iannilli and others (2011) found differences in functional activations between anosmics and normosmics, more recent studies have focused on differences in the processing network as a whole by employing independent component analysis (ICA) and connectivity analyses. In a recent study presenting three trigeminal substances (menthol, cinnamon, CO_2), the spatial extent of networks active during stimulation was comparable between controls and anosmics (Kollndorfer and others 2015a). In both groups, mainly three networks (an olfactory network, a somatosensory network, and an integrative network) were involved in the processing of the trigeminal odors. However, a seed-based functional connectivity analysis indicated that in anosmics, less functional connections of the networks' global maxima to other brain regions were present than in controls. Possibly, while the functional processing networks were still existent in the anosmic sample, the lack of afferent olfactory

Table 5. Overview of Studies Investigating Changes in Brain Function after Partial or Total Olfactory Loss/Regain.

Study	Sample	Paradigm	Statistical Methods	Results
Iannilli and others (2007)	11 anosmics (4 postinfectious, 7 congenital), 12 normosmics	Stimulation with CO_2	General linear model	N > A: PFC, somatosensory cortex, left insula A > N: SMA, superior and middle temporal lobe, left parahippocampal gyrus, left putamen and right insula
Iannilli and others (2011)	17 anosmics (7 idiopathic, 5 postinfectious, 5 posttraumatic), 17 normosmics	Stimulation with menthol in two concentrations (high/low)	General linear model	N > A: cerebellum A > N: frontal lobe, DLPFC (BA9), ACC (BA32) Anosmics: no effect of stimulus intensity on brain activation (effect only found in controls)
Kollndorfer and others (2015b)[a]	11 anosmics (postinfectious), 14 healthy controls	Sniffing paradigm	Group ICA and functional connectivity analysis	Spatially unchanged olfactory network in patients, but alterations in functional connectivity (decrease in patients)
Kollndorfer and others (2014)[a]	7 anosmics (postinfectious) pre and post 12-week olfactory training	Sniffing paradigm	Functional connectivity analysis	Decreased connectivity of piriform cortex with nonolfactory regions after olfactory training
Kollndorfer and others (2015a)[a]	10 anosmics (postinfectious), 14 healthy controls; subgroup of 7 patients pre and post 12-week olfactory training	Chemosensory stimulation paradigm: menthol, cinnamon, CO_2	Group ICA, functional connectivity analysis	Anosmics and controls use same networks for processing of chemosensory input (same spatial extent, but decreased connectivity in patients); after training modified functional connections in patients (increase of connections to network seed regions)
Pellegrino and others (2016)	11 hyposmic women (6 postinfectious, 4 idiopathic, 1 posttraumatic), 12 controls	Olfactory stimulation: peach, coffee	General linear model	N > H: Anterior cingulate cortex, orbitofrontal cortex H > N: parahippocampal and posterior cingulate gyrus

N = normosmics; H = hyposmics; A = anosmics. For assessment of olfactory function, all studies included in the table used the Sniffin' Sticks test battery (Hummel and others 1997).
a. The three studies of Kollndorfer and others included partially the same participants.

information led to a weakening of connections to other areas over time. This assumption was further strengthened by the finding that after successful olfactory training, an increase in functional connections was observed (Kollndorfer and others 2015a; see Fig. 3).

As demonstrated above, several studies found changes in central processing of trigeminal stimuli after olfactory loss, reflecting the tight connection between these two sensory systems. Another approach used to investigate functional changes after olfactory loss is the application of a pure sniffing paradigm without olfactory stimuli (Kollndorfer and others 2015b). This approach is based on evidence showing that parts of the olfactory network can be activated by the sensorimotor act of olfaction (sniffing) alone (Sobel and others 1998a; Sobel and others 1998b). The spatial extent of the functional networks active during sniffing was comparable between anosmics and controls, indicating that the olfactory network can still be activated in anosmics despite their inability of perceiving odors (Kollndorfer and Hummel 2015b). A detailed functional connectivity analysis, however, showed that in healthy controls, additional connections were present during sniffing. These additional functional connections did not only comprise regions involved in olfactory processing, but also extended beyond olfactory areas, for example, to the premotor area and the supramarginal gyrus. The authors concluded that the loss of olfactory input might not only lead to reduced sensory-specific connections, but also reduced connectivity in global brain networks.

In a subgroup of the anosmic patient group, Kollndorfer and others conducted 12 weeks of olfactory training (Kollndorfer and others 2014; Kollndorfer and others 2015a). The training led to improvements in odor detection threshold in six of seven investigated patients.

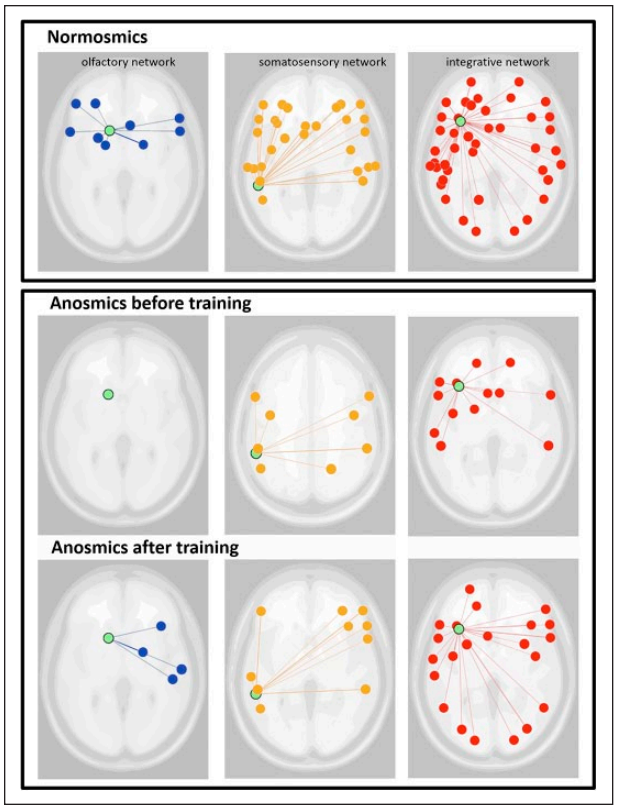

Figure 3. Functional connectivity during chemosensory stimulation in normosmics and anosmic patients before and after olfactory training, overlaid on an axial template in MNI space. Green dots represent selected ROIs (olfactory network: caudate nucleus [MNI −14, 14, 2]; integrative network: insular cortex [−34, 22, 10]; somatosensory network: supramarginal gyrus [−58, −42, 36]; the blue/orange/red dots show the statistically significant functionally connected brain areas. Adapted with permission from Kollndorfer and others (2015a).

Moreover, after training, the authors observed a decrease of functional connections of the piriform cortex during sniffing in anosmics. In more detail, before training the piriform cortex showed a multitude of connections to nonolfactory regions, which declined after training. These findings suggest that olfactory training might lead to neural reorganization, abolishing the aberrant connections of this region found in anosmics before start of the training (Kollndorfer and others 2014). The training also affected the neuronal networks active during chemosensory stimulation with trigeminal odorants in anosmics: After training, an increase of functional connections in all three networks was visible (see Fig. 3; Kollndorfer and others 2015a).

A recent study investigated brain activation in response to odor stimulation in partial olfactory loss (Pellegrino and others 2016). The group found that hyposmics generally showed activation in similar regions as normosmic controls (e.g., insula, OFC, limbic areas). However, in several areas (amygdala, ACC, OFC) decreased activation was reported in hyposmics compared to normosmics, while in others increased activation was observed in hyposmics (parahippocampal and cingulate gyrus). As observed by the authors, this finding might indicate that in hyposmics partial olfactory loss is compensated with increased olfactory memory recruitment (Pellegrino and others 2016).

In sum, the functional studies conducted to date suggest that olfactory loss entails widespread changes in functional brain networks. Moreover, they underline the interconnectedness of the trigeminal and olfactory systems: Loss of the sense of smell also leads to changes in the processing of trigeminal stimuli. When comparing the results of the studies investigating brain structure and function, divergent results become apparent: For instance, while several studies report decreases in volume of the ACC and the insula in anosmics, increases in functional activations in the same areas are reported as well. At the current state of research, these discrepancies cannot be resolved yet. One can only speculate whether the volume decrease of specific areas in anosmics might be related to (possibly compensatory) increased activations when presented with trigeminal stimuli. Future studies investigating brain structure and function conjointly will enable clearer conclusions on this topic and shed more light on neuroplastic changes of structure-function networks over time. Another aspect worth investigating in more detail is the correspondence between changes in brain function and sensory experience of patients, in particular to answer the question of how and when neuroplasticity effects are reflected in changes in sensory perception.

The Special Case of Congenital Anosmia

About 1% to 3% of anosmic individuals were born without a functioning sense of smell (often referred to as "congenital anosmia"). The study of congenitally anosmic persons is crucial for gaining an understanding of the functioning of the normal "smelling brain," as it might shed light on questions such as: Is olfactory input a prerequisite for the development of olfactory brain regions? Does congenital anosmia lead to changes in the development of other senses, for example, the gustatory sense? Unfortunately, not many studies have focused on this condition yet, which might be due to the low prevalence and methodological difficulties associated with the co-occurrence with other diseases. For instance, about 12% of patients suffering from congenital anosmia suffer from "Kallmann syndrome," a condition with additional symptoms such as color blindness and hypogonadism (Henkin and Levy 2002). In these instances, it is difficult to

dissociate alterations associated with the co-occurring symptoms from anosmia-related effects. Thus, it is of special importance to focus research efforts on isolated congenital anosmia. Recently, in isolated congenital anosmia an impaired taste identification ability and reduced activations in medial orbitofrontal cortex during tasting were reported (Gagnon and others 2014). Several studies have reported an absence or decreased volume of the OB and flattening of the olfactory sulcus in isolated congenital anosmia (e.g., Rombaux and others 2009). These findings are in line with the correlations observed between olfactory function and OB volume (see section "Olfactory Bulb Volume and Olfactory Function"). Interestingly, regarding higher order areas, in contrast to acquired anosmia, congenital anosmia was associated with an *increased* cortical volume and thickness in olfactory areas (Frasnelli and others 2013). More specifically, congenital anosmics showed GM volume increases in entorhinal and piriform cortex. Moreover, cortical thickness of orbitofrontal cortex and left piriform cortex was increased. These results contrast with those reported on acquired anosmia (see sections "Structural Reorganization after Olfactory Loss" and "Functional Reorganization after Olfactory Loss"), where mainly decreases in GM volume and brain activation were observed. As suggested by Frasnelli and others, in congenital anosmia the complete lack of olfactory input might lead to a reduced or absent "pruning" of synapses (Frasnelli and others 2013). In normal sensory functioning, after an initial increase in the first days of life, synaptic connections decrease over time. In congenital anosmics, due to the missing afferent input, the synaptic connections might be maintained and contribute to the observed increased cortical thickness.

If and to what extent functional brain networks are intact in isolated congenital anosmia is almost completely unknown. Henkin and Levy investigated nine patients with congenital anosmia using a functional MRI paradigm (Henkin and Levy 2002). Patients showed brain activation in response to odors in the frontal and the temporal cortex. Activations were significantly lower than in normosmia and acquired anosmia. However, these results should be interpreted with caution as one patient with symptoms of hypogonadotrophic hypogonadism and one patient with residual olfactory function were included in their sample. Regarding changes in both brain structure and function, further studies on larger samples of isolated congenital anosmia are required to confirm and extend the existing findings. Furthermore, recent developments of modelling the human sense of smell as a system using network-based approaches with multi-imaging inputs could be helpful in understanding the neuronal basis and consequences of congenital anosmia. Even single subject observations could then be used to shed light on the organization of brain characteristics in this condition.

Open Questions and Challenges

A multitude of changes occurs in the brain after sensory loss—on functional and structural levels (for a summary, see Table 6). However, many questions remain to be answered. More longitudinal studies focusing on the rehabilitation of the sense of smell are needed to distinguish more clearly between cause and effect of sensory loss. Moreover, many of the comparatively few existing studies on structural and functional reorganization after olfactory loss suffer from methodological drawbacks (such as heterogeneous samples, liberal statistical thresholds and small sample sizes). Potentially important confounding factors, such as comorbidities or medication use of the patients, are not reported in the majority of studies. Thus, further studies including larger samples and with a stronger focus on participant selection are necessary to validate and extend the results.

Since olfactory training was shown to be successful in a randomized, controlled, multicenter study in postinfectious olfactory loss (Damm and others 2014), especially in a clinical context it is considered as the most promising noninvasive therapeutic option for various types of smell loss. However, whenever discussing potential improvements after olfactory training, it should be considered that these changes might also reflect a regression to the mean rather than true training-related improvements. The statistical phenomenon of regression to the mean occurs due to random fluctuations when repeated measurements are performed on the same participants. In particular, in these situations, extremely high or low values at the first time point are likely to be followed by less extreme values in the next measurement (Barnett and others 2005). Thus, when only participants scoring low on an olfactory test are included in a training study, an observed improvement after training might be due to statistical fluctuations rather than due to true training effects. These effects can be counteracted by more rigorous study designs, for instance by including the random allocation of subjects to control groups or by basing the subject selection on two or more initial measurements (Barnett and others 2005).

A future area of investigation is the joint analysis of structural and functional brain data, to detect more subtle reorganization processes and take advantage of the close connection between brain structure and function. In the past, due to analytical constraints, functional and structural changes were analyzed and interpreted mostly separately. However, new approaches enable the joint analysis of multiple modalities. For the employment of such promising approaches, methods have to be developed further, including modeling techniques that can integrate olfactory performance measures, neurobehavioral findings, and neuroimaging measures (structure, function, and also metabolism). Moreover, the application of stimulation techniques such as TMS (transcranial magnetic

Table 6. Summary of Main Results, Open Questions, and Future Challenges.

Structural brain changes after olfactory loss	Although the small number of studies conducted on this topic has to be taken into account, after olfactory loss decreases of gray matter volume were consistently reported in ACC, insula, piriform cortex, orbitofrontal cortex, and cerebellum.
Functional brain changes after olfactory loss	The studies conducted on this topic yielded generally heterogeneous results. During trigeminal stimulation, both activation increases (e.g., in parahippocampal gyrus, putamen, right insula, ACC, DLPFC) and decreases (e.g., in PFC, somatosensory cortex, left insula, cerebellum) were apparent in anosmics/hyposmics compared to controls. Moreover, a reduced connectivity in olfactory networks was reported after olfactory loss.
Open questions and future challenges	Due to methodological shortcomings and the small number of studies existing to date, independent replications and extensions of previous studies are necessary to substantiate the reported findings. Furthermore, future research should investigate more closely how structural and functional brain changes relate to each other. The integration of several MRI modalities (e.g., brain structure, function, metabolism) in joint analyses will lead to new insights.

stimulation) and their potential indirect impact on olfaction and on multimodal processing, as shown in healthy subjects (Henkin and others 2011; Jadauji and others 2012) deserves to be further investigated. These approaches will help to understand the underlying mechanisms of olfactory loss and will foster the development of biomarkers, for instance to predict the success of olfactory training or to provide better prognoses of recovery.

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