From Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

NEURAL AND BEHAVIORAL PLASTICITY IN OLFACTORY SENSORY DEPRIVATION

Moa Peter

Karolinska Institutet

Neural and behavioral plasticity in olfactory sensory deprivation
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Moa Peter

Principal Supervisor:
Associate Professor Johan N. Lundström
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Co-supervisor(s):
Professor Mats J. Olsson
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Professor Eric Westman
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Clinical Geriatrics

Professor Peter Fransson
Karolinska Institutet
Department of Clinical Neuroscience
Division of Neuro

Opponent:
Professor Jay A. Gottfried
University of Pennsylvania
Department of Psychology
Department of Neurology

Examination Board:
Professor Henrik Ehrsson
Karolinska Institutet
Department of Neuroscience

Professor Maria Engström
Linköping University
Department of Health, Medicine and
Caring Sciences

Professor Steven Nordin
Umeå University
Department of Psychology

ABSTRACT

The human brain has a remarkable ability to reorganize as a consequence of altered demands. This ability is particularly noticeable when studying the neural effects of complete sensory deprivation. Both structural and functional cerebral reorganization have repeatedly been demonstrated in individuals with sensory deprivation, most evident in cortical regions associated with the processing of the absent sensory modality. Furthermore, sensory deprivation has been linked to altered abilities in remaining sensory modalities, often of a compensatory character. Although anosmia, complete olfactory sensory deprivation, is our most common sensory deprivation, estimated to affect around 5 % of the population, the effects of anosmia on brain and behavior are still poorly understood. The overall aim of this thesis was to investigate how the human brain and behavior are affected by anosmia, with a focus on individuals with congenital (lifelong) sensory deprivation. Specifically, **Study I** and **Study IV** assessed potential behavioral and neural multisensory compensatory abilities whereas **Study II** and **Study III** assessed potential reorganization beyond the processing of specific stimuli; the latter by determining morphological and resting-state functional connectivity alterations.

Integration of information from different sensory modalities leads to a more accurate perception of the world around us, given that our senses provide complementary information. Although an improved ability to extract multisensory information would be of particular relevance to individuals deprived of one sensory modality, multisensory integration has been sparsely studied in relation to sensory deprivation. In **Study I**, multisensory integration of audio-visual stimuli was assessed in individuals with anosmia using two different experimental tasks. First, individuals with anosmia were better than matched controls in detecting multisensory temporal asynchronies in a simultaneity judgement task. Second, individuals with congenital, but not acquired, anosmia demonstrated indications of an enhanced ability to utilize multisensory information in an object identification task with degraded stimuli. Based on these results, the neural correlates of audio-visual processing and integration were assessed in individuals with congenital anosmia in **Study IV**. Relative to matched normosmic individuals, individuals with congenital anosmia demonstrated increased activity in established multisensory regions when integrating degraded audio-visual stimuli; however, no compensatory cross-modal processing in olfactory regions was demonstrated. Together, **Study I** and **IV** suggest that complete olfactory sensory deprivation is linked to enhanced audio-visual integration performance that might be facilitated by increased processing in multisensory regions.

In **Study II**, whole-brain gray matter morphology was assessed in individuals with congenital anosmia. Both increases and decreases in the orbitofrontal cortex, a region associated with olfaction and sometimes referred to as secondary olfactory cortex, were observed in individuals with congenital anosmia in relation to matched controls. However, in contrast to our expectations, no sensory deprivation-dependent effects were demonstrated in piriform cortex, a region commonly referred to as primary olfactory cortex. Furthermore, **Study III** revealed an absence of differences in resting-state functional connectivity between individuals with

congenital anosmia and normosmic individuals within the primary olfactory cortex (including piriform cortex) as well as between core olfactory processing regions.

In conclusion, the studies presented within this thesis suggest the existence of a potential multisensory compensatory mechanism in individuals with anosmia, but demonstrate a striking lack of morphological and functional alterations in piriform (primary olfactory) cortex. These results demonstrate that complete olfactory deprivation is associated with a distinct neural and behavioral reorganization in some regions but also a clear lack of effects in other regions; the latter underline the clear differences between our senses and suggest that extrapolating from individual senses should be done cautiously.

LIST OF SCIENTIFIC PAPERS

I. **Peter, M.G.**, Porada, D.K., Regenbogen, C., Olsson, M.J., & Lundström, J.N. (2019). Sensory loss enhances multisensory integration performance. *Cortex* 120, 116-130. doi:10.1016/j.cortex.2019.06.003

II. **Peter, M.G.**, Mårtensson, G., Postma, E.M., Nordin, L.E., Westman, E., Boesveldt, S., & Lundström, J.N. (2020). Morphological changes in secondary, but not primary, sensory cortex in individuals with life-long olfactory sensory deprivation. *NeuroImage* 218, 117005. doi:10.1016/j.neuroimage.2020.117005

III. **Peter, M.G.**, Fransson, P., Mårtensson, G., Postma, E.M., Nordin, L.E., Westman, E., Boesveldt, S., & Lundström, J.N. (2020). Normal olfactory functional connectivity despite lifelong absence of olfactory experiences. *Cerebral Cortex*. doi:10.1093/cercor/bhaa217

IV. **Peter, M.G.**, Mårtensson, G., Postma, E.M., Nordin, L. E., Westman, E., Boesveldt, S., & Lundström, J.N. (2020). Seeing beyond your nose? The effects of lifelong olfactory sensory deprivation on cerebral audio-visual integration. *Manuscript*.

CONTENTS

LIST OF ABBREVIATIONS

BOLD   Blood-Oxygen-Level-Dependent

fMRI   Functional Magnetic Resonance Imaging

MNI   Montreal Neurological Institute

MRI   Magnetic Resonance Imaging

OSN   Olfactory Sensory Neuron

ROI   Region Of Interest

1 INTRODUCTION

1.1 OLFACTION

Our senses are the only tools we have to form a perception of the world around us, and our sensory input is vital to our ability to interact with our environment. When comparing our sensory modalities, the prevailing opinion is that vision is the dominant sense in humans (Palmer, 1999). In contrast, olfaction is generally considered the least important of our senses and, if forced to pick one, is often chosen as the sensory modality to lose, (Karstensen & Tommerup, 2012). Although a discussion about a sensory hierarchy is beyond the scope of this thesis, I want to take this opportunity to emphasize that human olfactory abilities are often greatly underestimated. The prevalent perception is that human olfactory abilities are inferior to those of non-human animals, but in fact humans do possess the capacity for the use of olfaction in the same types of tasks as non-human animals. This includes more obvious functions such as food selection, but also less obvious ones, such as spatial orientation (Laska, 2017). In fact, we are more sensitive than most studied mammal species in detecting a majority of tested odors (Laska, 2017). For the interested reader, I recommend a review paper by John P. McGann (2017), where the author outlines the basis of the misconception that human olfactory abilities are poor and summarizes what olfactory research actually tells us about the olfactory sense in humans, relative to other mammals.

An understanding of normal olfactory processing is vital for the study of olfactory sensory deprivation, both in terms of hypothesis building and for the interpretation of findings. Key aspects of the human brain's complex olfactory network are outlined here, with a focus on the two cortical olfactory processing regions most relevant to the studies included in this thesis, namely the piriform and orbitofrontal cortices.

1.1.1 From molecule to brain

Olfaction is a chemical sense, meaning that olfactory sensory input is based on molecules in our environment, in contrast to, e.g., vision and audition, wherein sensory input is based on the amplitude and wavelength of electromagnetic and pressure waves, respectively. The molecules that trigger our olfactory sense are called odorants. When we breathe in (or sniff) through our nose, air containing odorants flows in through our nostrils and reaches the olfactory epithelium at the roof of the nasal cavity (Figure 1). In contrast to the respiratory epithelium that lines the majority of the nasal cavity, the olfactory epithelium contains olfactory sensory neurons (OSN). Each OSN contains only one specific type of olfactory receptor, showing high affinity for a specific molecular feature of an odorant rather than for a specific molecule. Therefore, an odorant has the potential to bind to multiple receptors, and a receptor has the potential to bind different odorants, giving rise to a complex pattern coding for odor identity (Malnic, Hirono, Sato, & Buck, 1999). Humans express nearly 400 olfactory receptor types (Breer, Fleischer, & Strotmann, 2017), enabling us to discriminate between a vast number of odors (over a trillion odors, claim Bushdid, Magnasco, Vosshall, & Keller, 2014; albeit criticized by Gerkin & Castro, 2015; Meister, 2015). The odorants reaching the olfactory epithelium are dissolved in a mucus layer in which the OSNs are embedded, enabling binding to the olfactory receptors. Binding generates an action potential that propagates through the OSNs' axons, which extend

out through a perforated bone structure in the basal skull called the cribriform plate, and synapse directly to the ipsilateral (in the same hemisphere of the brain) olfactory bulb, forming the olfactory nerve (cranial nerve I; Figure 1).
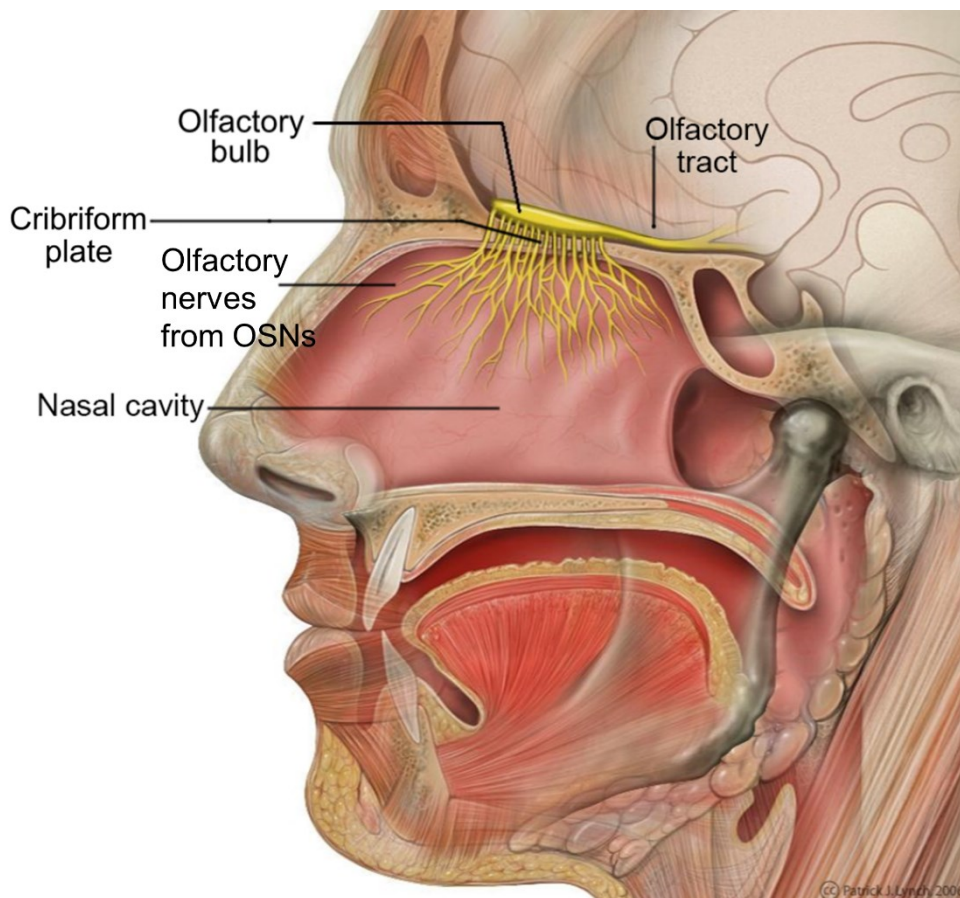
Figure 1 Anatomy of the olfactory pathway to the brain. Odorants bind to the olfactory sensory neurons' (OSN) olfactory receptors, located in the roof of the nasal cavity. The axons of the OSNs form the olfactory nerve, that projects through a perforated bone structure (the cribriform plate) and reaches the olfactory bulb. Figure adapted based on work by Patrick J. Lynch available at commons.wikimedia.org/wiki/File:Head_Olfactory_Nerve_Labeled.png under a CC-BY license.

1.1.1.1 The olfactory bulb

The olfactory bulbs are two cotton swab-shaped structures located behind our eyebrows (Figure 1). Afferent signals from the OSN axons synapse on mitral and tufted cells in structures called glomeruli in the olfactory bulb. Although OSNs expressing a specific type of receptor are scattered in the olfactory epithelium, their axons converge in the olfactory bulb where they project to the same glomeruli. In this way, a spatial representation of an odorant is formed in the olfactory bulbs (Freiherr, 2017). Olfactory signal processing, such as signal amplification, and inhibition based on input from downstream olfactory processing regions, occur already in the olfactory bulb (Freiherr, 2017; Haberly, 2001). The axons of the mitral and tufted cells form the olfactory tract, which projects to a number of cortical and subcortical regions in the basal frontal and medial temporal lobe, forming a distributed network of olfactory processing just two synapses from the sensory receptors (Figure 2).

1.1.2 Primary olfactory cortex

A prevailing standpoint within the olfactory community has been that all regions receiving direct input from the olfactory bulb constitute the primary olfactory cortex (Gottfried, 2006; Zhou, Lane, Cooper, Kahnt, & Zelano, 2019). This includes a number of regions in the limbic system: the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, nuclei of the amygdala, and the entorhinal cortex (Figure 2). A primary sensory cortex typically processes simple representations of the sensory input it receives, and it has been argued that the regions receiving input from the olfactory bulb are in fact involved in processing much too complex to be regarded as primary sensory cortices (Freiherr, 2017; Lundström, Boesveldt, & Albrecht, 2011). Hence, considering the olfactory bulb, itself, as the primary olfactory cortex has been put forward as an alternative, as it is in the olfactory bulb where spatial patterns of molecular features are represented and simple processing takes place (Haberly, 2001).

This controversy is interesting, particularly in the context of comparing the cerebral processing of different sensory modalities, and it is especially relevant for the studies included in this thesis that compare the effects of sensory deprivation in different senses. However, in this thesis, I will refrain from further comments on the debate on what constitutes primary olfactory cortex and merely acknowledge that opinions differ. Instead, I will focus on what is known about core olfactory processing regions, independent of whether they should be labeled as primary, secondary, or associative, and, for simplicity, regions receiving direct bulbar input will be referred to as primary olfactory cortex.
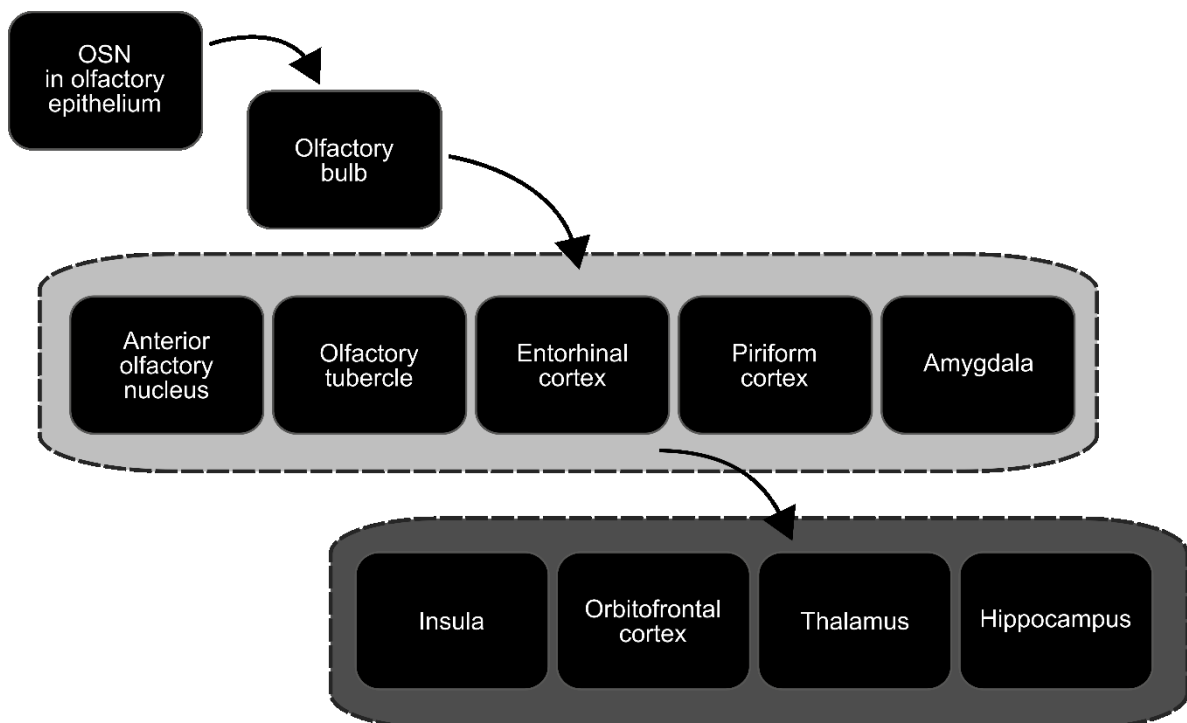
Figure 2 Major olfactory processing pathways. Regions within the light gray box receive direct input from the olfactory bulb; in this thesis, these regions are referred to as primary olfactory regions. Regions within the darker gray box receive direct input from primary olfactory regions; in this thesis, these regions are referred to as olfactory association cortex. Note that many of the connections between the olfactory bulb and primary olfactory cortex as well as the connections between primary olfactory cortex and olfactory association cortex are bidirectional, despite illustrated as unidirectional arrows. OSN = olfactory sensory neuron. Based on (Gottfried, 2010; Mainland, Lundström, Reisert, & Lowe, 2014).

1.1.2.1 Piriform cortex

The piriform cortex is the most prominently-studied region of the olfactory processing network for good reason: it is the main signaling recipient from the olfactory bulb (Gottfried, 2006; Lundström et al., 2011), and it yields the highest consistency of odor activation in neuroimaging studies of olfactory processing (Seubert, Freiherr, Djordjevic, & Lundström, 2013). In contrast to other sensory systems, olfactory information is conveyed ipsilaterally rather than contralaterally, i.e., the majority of olfactory connections remain in the same hemisphere of the brain, with the information from the right nostril reaching the right olfactory bulb, which in turn projects to the right piriform cortex. The piriform cortex forms reciprocal connections with the olfactory bulb and with multiple downstream regions in the olfactory network, including the orbitofrontal cortex and the anterior insula. The fact that piriform cortex consists of paleocortex, an evolutionarily old, three-layered cortical structure, and not the evolutionarily younger, six-layered neocortex that comprises the primary sensory cortices of other sensory modalities, further separates olfactory structures and function from those of other sensory modalities.

The piriform cortex is located in the medial junction of the frontal and temporal lobes and is commonly divided into anterior (frontal) and posterior (temporal) parts, a division based on both anatomy and function. Although piriform cortex has been associated with multiple aspects of olfactory-related processing, an interesting separation of function between the anterior and posterior parts has emerged. The anterior piriform cortex demonstrates representations of the chemical composition of an odorant, whereas the activity in the posterior piriform cortex has been associated with the perceptual qualities of an odor, often referred to as odor object or odor category (Freiherr, 2017; Gottfried, 2010). Although direct measures of cerebral activity in humans is rare, due to its invasive nature, the use of functional magnetic resonance imaging (fMRI) has enabled non-invasive, indirect study of cerebral activity in humans, yielding support for this functional division of the human piriform cortex. An interesting example is the study by Howard, Plailly, Grueschow, Haynes, and Gottfried (2009), in which the pattern of fMRI blood-oxygen-level-dependent (BOLD) signal in the posterior piriform cortex was studied for different odors. The evoked BOLD-signal patterns were unique for clearly distinct odorants, but as the similarity in perceived odor quality increased, the patterns' similarity increased as well, supporting odor category representation in the posterior piriform cortex (Howard et al., 2009). In addition, the activity within piriform cortex seems to be modulated by attention (Zelano et al., 2005) and linked to predictive activity, with similar patterns of activity generated by searching for a specific odor and for the actual processing of that odor (Zelano, Mohanty, & Gottfried, 2011). Interestingly, pure sniffing of odorless air has also been shown to activate piriform cortex, an activation that seems to be related to the sensation of airflow in the nose rather than the act of sniffing (Sobel et al., 1998). Even though we are still far from a complete understanding of the functional repertoire of the piriform cortex in olfactory processing, it is safe to say that – although a representation of an odor's chemical identity is present in the piriform cortex – this structure is associated with much more complex

tasks than would be expected from a primary sensory region (Courtiol & Wilson, 2017; Freiherr, 2017; Gottfried, 2010; Haberly, 2001; Lundström et al., 2011).

1.1.3 Olfactory association cortex

Cerebral regions receiving direct input from the primary olfactory cortex, i.e., regions two synapses from the olfactory bulb, are generally referred to as secondary olfactory cortex or olfactory association cortex. The olfactory association cortex consists of a network of multimodal regions associated with functions such as memory and emotion (Freiherr, 2017). Both cortical regions, such as the orbitofrontal cortex and anterior insula, the two regions demonstrating the most consistent activation in olfactory neuroimaging studies after piriform cortex (Seubert, Freiherr, Djordjevic, et al., 2013), and subcortical regions, such as the hippocampus and thalamus, get direct input from primary olfactory regions (Figure 2). Note that thalamus appears in the olfactory processing network first after the primary olfactory cortex. This lack of obligatory thalamic relay separates olfactory processing from the processing of other sensory modalities. Although there is a pathway from piriform cortex through thalamus to the orbitofrontal cortex, a pathway associated with attention to odors (Plailly, Howard, Gitelman, & Gottfried, 2008), olfactory information also reaches neocortical regions such as the orbitofrontal cortex without first passing through thalamus (Courtiol & Wilson, 2015).

1.1.3.1 Orbitofrontal cortex

The orbitofrontal cortex constitutes the entire ventral surface of the frontal lobe, and subregions of this large cortical region have been strongly linked to olfactory processing in human neuroimaging studies (Gottfried & Zald, 2005; Seubert, Freiherr, Djordjevic, et al., 2013). The orbitofrontal cortex is one of the most multimodal regions in the brain, receiving visual, somatosensory, visceral, auditory, gustatory, and olfactory input (Kringelbach & Rolls, 2004; Ongür & Price, 2000). Perhaps the most dominant functional association of the orbitofrontal cortex is reward processing, but its functional role has also been described in related terms, such as value coding, associative learning, emotion, and social behavior (Gottfried & Zald, 2005; Kringelbach & Rolls, 2004). Direct stimulation of the human orbitofrontal cortex has been shown to elicit both sensory (olfactory, gustatory, and somatosensory) and emotional experiences, which has been interpreted as support for the orbitofrontal cortex playing a key role in the integration of sensory and affective processing (Fox et al., 2018).

The orbitofrontal cortex is the main neocortical projection target of the primary olfactory cortex (Gottfried & Zald, 2005), with strong reciprocal connections to the piriform cortex (Seubert, Regenbogen, Habel, & Lundström, 2017). The multimodal nature of the orbitofrontal cortex's connections impose the notion that it plays an important role for the integration of sensory input from multiple sensory modalities. Accordingly, it has been suggested to play an important role in food consumption, combining olfactory, gustatory, and somatosensory information (Price, 2008; Rolls, 2005). The orbitofrontal cortex has further been linked to conscious olfactory perception in a case study of a patient with traumatic injury restricted to the right orbitofrontal

cortex. The patient demonstrated complete anosmia after the injury, while still demonstrating both autonomic (indicated by skin conductance) and neural (indicated by fMRI) response activity to odor stimuli (Li et al., 2010). However, other patient studies of orbitofrontal lesions indicate functioning odor detection, but difficulties in higher-order olfactory functions such as odor identification, memory, and discrimination (Gottfried & Zald, 2005). The latter results line up well with the general consensus that the orbitofrontal cortex is linked to higher-order cognitive aspects of olfactory processing. Still, the exact role played by the orbitofrontal cortex in olfactory perception is yet to be fully determined as the orbitofrontal cortex, similar to the piriform cortex, has been associated with numerous olfactory-related functions. These functions include, among others, olfactory decision making, associative and discrimination learning, affective coding, reward, valence processing, and integration of olfactory information with sensory information from other sensory modalities (Freiherr, 2017; Gottfried & Zald, 2005; Gottfried, 2010; Lundström et al., 2011). Furthermore, the orbitofrontal cortex has been, together with the piriform cortex, implicated in predictive coding of olfactory stimuli (Zelano et al., 2011) and has been argued to be specifically important for prediction of perceptual outcomes and value (Gottfried & Zelano, 2011). A recent study demonstrated that the orbitofrontal cortex plays an important role in olfactory value learning in rodents, in contrast to the piriform cortex, wherein odor identity is represented independent of associated value (P. Y. Wang et al., 2020). It has also been argued that the orbitofrontal cortex is involved in forming an object-specific link to expected reward (Howard, Gottfried, Tobler, & Kahnt, 2015). These studies contribute to the vast literature linking the orbitofrontal cortex to reward processing, and although the role of the orbitofrontal cortex in olfaction might seem multifaceted, it is important to keep in mind that single studies have the tendency to interpret results based on the specific questions they ask. It is plausible that the same process in the orbitofrontal cortex could be interpreted as a basis for olfactory decision making in one experimental paradigm and value coding in another, due solely to the framework used to explain the results.

1.1.4 Final remarks about neural olfactory processing

The olfactory system consists of a wide network of regions extending far beyond those highlighted here, the piriform and orbitofrontal cortices. And, even for these relatively well-documented regions, their full contribution to the processing of olfactory input and the formation of the olfactory percept in humans has not been clearly determined. It is noteworthy that multiple regions of the limbic system, which is strongly associated with emotion and memory, appear early in the olfactory processing network; the amygdala is among the primary olfactory regions receiving direct input from the olfactory bulb. Hence, the olfactory system has a shortcut into the limbic system and into associative cortical regions without the thalamic relay obligatory in other sensory systems, which is associated with, e.g., perceptual awareness and feature extraction (Courtiol & Wilson, 2015; Gottfried, 2010). In addition, many of the regions involved in early stages of olfactory processing are heteromodal, receiving input from multiple senses. How these peculiarities of the olfactory system might be linked to the

behavioral and neural effects of olfactory sensory deprivation is an important theme in this thesis.

1.2 OLFACTORY DEPRIVATION

Generally, humans are generally bad at estimating their own olfactory abilities. Despite the common perception that the human sense of smell is worse than other animals', individuals tend to have an inflated perception of their olfactory abilities. Self-reported olfactory dysfunction is specific, meaning that the individuals who report olfactory sensory deprivation do actually have a decreased sense of smell. It is, however, not sensitive: in studies where both self-reported olfactory ability and objective olfactory tests are performed, a surprisingly high number of individuals perceiving themselves as *normosmic*, i.e., as having a normal sense of smell, when tested, demonstrate a decreased sense of smell (*hyposmia*) or, quite remarkably, even complete olfactory sensory deprivation (*anosmia*) (Boesveldt et al., 2017). Murphy et al. (2002) reported that the actual prevalence of olfactory deprivation was more than double the level of self-reported dysfunction among older adults, and Temmel et al. (2002) found that even among patients referred to a healthcare facility for olfactory problems, 4 % perceived themselves as having a normal sense of smell while demonstrating either hyposmia or anosmia when tested. Moreover, based on a sample of over 9000 individuals from the general population, at least 0.45 % of individuals reporting a normal sense of smell were classified as anosmic (Anna Oleszkiewicz & Hummel, 2019).

Normosmia – a normal sense of smell.

Hyposmia – a decreased sense of smell.

Functional anosmia – a sense of smell decreased to such an extent that there is a complete lack of functional use of the sense.

Anosmia – a complete absence of the sense of smell. Because anosmia and functional anosmia are often used interchangeably, the term anosmia will in this thesis be used as a collective term covering both complete and functional anosmia.

Several studies have concluded that the estimated prevalence of olfactory sensory deprivation in the general population is around 20 %, with 15 % classified as hyposmia and the remaining 5 % classified as *functional* anosmia (Boesveldt et al., 2017; Brämerson, Johansson, Ek, Nordin, & Bende, 2004; T Hummel et al., 2017; Landis, Konnerth, & Hummel, 2004; Vennemann, Hummel, & Berger, 2008). Functional anosmia is a more inclusive term, which captures both individuals with a complete lack of olfactory abilities as well as individuals with sensory loss to such an extent that it lacks all functional use (T Hummel et al., 2017; Kobal et al., 2000). These numbers are indeed high, particularly when compared to the prevalence of complete visual and complete auditory sensory deprivation, estimated to approximately 0.3 % and 0.1 % of the Swedish population, respectively (Statistiska Centralbyrån, 2020). Despite being much more prevalent, olfactory deprivation has been overlooked, and patients experience

difficulties in finding the desired level of information and care (Landis, Stow, Lacroix, Hugentobler, & Hummel, 2009). Not until very recently did olfactory sensory deprivation begin to receive increased attention from either the scientific community or the media.

1.2.1 Causes
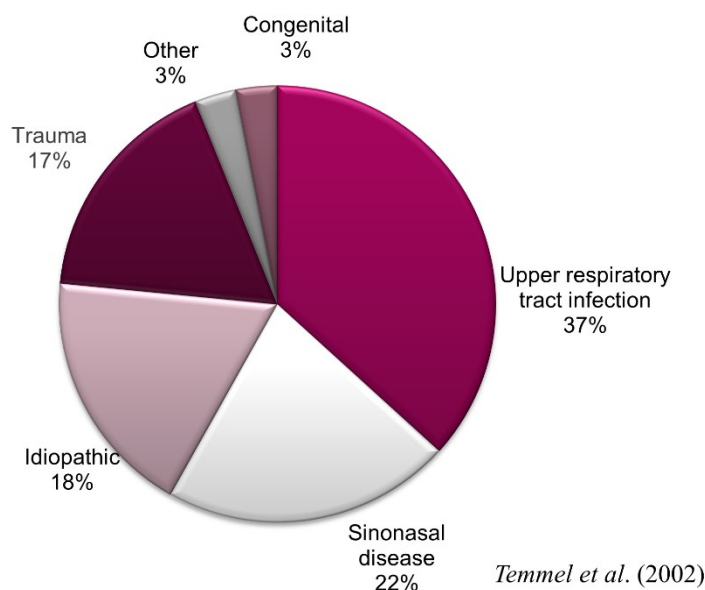
Figure 3 Common causes of ansomia based on 278 consecutive patients with olfactory deprivation at the department of otorhinolaryngology at the University of Vienna, Austria, and the University of Dresden, Germany. Note that this distribution might not represent the distribution in the general public.

With the worldwide and rapidly increasing spread of the coronavirus (SARS-CoV-2) during 2020 and with sudden onset of olfactory sensory loss as one of the more common symptoms of COVID-19 (Giacomelli et al., 2020), anosmia has become a more familiar term to many. However, COVID-19 is not the first disease to cause olfactory sensory loss. Upper respiratory tract infection, most commonly virus-induced, was reported as the single most common cause of anosmia among patients seeking clinical care (Figure 3) (Blomqvist, Brämerson, Stjärne, & Nordin, 2004; Temmel et al., 2002). Sinonasal diseases, including nasal polyps and chronic sinusitis, also rank among the most common causes. Sinonasal problems, in contrast to other causes of olfactory sensory deprivation, are often associated with a fluctuating sense of smell due to the variability of the severity of disease (T Hummel et al., 2017). Head trauma can also cause anosmia, either due to damage to the olfactory nerve on its passage through the cribriform plate, direct injury to the nasal pathway blocking odorants from reaching the olfactory epithelium, or damage to central structures involved in olfactory processing (T Hummel et al., 2017). Furthermore, olfactory sensory deprivation can be related to a number of neurological problems, such as the neurodegenerative Alzheimer's and Parkinson's diseases. In fact, olfactory loss often appears as one of the earlies signs of these diseases, manifesting long before the cognitive decline and motor symptoms often recognized as their hallmark symptoms (Marin et al., 2018). Drug and toxin exposure are also known sources of olfactory loss, as is idiopathic (without known cause) loss, which is not uncommon. Importantly, a decline in olfactory function is associated with aging, albeit often linked to other health related problems (Seubert, Laukka, et al., 2017) and not as prevalent in elderly with good medical health and cognitive

ability SOIT; (Steven Nordin, Almkvist, & Berglund, 2012). Still, aging is a strongly contributing factor to the high prevalence of olfactory deprivation in the general population: in some age groups, the proportion of olfactory deprivation reaches levels as high as 62 % (Murphy et al., 2002). Finally, although less common than many other causes of olfactory deprivation, some individuals are born with complete olfactory sensory deprivation, i.e., have congenital anosmia.

1.2.1.1 *Congenital anosmia*

Congenital anosmia constitutes a small proportion of the individuals with complete olfactory sensory deprivation. The prevalence of isolated congenital anosmia, i.e., congenital anosmia not related to any known cause or syndrome, is estimated at somewhere between one in 2000 (H G Karstensen & Tommerup, 2012) and one in 8000 (Thomas Hummel, Landis, & Rombaux, 2017). The isolated form of congenital anosmia is the most common form, but congenital anosmia can also be one of multiple characteristics in genetic conditions, such as Kallmann syndrome, in which endocrine problems are also manifested (H G Karstensen & Tommerup, 2012). Although a genetic origin of isolated congenital anosmia is plausible, and perhaps even likely based on the numerous reports of multiple cases in the same family, associated genes have yet to be found (T Hummel et al., 2017; H G Karstensen & Tommerup, 2012). Physical signs of congenital anosmia typically include aplastic (absent) or hypoplastic (underdeveloped) olfactory bulbs (Abolmaali, Hietschold, Vogl, Hüttenbrink, & Hummel, 2002; Yousem, Geckle, Bilker, McKeown, & Doty, 1996), which can be confirmed using magnetic resonance imaging. Furthermore, individuals with congenital anosmia often demonstrate an absence of olfactory epithelium, with biopsies of the olfactory area indicating either only respiratory epithelium highly abnormal olfactory epithelium (Jafek, Gordon, Moran, & Eller, 1990; Leopold, Hornung, & Schwob, 1992). These findings, however, do not separate isolated congenital anosmia from other forms of congenital anosmia, as individuals with Kallmann syndrome display the same characteristic physical attributes (H G Karstensen & Tommerup, 2012; Leopold et al., 1992). Consequently, the diagnosis of isolated congenital anosmia is one of exclusion: individuals with anosmia who lack any recollection of olfactory experiences and with no known potential causes of anosmia, such as head trauma early in life or endocrine problems, are diagnosed with congenital anosmia (H G Karstensen & Tommerup, 2012). It is noteworthy that, for individuals with congenital anosmia, the sensory deprivation is often not detected until early puberty, with diagnosis typically made around the age of 12-16 years (T Hummel et al., 2017), if diagnosed at all. While complete visual and auditory deprivation can easily be detected quite early by parents, anosmia is less noticeable to others, and children with congenital anosmia are seldomly aware of their deficit as they have no comprehension of what a smell is, hindering early diagnosis. Individuals with a congenital olfactory sensory deprivation differ from individuals with an acquired loss in that they have not experienced a sensory *loss*; they have never had olfactory abilities, and they do not have a clear frame of reference for the kind of perceptual experiences they lack. Therefore, the perceived personal consequences of the anosmia typically differ between individuals with congenital and acquired olfactory sensory deprivation.

1.2.2 Consequences

Olfactory experiences can be both positive and negative. Enjoying the full flavor of a favorite meal is completely dependent on olfaction, as is the realization that the garbage should probably have been taken out before leaving, rather than after returning home from vacation. Albeit unpleasant, the negative aspects of olfactory experiences are highly relevant to us, in that they often serve as a warning system, for example by indicating that the milk has gone bad or that something is burning. Individuals with olfactory sensory deprivation tend to suffer from the loss of both aspects of the olfactory spectrum, the enjoyment as well as the warning signal (Blomqvist et al., 2004; Smeets et al., 2009; Temmel et al., 2002). Problems related to a lack of body odor perception and anxiety over hygiene problems are prevalent and can cause problems in social situations, and problems related to food and eating, such as worrying about consuming spoiled food or a loss of appetite, also affect these individuals to a large extent (Temmel et al., 2002). The strong connection between olfactory abilities and food consumption becomes even more evident when considering that individuals with sudden olfactory loss commonly report a loss of taste, although they rarely have impaired gustatory abilities when tested (Negoias, Meves, Zang, Haehner, & Hummel, 2020).

Individuals with olfactory sensory deprivation demonstrate a general decrease in their experienced quality of life and increased scores on scales of depression (Blomqvist et al., 2004; Croy, Nordin, & Hummel, 2014; Smeets et al., 2009; Temmel et al., 2002). These negative consequences of olfactory deprivation are likely due to a combination of direct and indirect factors. A direct effect of the sensory loss might be the loss of a source of enjoyment, like drinking a nice wine, and a secondary, indirect effect would be the loss of social interaction coming from an individual's avoidance of associated activities, sush as wine tastings, which become less enjoyable without the ability to perceive the distinguishing notes of different wines. Furthermore, in a number of different causes of olfactory deprivation, there is also comorbidity with, e.g., headache or a constantly stuffy nose in sinonasal disease, which likely also affect general well-being (Croy et al., 2014). Interestingly, well-being is not affected in individuals with olfactory deprivation who perceive themselves as having normal olfactory abilities (A Oleszkiewicz, Kunkel, Larsson, & Hummel, 2020), and individuals with congenital deprivation do not report a decrease in quality of life (Temmel et al., 2002). This suggests that the reported decreased well-being is related to an experienced loss, rather than to decreased or absent olfactory abilities.

We know very little about how changes to olfactory input affect cortical processing and networks, as few studies on anosmia-related behavioral and cerebral reorganization exist. The literature does, however, provide insights into the effects of other types of sensory loss, auditory and, most commonly, visual loss, which can be used as a frame of reference when investigating anosmia-related plasticity.

1.3   BEHAVIORAL PLASTICITY IN SENSORY DEPRIVATION

"When we direct our whole attention to any one sense, its acuteness is increased; and the continued habit of close attention, as with blind people to that of hearing, and with the blind and deaf to that of touch, appears to improve the sense in question permanently." (Darwin, 1890)

The scientific community has for a long time been interested in the potential effects a complete sensory deprivation has on the abilities in spared sensory modalities, as the quote by Charles Darwin illustrates. Many would intuitively agree with the claim that abilities in remaining sensory modalities benefit from the absence of one sense, perhaps referring to anecdotes about extraordinary abilities such as echolocation in blind individuals. This view, however, is not undisputed: two competing hypotheses exist regarding the effects of sensory deprivation on the spared senses (Pavani & Bottari, 2012). The *sensory compensation hypothesis* argues, in line with the view presented by Darwin, that sensory deprivation enables enhanced, or compensatory, abilities in the remaining senses. In contrast, the *perceptual deficit hypothesis* argues that input from all of our senses are required for proper sensory development and function;, i.e., that the different sensory modalities work in symbiosis and are needed for mutual calibration. From this perspective, sensory deprivation affects all senses negatively.

A vast number of studies have investigated the behavioral outcomes of complete sensory deprivation in the visual and auditory senses, whereas only a handful of studies have assessed the effects of anosmia on behavioral performance. Because the literature on anosmia is limited, the understanding of sensory deprivation-related behavioral (and cerebral) alterations is mainly based on the effects of complete visual and auditory sensory deprivation. Therefore, an overview of the effects of visual and auditory sensory deprivation, followed by anosmia, are presented in the reviewed literature.

1.3.1   Visual and auditory sensory deprivation

Many have explored the performance of blind individuals on spatial auditory tasks on the account of the dominant role the visual sense plays in spatial perception and the importance for blind individuals of using auditory cues for navigation (Collignon, Voss, Lassonde, & Lepore, 2009). Congenitally and early-onset blind individuals, i.e., individuals either completely lacking visual experiences or having experienced vision during a very restricted time period early in life, rarely demonstrate decreased auditory spatial performance when compared to sighted controls (Collignon, Voss, et al., 2009; Occelli, Spence, & Zampini, 2013). This indicates that visual spatial perception is not necessarily needed to develop accurate auditory spatial perception. In certain tasks, blind individuals even outperform sighted controls. For example, in auditory spatial attention tasks, both congenitally blind individuals and individuals who lost their sight later in life demonstrated performance similar to sighted controls when attending to centrally positioned stimuli but demonstrated a heightened performance when attending to stimuli in the periphery (Fieger, Röder, Teder-Sälejärvi, Hillyard, & Neville, 2006; Röder et al., 1999). Similarly, P. Voss et al. (2004) showed that blind and sighted individuals performed comparably on an auditory spatial discrimination task when stimuli were presented in front of them, but an enhanced performance by early blind with peripheral stimuli, further

supporting the notion of facilitated peripheral auditory processing as a result of visual deprivation. However, a general enhancement of auditory spatial skills as a result of congenital blindness has also been claimed, e.g., in a study by Battal, Occelli, Bertonati, Falagiarda, and Collignon (2020) in which enhanced performance on an auditory spatial task was demonstrated independent of whether the stimuli were presented centrally or in the periphery.

Enhanced performance by blind individuals in sensory domains other than auditory has also been demonstrated. Tactile benefits have been suggested based on enhanced performance on a tactile discrimination task (Goldreich & Kanics, 2003) and an absence of the age-related decrease in tactile acuity, which is demonstrated by sighted controls (Legge, Madison, Vaughn, Cheong, & Miller, 2008). In line with what has been demonstrated for auditory tasks, there are also indications that the tactile performance enhancements are limited to specific tactile tasks and that performance is similar to that of controls in other tasks. For example, in a study by Alary et al. (2009), three different tactile discrimination tasks were performed by blind individuals and compared to the performance of two different control groups. In only one of the three tasks tested was an enhanced performance by the blind group demonstrated. Furthermore, the enhancement was only significant in comparison to one, but not the other, control group, shining light upon the potential effect that the choice of control group has on the experimental outcome (for further discussion on the importance of group, see chapter 5.4).

Indications of enhanced olfactory abilities in blind individuals have also been demonstrated. Early blindness has been linked to improved odor discrimination as well as free odor identification (Cuevas, Plaza, Rombaux, De Volder, & Renier, 2009; Rombaux et al., 2010). However, a subsequent study failed to confirm these results, showing no group differences between early blind, late blind, and sighted controls for odor threshold, discrimination, identification, or recognition (Cornell Kärnekull, Arshamian, Nilsson, & Larsson, 2016), and a meta-analysis of studies of olfactory performance in blind individuals came to the conclusion that no enhancements (nor worse performance) could be supported (Sorokowska, Sorokowski, Karwowski, Larsson, & Hummel, 2018).

Parallels can easily be drawn between auditory abilities in blind individuals and visual abilities in deaf individuals: the performance of the sensory deprived individuals is in many cases indistinguishable from that of controls, although significant improvements have been demonstrated under specific circumstances. Deaf individuals show enhanced abilities, as compared to hearing controls, in tasks related to, e.g., attention in the peripheral visual field (Bavelier, Dye, & Hauser, 2006; Frasnelli, Collignon, Voss, & Lepore, 2011; Prasad, Patil, & Mishra, 2017). Furthermore, as for blind individuals, enhanced tactile performance has been reported for deaf individuals, e.g., congenitally deaf individuals have demonstrated enhanced detection of shifts in vibration frequency (Levänen & Hamdorf, 2001). However, an impairment in temporal, but not spatial, tactile discrimination in congenitally deaf individuals has also been reported (Bolognini et al., 2012), preventing general conclusions about tactile perception in auditory sensory deprivation.

Although a plethora of studies support the notion of comparable or enhanced performance in spared senses in individuals with complete visual sensory deprivation, results from other studies suggest that the consequences of blindness are more complex, in line with the above discussed tactile perception in congenital deafness. There are, for example, studies indicating that the enhanced spatial acuity in blind individuals might be restricted to the horizontal plane: for vertically placed targets in front of the participants, blind individuals have been shown to perform worse than sighted controls (Lewald, 2002; Zwiers, Van Opstal, & Cruysberg, 2001; however see Battal et al., 2020). Other studies suggest that some, but not all, blind individuals compensate for their lack of vision with enhanced spatial auditory acuity. In a noteworthy study, half of the congenitally or early blind participants displayed a performance equivalent to sighted controls on a monaural sound localization task with horizontally positioned sound sources, whereas half significantly outperformed the controls (Lessard, Paré, Lepore, & Lassonde, 1998); a similar division of blind individuals showing enhanced and normal performance was later done by Gougoux, Zatorre, Lassonde, Voss, and Lepore (2005). The underlying mechanisms of these individual differences are not known.

In visual and auditory sensory deprivation, most evidence disagrees with the perceptual deficit hypothesis, albeit some demonstrated deficits in spared senses do exist. The abilities in remaining senses are often comparable to those of individuals with intact sensory modalities, and in some cases, the abilities of individuals with sensory loss are enhanced, supporting the sensory compensation hypothesis. In particular, certain aspects of the remaining senses related to higher-order processing can show improvement, whereas basic sensory functions, such as detection thresholds, usually remain unaffected by deprivation in other senses (for reviews, see Bavelier & Neville, 2002; Frasnelli et al., 2011).

1.3.2 Anosmia

The effects of olfactory sensory deprivation on the abilities in spared sensory modalities remain sparsely studied, and the existing literature has focused on the two remaining chemical senses, gustation and the trigeminal sense. In contrast to visual and auditory sensory deprivation, the majority of studies on olfactory deprivation have demonstrated decreased rather than increased capabilities in the remaining senses. Individuals with anosmia demonstrate both decreased sensitivity for trigeminal stimuli (Frasnelli, Schuster, & Hummel, 2010; Gudziol, Schubert, & Hummel, 2001) and decreased gustatory function (Gagnon et al., 2014). The fact that olfactory impairment leads to worse rather than improved performance in chemical senses has been argued to be related to the shared cortical processing pathways of the chemical senses (Lundström et al., 2011), i.e., that the sensory modalities might be dependent on each other to develop and function correctly (Frasnelli et al., 2011; Reichert & Schöpf, 2018). This notion is in line with the perceptual deficit hypothesis. As for the effect of olfactory sensory deprivation on the performance in, and processing of, other sensory modalities than the chemical ones, little is known.

1.3.3 Mechanisms of behavioral plasticity in sensory deprivation

Although many aspects of performance in remaining senses seem to remain unaltered in individuals with sensory deprivation, there is evidence pointing towards alterations in abilities. These alterations are more often improvements than declines. There is undoubtedly a need for individuals who are completely deprived of a sense to develop strategies to sufficiently cope with navigating an environment that often requires intact sensory abilities. This aspect should not be neglected when discussing the basis of behavioral alterations, as it most likely requires the individual to devote much more attention to the spared senses than is required by individuals with intact senses to gain the same amount of useful information. It is therefore difficult to distinguish between heightened abilities that are purely based on changes in attention to, or an extended use of, remaining senses, and enhancements in abilities that are in fact facilitated by the sensory absence in the form of, e.g., new functional pathways in the brain that are accessible only as a consequence of sensory deprivation. For instance, it has been suggested that the enhanced performance blind individuals demonstrate on tactile tasks could be an effect of Braille reading. This argument was contradicted by Goldreich and Kanics (2003), however, who showed that both blind Braille readers and blind non-readers demonstrated enhanced tactile acuity, as compared to sighted controls. In a similar manner, it has been argued that heightened performance on visual tasks in deaf individuals cannot be attributed solely to the acquisition of sign language because both deaf signers and non-signers have demonstrated enhanced performance on a visual attention task (Dye, Hauser, & Bavelier, 2009). Moreover, the attentional shift towards the peripheral visual field in deaf individuals has been attributed to deafness rather than the use of sign language, as this effect was not evident in hearing signers (Bavelier et al., 2001). Based on these results, it is reasonable to assume that there are behavioral benefits resulting from sensory loss-dependent plasticity, rather than solely from the training of particular tasks. However, it is important to acknowledge that these results do not necessarily exclude the possibility of enhanced abilities based on altered attention to, and increased usage of, the sense in which performance gains are demonstrated; it merely indicates that the gain is not purely based on the acquisition of a specific skill.

Importantly, behavioral effects of sensory deprivation seem to differ depending on when in life the sensory abilities were lost. For a loss acquired later in life, the effects tend to be reduced as compared to those in early sensory loss, albeit not absent. Such differences in sensory deprivation-related effects between congenital and late acquired sensory deprivation have been argued to be linked to critical, or sensitive, periods early in life (P. Voss, 2013), during which the levels of neural, and therefore also behavioral, plasticity are high. This concept is based on the seminal work by Wiesel and Hubel, demonstrating that visual deprivation in kittens during the first three months of life resulted in severely impaired visual function despite long recovery periods (Wiesel & Hubel, 1965). Of high importance to the concept of critical periods are the results from a follow-up study demonstrating that the severe, long-lasting consequences of shorter periods of visual deprivation declined with the age of sensory deprivation onset and vanished around the third month, based on investigation of the effects of induced visual deprivation in older kittens and cats (Hubel & Wiesel, 1970). Similarly, monkeys deprived of

all visual input during their first year of life by suturing their eyelids shut shortly after birth remained functionally blind after opening of the eyes (Hyvärinen, Carlson, & Hyvärinen, 1981), supporting the importance of this early developmental period for primates, as well. These types of experiments are, for obvious ethical reasons, not performed in humans (and a discussion regarding the ethics of performing them using animals could of course also be relevant, albeit outside the scope of this thesis), but studies comparing individuals differing in sensory deprivation onset point towards similar differences in humans. For example, P. Voss et al. (2004) investigated three different aspects of auditory spatial perception in early blind, late blind, and sighted controls. Enhanced performance, as compared to sighted controls, was demonstrated in two of three tasks for early blind individuals and in one of three tasks for late blind individuals; sighted controls did not outperform the blind groups in any task. Congenital and early blind individuals have also been shown to outperform both late blind and sighted controls in an auditory pitch discrimination task (Gougoux et al., 2004), supporting a difference between those who have lost their sense before or during an early sensitive period and those who were deprived later in life. However, Gougoux et al. (2004) also included an alternative analysis approach in which all blind participants were treated as a continuum in respect to the age at sensory loss onset, rather than dichotomizing the blind individuals into two groups. This analysis resulted in an effect of age at blindness onset, with behavioral performance correlating negatively with age at deprivation. Hence, a strict group division of sensory deprived individuals based on onset at a particular age, related to an assumed end of a critical period after which the behavioral effects of sensory deprivation rapidly decreases, might be an oversimplification.

It has been suggested that enhancements in behavioral performance as a result of sensory deprivation requires that the absent and remaining sense both possess sufficient capability in the studied function (Bell et al., 2019). For example, improved auditory spatial performance has repeatedly been demonstrated in blind individuals. The studied function, spatial processing, is performed by both vision and audition in individuals with intact sensory abilities, although vision is believed to be dominant for this particular function. Therefore, audition is capable of compensating by enhanced performance in spatial processing when an individual is deprived of visual input. These types of behavioral benefits in individuals with sensory deprivation have been linked to altered use of cortical regions normally dedicated to the processing of the absent sense, which will be further discussed in the following chapter (Collignon, Voss, et al., 2009; Merabet & Pascual-Leone, 2010).

1.4 NEURAL PLASTICITY IN SENSORY DEPRIVATION

Brain plasticity is commonly referred to as the brain's capability to reorganize in response to altered demands (Lindenberger, Wenger, & Lövdén, 2017). Before discussing the cerebral morphological and functional alterations demonstrated as a consequence of complete sensory deprivation, it is important to note that opinions differ about when the term plasticity is appropriate or accurate to use. Is there, for example, a requirement to demonstrate that a physical change, e.g., altered dendritic density, has occurred in response to an event to

accurately claim plasticity? The research topic in this thesis is human olfactory sensory deprivation, a topic that enables exploration of the wide range of functional and structural states the human brain can function in as a result of considerable deviations in sensory input. The vast majority of studies investigating the effects of human sensory deprivation are based on between-group comparisons where individuals with sensory deprivation are compared to individuals with intact sensory functions. Hence, actual demonstrations of plastic reorganization are rarely displayed but instead inferred based on group differences, with atypical results in the sensory deprived group interpreted as signs of the human brain's ability to reorganize based on experienced demands. Because the term plasticity is frequently used in these types of studies, I have used it in this thesis despite recognizing a lack of universal agreement on whether or not plasticity is the correct term to use in reference to the atypical morphology and function demonstrated by individuals with sensory deprivation.

1.4.1 Visual and auditory sensory deprivation

When one of our senses is deprived of all function, a substantial decrease in input to the brain regions normally devoted to the processing of the absent sensory modality naturally follows. In blind and deaf individuals, the lack of sensory input is associated with both functional and structural reorganization of early sensory processing regions of the deprived sense, alterations that at least partially have been linked to the behavioral alterations discussed in the previous chapter.

1.4.1.1 Cross-modal processing

Processing of information from one sensory modality in regions normally thought of as devoted to input from another sense is commonly referred to as cross-modal processing. For example, auditory stimuli in the form of different natural sound environments have been shown to induce activity patterns in the early visual cortex of sighted individuals, and these patterns are specific enough to identify the auditory environment above chance level in a decoding paradigm (Vetter et al., 2020). It could be imagined that these patterns of activation are a result of visual imagery related to the auditory stimuli. However, based on the demonstration that congenitally blind individuals, i.e., individuals who have never had any visual experiences, also show auditory-induced decodable activity in early visual cortical regions, it was concluded that visual imagery could not be the only driving force of the cross-modal processing (Vetter et al., 2020). In fact, processing of input from spared sensory modalities tends to increase in the deprived cortical regions in individuals with visual and auditory sensory deprivation (Bavelier & Neville, 2002; Frasnelli et al., 2011).

Auditory-induced activation of cortical regions traditionally regarded as visual has repeatedly been demonstrated in blind individuals (Bedny, Richardson, & Saxe, 2015; Collignon, Voss, et al., 2009; P. Voss, Gougoux, Zatorre, Lassonde, & Lepore, 2008), and associations between this cross-modal processing and enhanced behavioral performance exist. Potential neural correlates of the enhanced spatial auditory abilities demonstrated by blind individuals was investigated in a positron emission tomography study in individuals with early or congenital

blindness onset (Gougoux et al., 2005). Whereas the sighted control group showed a deactivation in visual cortical regions during auditory spatial processing, the blind individuals did not. Furthermore, a correlation between accuracy on a second spatial auditory task and activation in the right extrastriate (visual) cortex was only found in blind individuals who demonstrated enhanced performance; this association was not present in either blind individuals with normal performance or in sighted controls, thus indicating a relationship between the enhanced abilities and cross-modal neural reorganization. The functional relevance of this cross-modal processing has been further highlighted by the use of repetitive transcranial magnetic stimulation, which has the ability to temporarily disrupt the normal function of a cortical region. Collignon, Lassonde, Lepore, Bastien, and Veraart (2007) showed that the use of transcranial magnetic stimulation to the right extrastriate cortex in individuals performing an auditory spatial task resulted in an increase in error rate for early blind, but not sighted control, participants. They further demonstrated that the cross-modal processing in the extrastriate cortex was functionally specific, because the use of repetitive transcranial magnetic stimulation did not result in any performance alteration in either group for auditory intensity discrimination or auditory pitch discrimination. This suggests that early blind individuals do not only show increased cross-modal auditory processing in the extrastriate cortex, but that the recruitment of this region is functionally specific to auditory spatial processing.

Similar to the behavioral effects of sensory deprivation, cross-modal functional reorganization exists in both individuals with a congenital or very early acquired sensory deprivation and in those with a later-acquired loss. However, also in line with the behavioral effects, there are differences between early and late onset of visual sensory deprivation in the recruitment of visual areas for auditory processing. In a study investigating the processing of auditory pitch and auditory spatial attributes in both congenitally and late-onset blind, a heightened activation in occipital areas was demonstrated in both groups of blind individuals, as compared to a sighted control group (Collignon et al., 2013). Congenitally blind individuals additionally demonstrated a heightened activation, as compared to late blind individuals, in subregions of the visual cortex during auditory processing. These results indicate the important role that early developmental periods have for functional cerebral reorganization.

In addition to the cross-modal processing of auditory stimuli in visual cortex of blind individuals, the visual cortex of blind individuals has also been associated with cross-modal processing of tactile and olfactory stimuli (Araneda, Renier, Rombaux, Cuevas, & De Volder, 2016; Burton, Sinclair, & McLaren, 2004; Frasnelli et al., 2011; Noppeney, 2007). Similar to what is described above, cerebral regions normally devoted to auditory processing are recruited in deaf individuals when performing both visual and tactile tasks (Frasnelli et al., 2011; Merabet & Pascual-Leone, 2010). For cross-modal processing, as for behavioral alterations, it is important to take the effects of acquiring new skills and shifting attention to different senses into account when studying group differences. For example, the attentional shift towards the peripheral visual field in deaf individuals has been ascribed as an effect caused by deafness rather than sign language, as this effect was not evident in hearing signers (see chapter 1.3.3). The lateral attention shift in deaf signers has furthermore been supported using functional MRI.

Compared to hearing signers, deaf individuals demonstrate a greater activation caused by peripheral attention to motion in area MT (a motion sensitive cortical region); in contrast, hearing individuals demonstrated higher activation for centrally attended motion (Bavelier et al., 2001). However, the same study demonstrated that a left hemisphere lateralization in visual motion processing could be attributed to signing, independent of auditory abilities, thereby emphasizing that skill acquisition also has strong effects on cerebral reorganization.

1.4.1.2 Functional connectivity

As discussed above, increased cross-modal processing in cortical regions normally processing an absent sense have been demonstrated in individuals with complete sensory deprivation. This relocation of cerebral processing reveals a lot about sensory deprivation-induced functional reorganization, but is quite specific to the specific stimuli and task(s) used to assess the potential reorganization. By instead assessing brain activity during rest, intrinsic functional connectivity that is unrelated to a specific task can be measured. As might be expected, visual sensory deprivation has been associated with altered functional connectivity within and from visual cortical regions; effects that are evident also in the absence of specific sensory input using resting-state functional connectivity. The functional connectivity between occipital and other sensory regions is decreased in early and congenitally blind individuals (Bauer et al., 2017; Burton, Snyder, & Raichle, 2014; Y. Liu et al., 2007; Yu et al., 2008) and a general decrease in whole brain connectivity has also been reported (Bauer et al., 2017).

More local measures of functional connectivity within the visual cortex are also affected by visual sensory deprivation. The regional homogeneity, an estimate of the functional connectivity between nearby voxels, is higher in blindness than in sighted controls (C. Liu et al., 2011), and this effect is even more pronounced in individuals with congenital than acquired blindness (A. Jiang et al., 2015). In contrast, the homotopic connectivity, i.e., the functional connectivity between corresponding regions in the opposite hemispheres, is reduced (Hou, Liu, Zhou, Zhou, & Li, 2017; Huang, Zhou, Dan, & Shen, 2019). Interestingly, both of these local connectivity measures change during normal development, showing a gradual decrease in regional homogeneity and increase in homotopic connectivity in sensory processing regions (Anderson, Zielinski, Nielsen, & Ferguson, 2014; Zuo et al., 2010). The reported atypical local connectivity in the visually deprived visual cortex represents a deviation from the alterations occurring during development, which suggests that the absence of the expected sensory input disturbs normal functional development.

Intuitively, the decreased connectivity from and within visual regions seems like a natural consequence of the lack of visual input, and it could be speculated that the brain is in need of the anticipated sensory stimuli to develop its intended processing pathways. Interestingly, other studies suggest that some functional networks, like the connectivity within the tonotopic organization of the auditory cortex and retinotopic connectivity in the visual cortex, are intact even in individuals with congenital sensory deprivation (Striem-Amit et al., 2015, 2016). This suggests that although the strength of connections in and from a sensory cortex deprived of its

intended sensory input might be altered, some processing pathways might be hardwired and remain despite substantial alterations in input.

1.4.1.3 Morphology

Sensory deprivation-induced reorganization is particularly apparent in regions normally processing the deprived sense. This is evident for functional processing of sensory input, functional connectivity during rest, as well as reflected in brain morphology. Congenitally blind individuals, as well as those with a later-acquired visual sensory loss, demonstrate gray matter volume atrophy in visual cortical structures, such as primary visual regions (A. Jiang et al., 2015; Noppeney, Friston, Ashburner, Frackowiak, & Price, 2005; Pan et al., 2007; Park et al., 2009; Ptito, Schneider, Paulson, & Kupers, 2008). Counterintuitively, the volumetric atrophy in individuals with a congenital or very early sensory deprivation is combined with an increase in cortical thickness within visual regions (Bridge, Cowey, Ragge, & Watkins, 2009; Park et al., 2009); this increase is not apparent in later onsets of sensory deprivation (J. Jiang et al., 2009; Park et al., 2009). An association between morphological reorganization, cross-modal processing, and behavioral performance has been suggested. For example, enhanced performance on auditory pitch and melody discrimination tasks have been linked to increased occipital cortical thickness in early blind individuals (P. Voss & Zatorre, 2012).

In contrast to the consistent demonstrations of gray matter volume atrophy in occipital regions in both congenital and acquired blindness, gray matter alterations in deaf individuals are less pronounced and highly inconsistent over studies (for a review, see Hribar, Šuput, Battelino, & Vovk, 2020). The most consistent morphological finding in individuals with auditory deprivation is decreased white matter in auditory regions (Hribar et al., 2020; Shibata, 2007).

As is evident from the literature, the auditory and visual systems are plastic and are unquestionably affected by the absence of input from the intended sensory modality, resulting in functional as well as morphological cerebral reorganization. To date, the absolute majority of studies assessing neural plasticity due to sensory loss have explored loss of the visual or auditory sense. Despite the high prevalence of anosmia, the literature on anosmia-dependent neuroplasticity is scarce.

1.4.2 Anosmia

In terms of brain plasticity, morphological studies dominate the literature on anosmia with a special focus on alterations in the olfactory bulb and olfactory sulcus in individuals with congenital anosmia. Complete, bilateral absence of the olfactory bulbs is very common in these individuals (84 % according to Yousem et al., 1996), although hypoplastic olfactory bulbs also exist. In some cases of congenital anosmia, this is accompanied by a complete absence of olfactory tracts (Abolmaali et al., 2002; Yousem et al., 1996). With absent olfactory bulb and tract, the depth of the olfactory sulcus, i.e., the sulcus in which the bulb and tract reside, is either completely absent or, more commonly, significantly decreased (Abolmaali et al., 2002; Huart et al., 2011). This decrease furthermore seems to be specific to the approximate location of the olfactory bulb (if there is one), coinciding with the plane of the posterior tangent to the

eye: no differences in either maximum sulcus depth or sulcus length has been demonstrated between individuals with congenital anosmia and controls (Abolmaali et al., 2002). Although individuals with a later-acquired olfactory sensory loss have smaller olfactory bulb volumes as compared to normosmic controls, with a negative correlation between duration of olfactory loss and bulb volume (Yao et al., 2017), a decrease in olfactory sulcus depth has not been demonstrated (Rombaux, Potier, Markessis, Duprez, & Hummel, 2010). This suggests that alterations in the depth of the olfactory sulci are dependent on early development and not likely to show plastic reorganization throughout the lifespan.

Beyond the olfactory bulb and sulcus, few have studied brain morphology in isolated congenital anosmia. Frasnelli, Fark, Lehmann, Gerber, and Hummel (2013) demonstrated that individuals with isolated congenital anosmia, as compared to controls, have higher gray matter density in the left entorhinal and piriform cortices, regions often referred to as primary olfactory regions. Furthermore, greater cortical thickness in bilateral medial orbitofrontal cortex, a region that is also strongly associated with olfactory processing, was demonstrated. Helena Gásdal Karstensen et al. (2018) also linked isolated congenital anosmia to increases in unilateral piriform cortex, albeit in the opposite hemisphere compared to Frasnelli, and demonstrated decreased gray matter volume in the left olfactory sulcus.

In contrast to congenital anosmia, acquired anosmia has been linked to gray matter atrophy in piriform cortex and in other olfactory-related cortical areas, such as the orbitofrontal cortex, anterior cingulate cortex, and insular cortex (Bitter et al., 2010; Peng et al., 2013; Yao et al., 2014, 2017). It is, however, important to note that many of these results do not show significant overlap between studies. One could speculate that heterogeneity in the cause of olfactory loss and, in some cases, very short durations of sensory deprivation, may contribute to the lack of consistent findings. Support for this theory is that larger atrophy has been shown in individuals with longer duration of olfactory loss (Bitter et al., 2010; Peng et al., 2013).

In blind and deaf individuals, processing of sensory stimuli originating from the spared sensory modalities have been shown in cortical regions normally devoted to processing the lost sense. Whether similar processes take place in olfactory areas as a result of olfactory loss is still an open question, although a handful of studies have tried to assess potential functional alteration and cross-modal processing in anosmia. A decrease in functional connectivity from olfactory regions has been demonstrated by individuals with acquired anosmia, as compared to controls, while performing an odorless sniffing task (Kollndorfer, Jakab, Mueller, Trattnig, & Schöpf, 2015). However, no group difference in functional connectivity strength during the resting blocks between the sniffing blocks were demonstrated. Furthermore, the spatial extent of the olfactory-related network did not differ between groups. These results suggest that the effects of acquired olfactory sensory deprivation on functional connectivity measures are existing, but small.

As for the behavioral studies discussed in the previous chapter, cerebral processing of non-olfactory stimuli in olfactory-deprived individuals have focused on the other chemical senses. Using functional MRI, Gagnon et al. (2014) showed that individuals with congenital olfactory

deprivation did not only demonstrate a decreased ability in bitterness identification, but also a decreased activity in the medial orbitofrontal cortex, a region highly associated with olfactory processing and flavor integration. The decreased trigeminal sensitivity in anosmia (Frasnelli et al., 2010; Gudziol et al., 2001) has, however, not been associated with altered central processing measured by event-related potentials (Frasnelli et al., 2010). However, indications of lower trigeminal induced activation in, e.g., somatosensory regions were demonstrated by individuals with anosmia, compared to controls, using functional MRI (Iannilli, Gerber, Frasnelli, & Hummel, 2007). These results contribute to the idea of an interdependence among the chemical senses, but do not provide evidence for increased cross-modal processing in olfactory regions as a consequence of olfactory deprivation.

1.4.3 Mechanisms of brain plasticity in sensory deprivation

The functional relevance of cerebral morphological reorganization has been demonstrated for a variety of functions, stretching far beyond sensory deprivation. For example, altered brain morphology has been linked to skill acquisition, such as practicing juggling, and intense learning when studying for a difficult exam (Lindenberger et al., 2017). However, despite the relevance of these morphological measures, the underlying cause of the morphological reorganization is not obvious. To infer potential neural processes that form a basis for the morphological and functional reorganization measured with MRI, such as gray matter atrophy or cross-modal processing, is a difficult task. Zatorre, Fields, and Johansen-Berg (2012) emphasizes the importance of remembering that alterations in the gray matter signal captured by T1-weighted MRI (the most commonly used structural MR-images for comparing human cerebral morphology) might not necessarily be caused by neuronal reorganization, as the signal is also influenced by glial cells and vasculature. Zatorre suggests four different mechanisms that could contribute to gray matter alterations captured by MRI: neurogenesis, gliogenesis, vascular changes, and changes in neuronal morphology. While neurogenesis might not be a strongly contributing mechanism beyond hippocampus (Zatorre et al., 2012), alterations in neuronal and synaptic morphology have been used as a potential explanatory mechanism for the counterintuitive increases in cortical thickness demonstrated in regions associated with the absent sense in both congenitally blind individuals and individuals with congenital anosmia (J. Jiang et al., 2009; Park et al., 2009; Frasnelli et al., 2013). The hypothesis is based on the idea that complete sensory deprivation early in life interrupts the normal synaptic pruning during development: an overgrowth of synapses early in life is normally compensated for by a later selective pruning, sparing only the most relevant connections. The lack of appropriate input from the intended sensory modality, as is the case for congenital or very early sensory deprivation, would likely disrupt this process. Furthermore, because no input is received from the normally dominant sense in early sensory processing regions of the deprived sensory modality, input from spared sensory modalities might play a more important part during this process. Hence, synapses that might have been redundant and therefor eliminated in the presence of input from the intended sense might be spared, forming a basis for the strong cross-modal processing (Park et al., 2009).

Synaptic overgrowth and pruning is a sign of a highly plastic period early in life. As discussed in the previous chapter regarding behavioral plasticity, these periods are often referred to as critical- or sensitive periods and are highly relevant for normal development of the brain, and thereby also our behavior. Critical periods in sensory development are supported by prominent studies by Wiesel and Hubel, demonstrating that visual deprivation during the first few months of a kitten's life severely affects cerebral morphology and connections (Hubel & Wiesel, 1970; Wiesel & Hubel, 1965). Following restoration of visual input after an early period of deprivation, the number of cells responding to visual input were decreased and often demonstrated abnormal responses. Only slight behavioral recovery was demonstrated; however, deprivation in adult cats did not show these striking effects. The importance of sensory input for cortical organization during this early period in life has also been demonstrated in humans. A brief period of visual deprivation early in life, caused by congenital cataracts treated between day 9 and 238, is associated with enhanced cross-modal auditory processing in visual regions lasting decades after the deprivation (Collignon et al., 2015). The start and duration of these periods that are critical or highly sensitive for normal development differ for different functions, such as language acquisition, and different sensory modalities (Hensch, 2004).

Importantly, cerebral reorganization occurs also in sensory deprivation acquired later in life, confirming neuroplasticity also beyond early sensitive periods (Castaldi, Lunghi, & Morrone, 2020). In fact, even very short-term alterations of sensory input have been demonstrated to alter cortical activity. Restriction of the use of the dominant arm, induced by casting, caused decreased functional connectivity from somato-motor regions responsible for the disused arm, as well as spontaneous activity pulses in these deprived regions (Newbold et al., 2020). Short-term visual sensory deprivation induced by blindfolding, combined with intense Braille reading training, has been linked to tactile cross-modal recruitment of visual cortex during the course of only a few days (Merabet et al., 2008). The recruitment of visual cortex was furthermore linked to Braille reading performance, a recruitment not observed in a non-blindfolded control group. Furthermore, a seven day period of olfactory deprivation, induced by occlusion of the nostrils, caused reversible alterations in in odor-evoked activity in both piriform and orbitofrontal cortex (Wu, Tan, Howard, Conley, & Gottfried, 2012). These drastic alterations after only days of altered input indicates that functional alterations, or cross-modal processing, are likely not based principally on a rewiring of the brain, but rather altered use of already existing connections. It has been argued that the cross-modal "takeover" of regions normally processing a deprived sensory modality is a consequence of a brain organization that is task-selective, rather than sensory-selective (Amedi, Hofstetter, Maidenbaum, & Heimler, 2017). In other words, brain regions are functionally specialized, not primarily sensory specific. This implies that if an individual is deprived of all input from the sensory modality that provides the most relevant information for a specific function, the brain region will continue to perform this function with input from spared senses, given that the spared senses can provide suitable information. The idea of task-selectivity lines up with the previously discussed argument that

enhanced (compensatory) performance in spared senses is contingent on both the spared and the absent sense having the ability to perform the studied function (Bell et al., 2019).

The behavioral and neuronal reorganizations originating from sensory deprivation that have been discussed thus far are mainly focused on the processing of remaining sensory modalities presented unimodally. This has been the main focus in studies on cross-modal reorganization in sensory loss. However, outside a controlled experimental environment, individuals are constantly bombarded with input to all of our intact senses. The discovery of important aspects of behavioral and cortical reorganization following sensory loss may be impaired by the very controlled approach of studying unisensory stimuli one sensory modality at a time.

1.5   MULTISENSORY INTEGRATION

Our senses are individually optimized for the collection of different types of information, each with its own distinct physical qualities. This limits their processing to specific aspects of the world. It is very likely, however, that a single object or event will give rise to different types of sensory signals, each compatible with our various sensory receptors. Combining these signals, which often contain both complementary and overlapping information, rather than treating them as separate entities, is beneficial for obtaining an improved and more holistic percept of our surroundings. Furthermore, as we are constantly bombarded with a stream of information from all of our senses, processing all inputs as equally important would require considerable resources. Instead, it is advantageous to let information from our different senses inform each other to guide attention towards events from which temporally, spatially, and semantically congruent information stems.

1.5.1   Behavioral multisensory integration

The interaction of information from different sensory modalities results in a response significantly different from the unimodal components and is often referred to as multisensory integration (Barry E Stein & Rowland, 2011). Multisensory integration can lead to significantly enhanced perception, as indicated by improved accuracy, detection, and response time in behavioral tasks when presented with bimodal, as compared to unimodal, information (Stevenson, Ghose, et al., 2014). Both on a behavioral and neural level, multisensory integration is dependent on the *spatial* as well as *temporal* proximity of the stimuli, with increased probability of integration effects if the components of bimodal input stem from the same location in space and reach us simultaneously (Murray, Lewkowicz, Amedi, & Wallace, 2016; B E Stein & Stanford, 2008). If the relative location or timing differs too much between the two stimuli, they are processed as two separate events instead of being integrated. However, if there is only a certain degree of spatial or temporal discrepancy between the stimuli, the input is integrated and produces a percept of a single event. This can be demonstrated using experimental paradigms inducing perceptual illusions based on the integration of auditory and visual stimuli. By manipulating the spatial distance between an auditory and visual signal presented simultaneously, the auditory signal is perceived as stemming from the same location as where the visual signal appears which produces the well-known ventriloquism effect (Jack

& Thurlow, 1973; Jackson, 1953). In contrast, when manipulating temporal aspects of the stimuli, by presenting two or more auditory stimuli in form of short beeps, while only presenting one visual stimuli in form of a bright flash, many perceive two visual flashes (Shams, Kamitani, & Shimojo, 2000). In addition to the temporal and spatial rules of multisensory integration, the semantic content of information in the unimodal stimuli is important for the integration. Note that *semantic congruency* in multisensory integration refers to the stimulus contents related to the object or event that emits the multisensory signal. For example, a semantically congruent multisensory stimulus would be seeing a dog while hearing a bark. Semantically congruent multisensory stimuli lead to enhanced performance, whereas incongruent stimuli lead to decreased performance (Chen & Spence, 2017; Laurienti, Kraft, Maldjian, Burdette, & Wallace, 2004). An common example of a multisensory illusion based on the integration of semantic information is the so-called McGurk effect, in which incongruent speech stimuli (visual: lips miming "ga"; auditory: a vocalization of "ba") result in an integrated perception that differs from the two stimuli ("da"; Mcgurk & Macdonald, 1976). The integration of multisensory stimuli also follow the *principle of inverse effectiveness*. This principle states that the weaker the information from the unisensory stimuli are, the stronger is the effect of multisensory integration (Barry E Stein & Meredith, 1993; Barry E Stein & Rowland, 2011). This originates from the fact that sensory input from different sensory modalities are affected by different types of noise. By combining the sensory input, a more reliable separation of signal and noise can be achieved. Reversely, if the information in one sensory modality is strong and reliable, there is little need for additional information and no significant behavioral benefit would be expected as a result of multisensory information.

Our ability to integrate multisensory information is innate in the sense that a human is born with a brain that is capable of processing multiple senses in intertwined processing pathways and that contains neurons with multisensory qualities (further discussed below). However, what we integrate is strongly dependent on our sensory experiences (Murray et al., 2016). For example, cats raised in an environment where visual and auditory stimuli were presented simultaneously but always at a set relative distance demonstrate a shift in the receptive fields of multisensory neurons (Wallace & Stein, 2007). In humans, the influence of sensory experiences on multisensory integration can be exemplified by the so-called temporal binding window, the limited span of temporal asynchronies between stimuli for which the stimuli are perceived as simultaneous. The audio-visual temporal binding window narrows during development (Chen, Shore, Lewis, & Maurer, 2016; Hillock-Dunn & Wallace, 2012) and typically demonstrates a more pronounced narrowing when an auditory stimulus is presented before a visual than the other way around (Cecere, Gross, & Thut, 2016; Hillock, Powers, & Wallace, 2011). This is a natural consequence of light travelling faster than sound, resulting in external event yielding auditory sensory input that reaches us after the visual input. However, our integration abilities do not only develop during early life but have also been demonstrated to be flexible during adulthood (Murray et al., 2016; Powers, Hillock, & Wallace, 2009; Barry E Stein & Rowland, 2011), with the potential of being influenced by strong sensory alterations such as sensory deprivation.

Spatial rule – Multisensory integration is dependent on the spatial proximity of the unisensory stimuli.

Temporal rule – Multisensory integration is dependent on the temporal proximity of the unisensory stimuli.

Semantic congruency – Multisensory integration is dependent on the congruency of the semantic content of the unisensory stimuli.

Principle of inverse effectiveness – The effects of multisensory integration are greater when the sensory information provided by the unisensory stimuli is weak.

Superadditivity – Superadditivity is a measure of multisensory integration originating from single cell recording, which states that the response to multisensory stimuli must exceed the summed responses to the individual unisensory stimuli. Superadditivity is sometimes used in fMRI analysis, although effects are rarely discovered due to areal convergence of multisensory and unisesnory neurons.

Maximum criterion – The maximum criterion, sometimes referred to as multisensory enhancement, states that the response to multisensory stimuli must exceed the largest response to the individual unisensory stimuli. The maximum criterion is commonly used for measures of accuracy and reversed response time (i.e. the response to multisensory stimuli must be faster than the fastest response to unisensory stimuli). In fMRI analysis, the maximum criterion is commonly applied, although a significant effect cannot strictly differentiate between multisensory integration and multisensory processing.

1.5.2 Neural multisensory processing

The neural basis for our ability to integrate stimuli lies in the multisensory neurons' specific responses to multisensory, as compared to unisensory, input. The earliest studies of these multisensory neurons were based on neurons in the cat superior colliculus, a midbrain region receiving visual, auditory, and somatosensory input. By measuring neuronal responses when presented with auditory, visual, and audio-visual stimuli, Meredith and Stein (1983) identified neurons with response profiles to audio-visual stimuli that could not be predicted by the responses to unimodal auditory and visual stimuli. The interaction of the auditory and visual input in these multisensory neurons yielded both response enhancements and depressions, and showed a dependence on the respective timing of the presented stimuli. Based on this seminal work, subsequent studies have demonstrated the same characteristics in multisensory neurons within different brain structures in multiple species (Stevenson, Ghose, et al., 2014).

Whereas the identification of multisensory neurons has primarily been done using single-cell recordings, often in the cat superior colliculus (Barry E Stein & Rowland, 2011), identification of multisensory cerebral regions in humans have depended mainly on neuroimaging techniques, such as functional MRI. However, the characterization of multisensory integration using fMRI is not as straight forward as the direct measure provided by single-cell recording. The problem with assessing multisensory integration using fMRI stems mainly from the low spatial resolution of the technique, which results in huge populations of neurons included in each voxel. Because multisensory and unisensory neurons are mixed in the brain (Stevenson, Ghose, et al., 2014), the signal captured in one voxel stems from a combination of multisensory and unisensory neurons even in typically multisensory brain regions. Different approaches to statistically characterize multisensory integration using fMRI exist, but two common approaches are the criterion of *superadditivity* and the *maximum criterion*. While the criterion of superadditivity is quite strict, requiring the multisensory response to be greater than the sum of the individual unisensory responses, the maximum criterion is more lenient and requires the multisensory response to be significantly greater than the largest of the individual unisensory responses (Calvert & Thesen, 2004; B E Stein & Stanford, 2008; Stevenson, Ghose, et al., 2014). While the maximum criterion detects signals that are multisensory, in the sense that input from both senses are causing the signal, it is not able to distinguish whether there is a mere areal convergence of auditory and visual neurons in the measured voxel or whether there is, in fact, multisensory integration. In contrast, by requiring superadditivity, the multisensory signal must be larger than the sum of the unisensory signals, and thereby identifies an interaction. However, based on the areal convergence of different types of neurons, this is a very conservative criterion that often cannot be fulfilled, even in known multisensory regions. For example, to assess the effect of different statistical criteria for multisensory integration in fMRI, Beauchamp (2005) used an experimental paradigm with auditory, visual, and audio-visual stimuli. The results of different multisensory integration criteria were assessed based on the use of a significant integration effect in the superior temporal sulcus as a performance measure due to the region's established role in audio-visual integration. Although the maximum criterion classified the superior temporal sulcus as a region of audio-visual integration, the criterion of superadditivity failed to demonstrate significant effects. This was interpreted as support of the notion that superadditivity is a less appropriate criterion when working with fMRI data. Still, studies finding superadditive multisensory effects using fMRI exist (Calvert, Hansen, Iversen, & Brammer, 2001). Despite the complication of areal convergence and statistical criterion for defining multisensory integration in data originating from neuroimaging methods, these methods have contributed extensively to a better understand of the processing and integration of multisensory stimuli in the human brain. In addition to the superior colliculus, the classical multisensory regions are located in posterior parietal cortex, superior temporal cortex, and prefrontal cortical regions; specifically, the intraparietal sulcus and the superior temporal sulcus have repeatedly been implicated in integration of auditory, visual, and tactile information (Ghazanfar & Schroeder, 2006; B E Stein & Stanford, 2008; Thesen, Vibell, Calvert, & Österbauer, 2004). The intraparietal sulcus and superior temporal

sulcus have furthermore been implicated in the integration of olfactory and visual stimuli (Gottfried & Dolan, 2003; Regenbogen et al., 2017).

Although brain regions strongly linked to integration of input from multiple sensory modalities exist, the brain is not divided into strictly uni- and strictly multisensory cortical regions. Rather, in line with the task-selective organization of the brain discussed in chapter 1.4.3, the brain could be considered as a more interactive network in which sensory interactions can take place even in cortical regions traditionally considered as unisensory (Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007; Murray et al., 2016; B E Stein & Stanford, 2008; Thesen et al., 2004). The cross-modal input to sensory cortices that forms a basis for early sensory integration likely contributes to the often increased cross-modal processing within deprived sensory regions in individuals with sensory deprivation (Lee & Whitt, 2015). In addition to the increased cross-modal processing, sensory deprivation has been linked to increased processing of the spared senses in multisensory regions (Bavelier & Neville, 2002; Merabet & Pascual-Leone, 2010). The literature on how sensory deprivation affects the integration of remaining sensory modalities is, however, still sparse.

1.5.3 Multisensory integration in sensory deprivation

When investigating the effect of sensory deprivation on the integration of input from the spared sensory modalities, we once again return to the question of whether sensory deprivation is associated with perceptual deficits or with compensation, i.e., are all senses needed to facilitate sensory integration or could the absence of a sense facilitate the integration of remaining senses, hence leading to compensatory performance.

There are only a handful of studies investigating multisensory integration of spared sensory modalities in individuals with complete sensory deprivation, and their results do not provide a straight-forward answer to the question of deficit versus compensation. The majority of these studies investigate audio-tactile integration in individuals with visual sensory deprivation. In a study by Collignon, Charbonneau, Lassonde, and Lepore (2009), early blind, late blind, and sighted control participants performed a lateralization task based on auditory, tactile, and audio-tactile stimuli. Overall, early blind individuals demonstrated an improvement in performance as compared to sighted controls. However, compared to both sighted controls and late blind individuals, early blind individuals demonstrated weaker integration effects, i.e., lower benefits from the integration of auditory and tactile information. The weak integration effects were particularly evident in an experimental condition where their arms had to be crossed, interpreted as a problem in aligning the internal (tactile) and the external (auditory) frames or reference in early blind individuals due to the lack facilitation of alignment provided by visual input. In line with these results, it has been suggested that congenitally and early blind individuals are better than sighted individuals in separating sensory streams; they demonstrate enhanced performance in multimodal tasks when attending to one modality while the other modality acts as a distractor, but they perform worse when the task requires the integration of senses (Occelli et al., 2013). For example, congenitally blind individuals were less prone than sighted controls to be fooled by task-irrelevant auditory stimuli in a tactile task (Hötting &

Röder, 2004). It should be noted, however, that the blind individuals also demonstrated enhanced performance in a control condition without the auditory distraction, suggesting that the ability to separate sensory streams might not be the main reason for enhanced performance on the distraction task. Based on the rule of inverse effectiveness, smaller benefits from multisensory integration are to be expected with enhanced unisensory performance. Hence, potential unisensory performance enhancements in sensory deprived individuals should be taken into account when evaluating the effect of sensory deprivation on multisensory integration. Analogous with a potential separation of sensory streams are findings that blind individuals are less prone to be deceived by multisensory illusions. For example, while sighted controls did perceived an audio-tactile illusion wherein the tactile perception is altered based on auditory frequency, neither early nor late blind individuals could perceive the illusion (Champoux et al., 2011). Blind individuals have furthermore demonstrated a resistance to the somatic rubber hand illusion, in which blindfolded sighted participants erroneously perceive that they are touching their own right hand with their left index finger, when they in fact are touching a rubber hand; an illusion that can occur if the participant's right hand is being touched in a manner synchronized with the participant's touching of the rubber hand (Petkova, Zetterberg, & Ehrsson, 2012). In contrast to the decreased interaction of bimodal stimuli in blind individuals, deaf individuals have demonstrated increased merging of sensory input. Early deaf individuals performing a task with visuo-tactile stimuli, asked to either focus on the visual stimulus with the tactile stimulus acting as a distractor, or on the tactile stimulus with vision as a distractor, demonstrated increased interference of the visual distractor on tactile performance, as compared to hearing controls (Heimler, Baruffaldi, Bonmassar, Venturini, & Pavani, 2017). This was interpreted as a visual dominance in visuo-tactile integration. However, congenitally deaf individuals have also demonstrated increased susceptibility to a touch-induced double-flash illusion that hearing controls do not perceive, which contradicts a visual dominance (Karns, Dow, & Neville, 2012). In contrast to these studies, which support increased sensory interaction in deaf individuals, Hauthal, Debener, Rach, Sandmann, and Thorne (2014) showed that congenitally deaf individuals demonstrated decreased visuo-tactile integration based on response times in a stimulus detection task compared to hearing controls, although significant integration effects were present in both groups. Based on the discrepancies in multisensory integration performance between blind and deaf individuals, as well as discrepancies within the groups, the effects of sensory deprivation on multisensory integration still need to be established.

2 RESEARCH AIMS

The general aim of this thesis was to investigate how complete olfactory sensory deprivation (anosmia) affects neural organization and remaining sensory perception. In four separate studies, we assessed brain structure, functional connectivity, and potential compensatory abilities in form of multisensory integration of audio-visual stimuli.

2.1 STUDY I

The aim of Study I was to assess whether individuals with anosmia demonstrate altered abilities to integrate audio-visual stimuli in two integration tasks: one task assessing the ability to perform temporal-specific sensory integration, and one task assessing multisensory integration of degraded stimuli based on the principle of inverse effectiveness.

2.2 STUDY II

The aim of Study II was to determine whether individuals with isolated congenital anosmia demonstrate atypical cerebral gray matter morphology beyond the olfactory bulb.

2.3 STUDY III

The aim of Study III was to assess potential effects of isolated congenital anosmia on the functional connectivity between core olfactory regions and within primary olfactory regions during rest

2.4 STUDY IV

The aim of Study IV was to determine whether the cerebral processing and integration of audio-visual stimuli is affected by lifelong olfactory sensory deprivation in individuals with isolated congenital anosmia, and in particular, if these potential effects are present in form of cross-modal processing in olfactory cortical regions or in established cortical multisensory integration regions.

3 MATERIALS AND METHODS

3.1 PARTICIPANTS

From the outset, I want to highlight the fact that the individuals with anosmia participating in the studies in this thesis are *not* a patient group. Individuals with olfactory sensory deprivation were not recruited from healthcare facilities, but rather volunteered for participation in these studies by contacting us, often after learning of our research through different media channels or by word of mouth.

Study I included a total of 74 individuals: 37 individuals with anosmia and 37 matched controls. **Study II-IV** are all part of the same data collection, hence included the same 68 individuals: 34 with anosmia (one removed from all analyses due to deviating anatomy) and 34 matched controls. In **Study I**, a combination of individuals with isolated congenital anosmia (N=25) and acquired non-traumatic anosmia (N=12; minimum duration of olfactory deprivation: 22 months) were included, whereas **Study II-IV** solely studied isolated congenital anosmia. In **Study II-IV**, inclusion in the isolated congenital anosmia group was based on self-reported lifelong inexperience of olfactory perception without any history pointing toward possible known causes of the anosmia, such as head trauma or endocrine problems. Furthermore, structural MR-scans confirmed either a complete bilateral lack of olfactory bulbs (27 out of the 34) or very small or an undeterminable presence of bulbs due to the limited spatial resolution of the images (7 of the 34). No individual possessed a clear presence of an olfactory bulb. Due to the rarity of isolated congenital anosmia, participants in **Study II-IV** were recruited and participated at two different sites: Stockholm, Sweden (46 participants), and Wageningen, the Netherlands (22 participants). Importantly, the matched control for an individual with anosmia was always recruited at the same site.

Control participants for Study **I-IV** were recruited via a testing recruitment system (ki-behavioraltesting.sona-systems.com) and by word of mouth. They were individually matched to participants with anosmia in terms of age (± 3 years), sex, and approximate educational level. Control participants reported normal olfactory abilities whereas the individuals with anosmia reported a lack of any sense of smell. Their reported olfactory (dis)abilities were confirmed using the Sniffin' Sticks olfactory test (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). Specifically, the cued odor identification subtest was used in **Study I**, and the complete test consisting of odor detection threshold, quality discrimination, and cued identification subtests were used in Study **II-IV**. All participants reported normal or corrected to normal visual and auditory abilities; in **Study I**, inclusion was furthermore dependent on normal performance on Snellen's visual acuity test (Snellen, 1862) and a computerized version of the whispered voice test (Pirozzo, Papinczak, & Glasziou, 2003). **Study II-IV** included screening for any contradictions to participating in an MRI-based study. Participants were naive to the hypotheses of the studies but aware that they participated either as a part of a control group or based on their condition (anosmia).

3.2 OLFACTORY TESTING

As discussed in chapter 1.2, subjective perceptions of one's own olfactory ability often do not correspond well with objective measures (Murphy et al., 2002; Oleszkiewicz et al., 2020; Temmel et al., 2002). Therefore, the inclusion of an objective measure of olfactory ability was an important control for the self-report of normal (control groups) or absent (anosmia groups) olfactory abilities.

Although a variety of different olfactory tests exist, many of the frequently used tests are based on similar premises: odor identification with alternatives. The University of Pennsylvania Smell Identification Test (UPSIT; Doty, Shaman, Kimmelman, & Dann, 1984), the Scandinavian Odor Identification Test SOIT; (SOIT; Nordin, Brämerson, Lidén, & Bende, 1998), and the odor identification subset of the Sniffin' Sticks (Hummel et al., 1997) are all commonly used, validated odor identification tests. It is, however, important to be aware of the fact that using only identification tests can be problematic as these tests cannot always separate olfactory ability from cognitive function (e.g., lacking the ability to name the odor) or from previous experiences (the test requires the odors to be familiar to the participant in order to be recognized and identified). More problematic, from a clinical perspective, is the fact that identification tests might be unable to isolate individuals with moderate hyposmia due to the fact that the suprathreshold intensity of the odors can make it difficult to detect lowered olfactory sensitivity. On the other hand, identification tests do sufficiently detect the complete inability to sense odors. To have a more precise estimate of an individual's olfactory abilities, a test battery including multiple types of measures would be preferable. Nonetheless, it should be noted that the completion of more extensive olfactory testing is a very time demanding procedure and is therefore not often used in larger population studies.

The studies included in this thesis used the Sniffin' Sticks testing battery (T Hummel et al., 1997), with the cued odor identification subtest in **Study I** and the complete battery consisting of odor detection threshold, discrimination, and identification in **Study II-IV**. In the olfactory tests, odors are delivered using felt-tip pens, so called Sniffin' Sticks. The threshold test consists of successive three-alternative forced-choice tasks. The participant is presented with three pens in succession, one pen containing an odor and two odorless, and is instructed to identify the odor-containing pen. A total of 16 different concentrations of the same odor (n-butanol, in this thesis) are included in the test, and a staircase procedure with seven reversals is used to determine the participant's detection threshold. In short, starting from the lowest concentration, pens containing increasing concentrations are presented until two subsequent correct identifications of the pen containing an odor are performed; the staircase is then reversed and decreasing concentrations are presented until an incorrect identification is made, which triggers another reversal of the staircase. The final threshold is defined as the mean of the four last reversals, with a minimum score of 1 and maximum of 16.

A three-alternative forced-choice test was also used for the odor quality discrimination test. Three pens containing odors of the same intensity are presented, but two pens contain the same odor and a third pen contains a different odor quality. The participant's task is to identify the

deviating pen. The discrimination task includes 16 sets of pens, yielding a score between 0 and 16. Importantly, during both the threshold and discrimination tests, the participant is blindfolded, and the pens within each triplet are presented in a randomized order.

For the cued odor identification test, 16 pens are used to present 16 different odors that should all be familiar. The participant is asked to identify the odor from four written alternatives, yielding a score ranging from 0 to 16. The summarized score from all three subtests, often shortened to 'TDI score', ranges from 1-48. Normative data are used as a basis of determining whether an individual's ability should be classed as normosmia, hyposmia, or functional anosmia. In the studies included in this thesis, classification was based on normative data from over 3000 subjects (Thomas, Kobal, Gudziol, & Mackay-Sim, 2007). Since then, an updated version of the normative data based on over 9000 subjects has been published (Oleszkiewicz, Schriever, Croy, Hähner, & Hummel, 2019). The most recent normative data confirms the previously presented TDI scores separating the different classes, as they are essentially the same in this larger sample.

3.3 MULTISENSORY INTEGRATION: EXPERIMENTAL STIMULI AND ANALYSIS OF PERFORMANCE

Study I and **Study IV** assessed behavioral and neural aspects of multisensory integration, respectively. Both studies were based on established audio-visual integration paradigms. Specifically, two different experimental paradigms were used to assess behavioral performance of audio-visual integration in **Study I**: a simultaneity judgement task to assess the audio-visual temporal binding window, and an object identification task using dynamic, degraded stimuli to assess multisensory enhancement, i.e., performance enhancement when presented with bimodal, as compared to unimodal, stimuli. **Study IV** assessed multisensory processing and multisensory integration using an object identification task similar to the one in **Study I** and based on the same stimulus set.

3.3.1 Temporal binding window

Temporal congruency is one of the basic principles of multisensory integration (see chapter 1.5.1). Congruency perception is commonly assessed using simple perceptual audio-visual stimulus pairs presented at different temporal asynchronies (or simultaneously). The participant is either instructed to judge the perceived simultaneity (i.e., are the auditory and visual stimuli presented simultaneously or not?), as was done in **Study I**, or the presentation order (i.e., was the auditory or visual stimulus presented first?). The outcome measure of interest commonly derived from these types of experimental paradigms is the temporal binding window, defining the span of temporal asynchronies between the two stimuli during which they are perceived as having been presented simultaneously. The temporal binding window typically narrows during development (Chen et al., 2016; Hillock-Dunn & Wallace, 2012) whereas a widened temporal binding window has been associated with clinical conditions such as autism spectrum disorders and schizophrenia (Stevenson, Siemann, et al., 2014; Wallace & Stevenson, 2014).
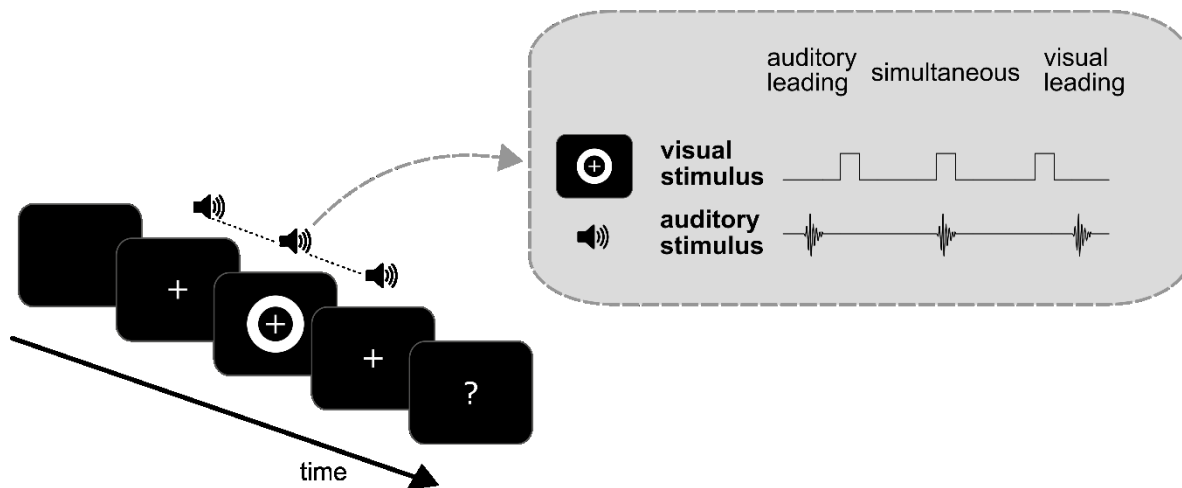
Figure 4 Simultaneity judgement task used in Study I. An auditory stimulus in the form of a short beep was presented either before, simultaneously with, or after a visual stimulus in the form of a flash (white circle presented on the screen). The participant was asked to judge whether the auditory and visual stimuli were presented simultaneously or not. Figure adapted from Figure 1 in Study I.

In **Study I**, the visual stimulus was presented as a flash in form of a white circle, and the auditory stimulus was a short beep (Figure 4). The stimuli were presented simultaneously or at stimulus onset asynchronies ranging from -300 ms (auditory stimulus presented before visual) to +300 ms (visual stimulus presented before auditory). Stimulus presentation was followed by a 2000 ms response period. Because of the extreme importance of accurate temporal stimulus presentation in this experiment, temporal precision was confirmed by measuring stimulus presentation with a photodiode on the screen and the auditory signal spectra using Powerlab (ADInstrument, Colorado Springs, CO).

In line with previous studies, the audio-visual temporal binding window was derived by fitting a Gaussian function to each participant's simultaneity perception data and defining the temporal binding window as the span of asynchronies during which the perception of simultaneity was at least 75% of the individual's peak simultaneity perception (Hillock et al., 2011; Hillock-Dunn & Wallace, 2012; Powers et al., 2009; Stevenson, Siemann, et al., 2014). Group differences in temporal binding window width were assessed with Welch's *t*-tests, to account for potential differences in variance.

3.3.2 Object identification tasks

In **Study I and IV**, dynamic audio-visual stimuli were used to assess multisensory integration performance and processing. Specifically, 2 s long matching audio and video clips depicting four common objects were used: wood fire, popcorn, flopping fish, and lawn mower (obtained from www.shutterstock.com). All four objects were used in **Study I**, whereas a subset of three (wood fire, flopping fish, lawn mower) were used in **Study IV** due to experimental constraints.

In **Study I**, the multisensory object identification task was preceded by an individual thresholding procedure during which noise was added to the stimuli (visual salt and pepper noise, auditory pink noise). The degrading of the stimuli was done to optimize inverse effectiveness (see chapter 1.5.1). The thresholding procedure is described in detail by

Regenbogen et al. (2018; 2016). In short, an adaptive staircase procedure was used for auditory and visual objects separately, aiming for 75 % identification accuracy for each unimodal object.
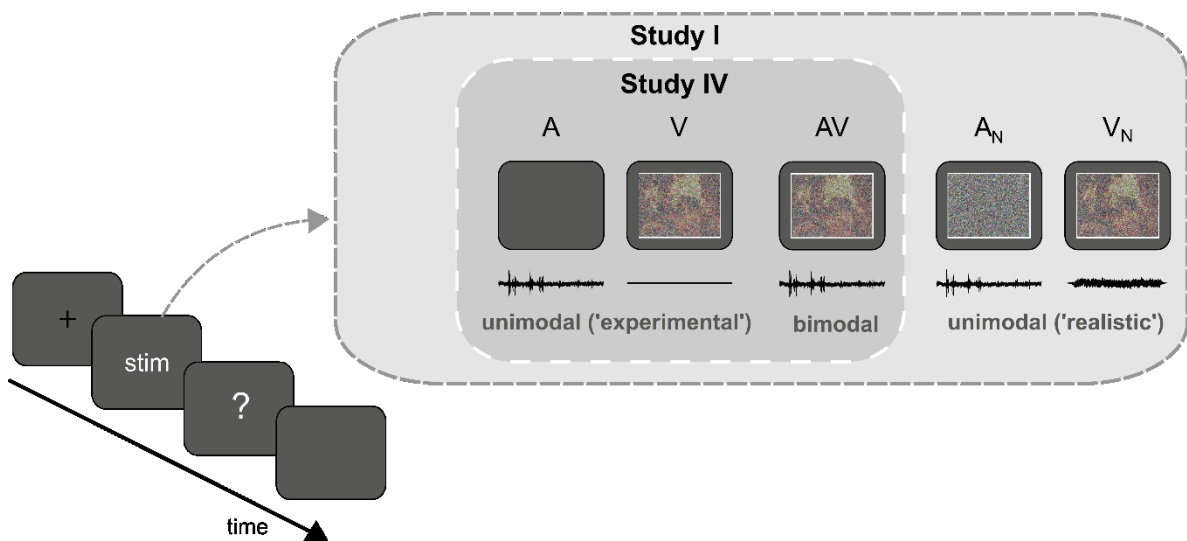

Figure 5 Object identification task used in Study I and IV*. Matching, degraded audio and video clips were presented either unimodally (auditory or visual object) or biomodally (audio-visual object). The participant was asked to identify the presented object based on options (the included object and the alternative "nothing"), here indicated with a question mark. A speeded response task was used in **Study I**, where participant pressed a response key during object presentation; the participant had to wait for stimulus presentation to finish before responding in **Study IV**. All five stimulus combinations depicted were used in **Study I**. That includes bimodal object presentation and two versions of unimodal object presentation: unimodal 'experimental' with only audio or video clip, and unimodal 'realistic' with audio or video clip combined with noise in the uninformative sensory modality. In **Study IV**, only the completely unimodal ('experimental') and bimodal stimuli were used. A = auditory, V = visual, AV = audio-visual, A_N = auditory with visual noise, V_N = visual with auditory noise. Figure adapted from Figure 3 in **Study I** and Figure 1 in **Study IV**.*

In the object identification task used in **Study I,** the individually degraded audio and video clips were presented either uni- or bimodally (Figure 5). Specifically, two different versions of unimodal object presentations were used. The individually degraded clips were either presented in combination with pure noise (visual salt and pepper noise, auditory pink noise) in the other modality, e.g., auditory flopping fish combined with 100 % visual salt and pepper noise, or presented completely unimodally, i.e., without anything presented in the other modality (Figure 5). The intention of the first ('realistic') version was to present the objects in a bimodal setting, making it more ecologically valid and minimizing the difference in sensory load between the bimodal and unimodal condition (Regenbogen et al., 2016). The second ('experimental') unimodal version is the more commonly used experimental approach when studying multisensory integration, comparing bimodal to completely unimodal stimuli. The participants performed a speeded response task in which they were asked to press the assigned response key during object presentation as soon as they could identify the presented object. This interrupted the object presentation and the participant was thereafter asked to identify the object. Individual performance was assessed and compared between the groups based on the performance-linked measure of drift rate from a drift diffusion model (see chapter 3.3.3). Specifically, multisensory enhancement in drift rate was assessed for both the 'realistic' and 'experimental' setting according to

$$v_{AV} - \max(v_A, v_V)$$

where v_{AV} is the drift-rate for audio-visual objects, v_A the drift-rate for auditory object, and v_V the drift-rate for visual object. The multisensory enhancement measure depicts the increase in drift rate when presented with audio-visual information compared to the best performance when presented with unimodal information. Group comparisons of multisensory enhancement were done using Welch's *t*-tests.

A simplification of the object identification tasks used in **Study I** and in the studies by Regenbogen et al. (2018, 2016) was used in **Study IV**, to better fit a functional MRI study aimed to determine potential group differences in cerebral multisensory processing (Figure 5). Specifically, stimuli with the same level of noise were presented to all participants (no individual thresholds were obtained) and unimodal object stimuli were presented unimodally (without noise in the other modality, referred to as the 'experimental' setting in **Study I**). This way, the number of trials per individual could be increased. Because the aim of **Study IV** was to investigate processing rather than performance, the statistical analysis of performance was limited to descriptive statistics of overall accuracy and response per group. For analysis of processing, see chapter 3.4.2.

3.3.3   Drift diffusion model

A drift diffusion model is a model of cognitive decision making developed for binary decision tasks, but has also proven useful in modelling multiple choice data (Ratcliff, 1978; A. Voss, Nagler, & Lerche, 2013). In short, the two alternatives in a binary decision task, or the accurate and inaccurate decision in a multiple choice task, are represented as an upper and a lower decision boundary (Figure 6). The model is based on the assumption that noisy information is continuously collected during the task until a decision boundary is reached and a decision is made. The variables in the drift diffusion model represent different processes. The variable of interest in **Study I** is the drift rate, which is the speed at which the correct decision boundary is reached, i.e., the speed of information uptake, mapping performance, or task difficulty. Threshold separation is the separation between the decision boundaries and is linked to decision style, where a larger separation indicates that an individual requires more evidence to make decision. The non-decision time maps processes such as response execution, and bias indicates whether there is a response bias towards one of the two alternatives in a binary decision task. Bias is not applicable when modelling accuracy data, as it would model a bias towards a correct or incorrect decision.
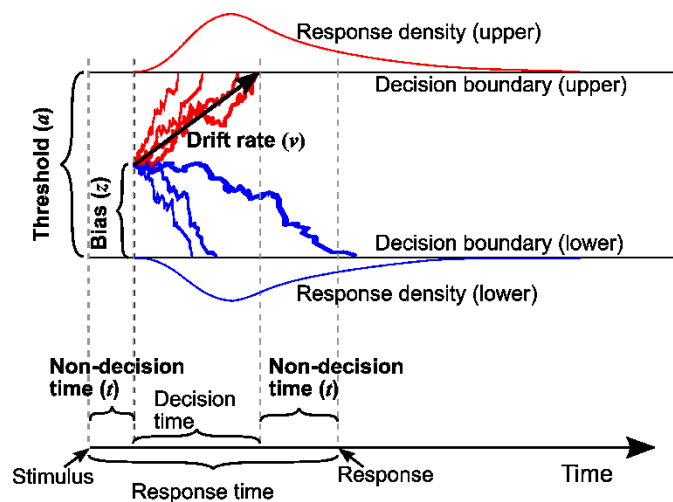
Figure 6 Overview of a drift diffusion model. *In a decision task, noisy evidence is continuously collected with an average drift rate v until a decision boundary is crossed and a decision made. The upper and lower decision boundaries (separated by threshold a) represent either the two decisions in a binary decision task or the accurate and inaccurate decision when modelling multiple choice data. The bias z represents the starting point of the decision process. The time between stimulus presentation and response during which no evidence is collected, such as response execution, is modelled by the non-decision time t. Figure corresponds to Figure 4 in* **Study I.**

By using a drift diffusion model rather than directly assessing accuracy or response time as the outcome measure in the object identification task in **Study I**, the inherent trade-off between accuracy and response time was avoided. Instead, a performance measure combining the information from both accuracy and response time measures could be used in the form of the drift rate. Specifically, a hierarchical drift diffusion model was used in which the individuals' parameter estimates are constrained by group distributions (Wiecki, Sofer, & Frank, 2013). Its usefulness has been demonstrated in modelling multisensory integration tasks very similar to the one used in **Study I** (Regenbogen et al., 2018, 2016).

3.4 MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) enables non-invasive study of the structure and function of the human brain *in vivo*. In essence, MRI is based on the magnetic qualities of protons, the so-called magnetic spin. When a strong external magnetic field is applied, as in the case of an MR scanner, the spins align with the magnetic field. By adding energy in form of a radio frequency pulse, a disruption of the alignment occurs. This is followed by a relaxation back to an equilibrium state, releasing energy that can be measured. MRI utilizes the fact that the time constant of the relaxation differs between types of tissue. By manipulating the disruption and time of data collection, images sensitive to different tissues can be acquired.

Different forms of functional MRI (fMRI) exist. The seminal work by Ogawa, Lee, Kay, and Tank (1990), demonstrating that the magnetic properties of oxygenated and deoxygenated hemoglobin differ and can therefore be used as a "naturally occurring contrast agent for MRI", is the basis upon which brain function is commonly studied using MRI. Combined with the fact that neuronal activity in the brain is linked to increased inflow of oxygenated blood (Roy & Sherrington, 1890), the blood-oxygenation-level-dependent signal, often called BOLD signal, detected in fMRI enables an indirect measure of neuronal activity.

In **Study II** structural MRI was used for morphometric analysis, whereas BOLD fMRI was used in **Study III** and **IV**.

3.4.1 Morphometric analysis

One of the most important obstacles to overcome when analyzing brain structure (and function) is the fact that brains differ in both size and shape. Hence, when making comparisons between individuals or summarizing results from multiple individuals, we need to ensure that we are assessing the same region in all of the included brains. This problem is commonly addressed by normalizing all individual brain images into a common brain template. This method is implemented as a part of standard processing pipeline in neuroimaging analysis software such as SPM (Wellcome Trust Centre for Neuroimaging, UCL; www.fil.ion.ucl.ac.uk/spm/), and was used for both for the structural (**Study II**) and functional (**Study III** and **IV**) analyses in the studies included in this thesis. An alternative method is to use individual regions of interest, i.e., brain regions that are specific to each individual but still representing the same functional or anatomical regions for all individuals. These regions can be delineated based on, e.g., activity when performing a specific task or specific anatomical landmarks.

In **Study II**, both volume-based and surface-based measures were used to assess potential morphological abnormalities in individuals with isolated congenital anosmia. Specifically, voxel-based morphometry (Ashburner & Friston, 2005) analysis was used for a group comparison of gray matter volume, following the standard pipeline for VBM-analysis in SPM12 by John Ashburner (2015). In short, the structural images were segmented into gray matter, white matter, and cerebrospinal fluid. The gray and white matter were used in an iterative process for inter-subject alignment (Ashburner, 2007), followed by a normalization of the gray matter into Montreal Neurological Institute (MNI) standard space, modulation, smoothing, and scaling with intracranial volume. Voxel-wise group comparisons of gray matter volume were done with age, sex, and scanning site as nuisance covariates.

Surface-based measures in the form of cortical thickness, area, and curvature were also included and compared between groups in **Study II**. The measures were derived using Freesurfer and preprocessed using the HiveDB database system (Muehlboeck, Westman, & Simmons, 2014). Detailed description of the processing pipeline can be found elsewhere (Fischl & Dale, 2000), but, in essence, the image processing included segmentation of subcortical white matter and gray matter, tessellation of the gray and white matter boundary, automated topology correction, and surface deformation to the gray/white matter boundary and the gray matter/cerebrospinal fluid boundary. The three measures of interest were calculated at each vertex point in individual space and thereafter aligned to an average template and smoothed. Corresponding to the volumetric analysis, cortical thickness, area, and curvature were compared between groups based on vertex-wise general linear models with age, sex, and scanning site as nuisance covariates.

The depth of the olfactory sulci in the plane of the posterior tangent through the eyeballs was measured in **Study II**, aiming to replicate the previously published decreases in olfactory sulcus

depth in individuals with congenital anosmia. The depth was measured manually by two raters blind to subject group, according to the method described by Huart et al. (2011). In short, a straight line measuring the depth of the sulcus was drawn on the first coronal slice posterior to the eyes in which the eyeballs were no longer seen. For sulci for which the two initial raters' measures were deemed as outliers, a third rater measured the olfactory sulcus depth. Olfactory sulcus depth was defined as the mean of all raters' measures.

3.4.2 Task-based functional MRI

Task-based fMRI is commonly used to study specific processes in the brain. These could be more perceptual processes, such as assessing which brain regions react when we smell a disgusting odor, or more cognitive processes, such as assessing which brain regions are involved when we solve a mathematical equation. The general idea of task-based fMRI is to let the participant perform some sort of task (smell an odor/solve an equation) while the BOLD signal is being measured. The BOLD response, i.e., the excessive blood-flow to a region induced by neuronal activity is preceded by an initial decrease in oxygen level. This initial dip is followed by an over-compensation peaking multiple seconds after the neuronal activity, returning to baseline after approximately 16 s. This process is often referred to as the hemodynamic response function and is commonly used in the analysis of task-evoked data. In task-based fMRI, the same task is typically repeated multiple times because the signal to noise ratio is low. In addition, a measure of the whole brain volume using BOLD fMRI commonly takes around 2 s, which means that collecting multiple measures of the same task performance leads to snapshots of different moments of the task performance, enabling a better estimation of the evoked signal.

Preprocessing of fMRI can include different processing steps, but the aim is typically to reduce noise and normalize the data into a common space. The same preprocessing steps were used for the task-based fMRI data in **Study IV** and the resting-state fMRI data in **Study III**, implemented in SPM12. In short, slice timing correction was used to account for the different timing of acquiring slices in each volume, realignment of all functional volumes to correct for motion during scanning, and normalization to the MNI standard space. In addition, for analyses based on voxel-based comparisons, smoothing with a Gaussian kernel was applied to decrease noise and the effects of inter-subject morphological differences. For analysis based on regions of interest (ROI), the extraction of the mean of all voxels within a ROI accounted for the 'smoothing' while still keeping the boundary between voxels within the regions and outside the region intact.

In **Study IV**, the integration and processing of audio-visual stimuli was assessed using an object identification task previously described. For each individual, a general linear model was used to model the auditory, visual, and audio-visually induced activity, based on the hemodynamic response function. To reduce effects of motion, the realignment parameters from the realignment preprocessing step were included in the model. Additionally, the multisensory enhancement, as indicated by the maximum criterion (see chapter 1.5.1), was computed by contrasting the effect of bimodal audio-visual processing with the larger of the two unimodal

effects. Both audio-visual processing and integration were compared between groups, based on the mean in specific ROIs and based on exploratory whole-brain voxel-wise group comparisons using a general linear models with age, sex, and scanning site as nuisance covariates.

3.4.3 Resting-state functional MRI

The correlation of low-frequency BOLD signal fluctuations in a brain during a state of rest, when no particular task is being performed, is referred to as resting-state functional connectivity (Biswal, Yetkin, Haughton, & Hyde, 1995). Specific networks of regions functionally connected during rest have repeatedly been detected, often using data driven approaches, such as independent component analysis. Perhaps the most prominent of these networks is the so-called default mode network (Raichle et al., 2001), related to introspection (Buckner & DiNicola, 2019). Resting-state fMRI has furthermore revealed networks related to extrospection (Fransson, 2005), such as an auditory and a visual network (Damoiseaux et al., 2006; Power et al., 2011).

In addition to data driven methods, functional connectivity is commonly measured using Pearson's correlation of BOLD time series. This measure is typically used when assessing the connectivity between two brain regions, or when exploring how one region functionally connects to the entire brain. The connectivity between homotopic regions, i.e., corresponding regions in opposite hemispheres, has been studied both region- and voxel-based; the later versions referred to as voxel-mirrored homotopic connectivity (Zuo et al., 2010). Of specific interest to the work in this thesis, homotopic connectivity in sensory regions tends to increase during development (Zuo et al., 2010) and alters in visual sensory deprivation (Hou et al., 2017; Huang et al., 2019). A local measure of functional connectivity is called regional homogeneity, assessing the similarity of BOLD time series in nearby voxels based on Kendall's coefficient of concordance (Zang, Jiang, Lu, He, & Tian, 2004). In contrast to homotopic connectivity, regional homogeneity tends to decrease in sensory regions during development (Anderson et al., 2014).

In **Study III**, 9 minutes long resting-state scans were collected early in the scanning sequence before any task-based scans were acquired. The participants were instructed to be as still as possible, to not think about anything in particular, and to keep their eyes open, looking at a fixation cross. The preprocessing of the data was done as described for the event based fMRI in **Study IV**. However, because functional connectivity analysis is very sensitive to noise, e.g., caused by motion, additional processing steps for noise reduction were performed. The denoising procedure was implemented in in the CONN functional connectivity toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) and included, among others, removal of white matter and cerebrospinal fluid signal components (Behzadi, Restom, Liau, & Liu, 2007) and scrubbing of volumes with high motion based on Power's frame-wise displacement measure (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). The functional connectivity between core olfactory processing regions, measured by Pearson's correlation of BOLD time series, and

the regional homogeneity and voxel-mirrored homotopic connectivity within primary olfactory cortex was assessed and compared between groups in **Study III**.

3.4.4 Regions of interest

Regions of interest (ROI) were used in the analysis of all three neuroimaging studies included in this thesis. Specifically, **Study II** included a piriform cortex ROI (Figure 7A) for post-hoc equivalence testing, because contrary to the *a priori* hypothesis, no significant group differences were discovered in this region. The region was based on manual delineation of the Atlas of the Human Brain (Mai, Majtanik, & Paxinos, 2015), explained in detail in Zhou et al. (2019). In **Study III**, an extended version of the piriform cortex ROI used in **Study II** was used (Figure 7B), which, besides the piriform cortex, also contained the two primary olfactory cortical regions; namely the anterior olfactory nucleus and the olfactory tubercle (Zhou et al., 2019). **Study III** furthermore used spherical ROIs for an olfactory network consisting of orbitofrontal, piriform, and insular cortex. The center coordinates of these regions were based on peaks of olfactory processing within a meta-analysis (Seubert, Freiherr, Djordjevic, et al., 2013) and in line with previous studies of olfactory resting-state connectivity (Lu et al., 2019; Tobia, Yang, & Karunanayaka, 2016). In **Study IV**, two olfactory (piriform and orbitofrontal cortex) and two multisensory (superior temporal and intraparietal sulcus) ROIs were included. To keep the definition of these four ROIs as similar as possible, the piriform ROI from **Study II** and **III** was replaced by a piriform ROI based on a combination of anatomical delineation and functional activation (Figure 7C)(Porada, Regenbogen, Seubert, Freiherr, & Lundström, 2019). The orbitofrontal, superior temporal, and intraparietal ROIs were all defined in a similar manner. Specifically, the orbitofrontal ROI was based on an olfactory functional activation map restricted by the Harvard-Oxford atlas (Seubert, Freiherr, Frasnelli, Hummel, & Lundström, 2013), whereas the superior temporal and intraparietal ROIs were based on a map of predicted multisensory integration (Dockès et al., 2020) restricted by the AICHA atlas (Joliot et al., 2015).

A   **B**   **C**

Study II
Piriform cortex

Study III
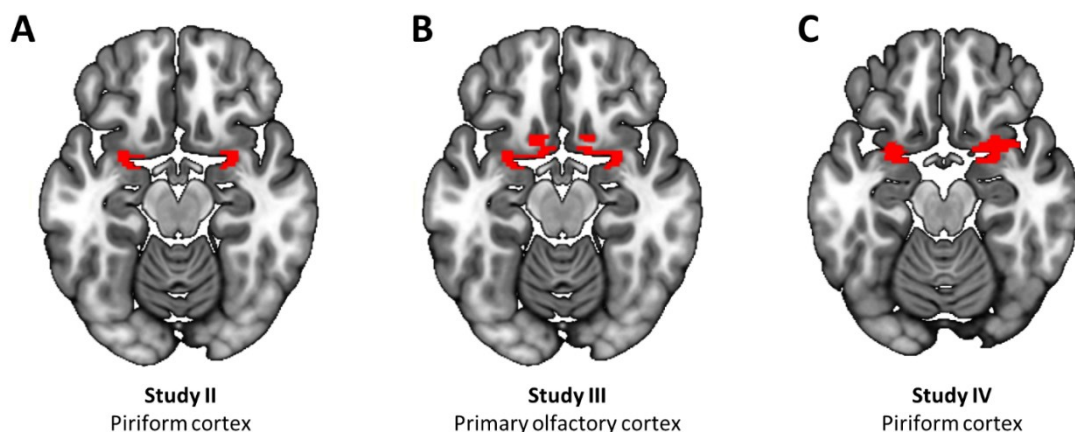Primary olfactory cortex

Study IV
Piriform cortex

Figure 7 Regions of interest. Piriform cortex and primary olfactory cortex ROIs used in the three neuroimaging studies in this thesis.

3.4.5 Methodological considerations

When using BOLD fMRI, it is important to always consider that although we want to measure neuronal activity in brain, BOLD fMRI only gives an indirect measure of this activity. This indirect measure is sluggish, taking around 16 seconds to return to baseline, and is on a completely different timescale than the neuronal activity of interest. This slow response also limits the way event-based fMRI studies can be performed. If presenting different stimuli too close in time, there will be carry-over effect, making it difficult to separate the BOLD signal related to the different stimuli. The limited number of presentations possible during a timespan combined with the noisy signal is suboptimal. In addition, a spatial resolution of 3·3·3 mm³ is common, although it differs between studies. This means that, in addition to being an indirect measure of what we want to study, the BOLD signal is also measured at a completely different temporal and spatial scale than actual neural activity. Additionally, the flexibility in fMRI data processing is vast, beginning at quality control and preprocessing and stretching to decisions on statistical tests and thresholds. Even with the same data set and scientific questions, results and conclusions drawn can show extensive variability (Botvinik-Nezer et al., 2020). Note, however, that the issue of analytical flexibility is not a problem preserved only for neuroimaging (Simmons, Nelson, & Simonsohn, 2011). Collecting MRI data is furthermore expensive, which often limits the number of participants to smaller sample sizes, relative to behavioral studies. For the studies included in this thesis, however, the number of participants was limited by the rarity of the subject group studied.

Motion is of particular concern in fMRI analysis, because head motion changes the part of the brain imaged in a specific voxel. Because different brain tissues have different intensities and BOLD fMRI analysis is based on intensity alterations in voxels that are assumed to be caused by alterations in the blood oxygen level, changing the part of the brain imaged in a voxel can be interpreted as a change in blood oxygen level. Due to intensity differences between different tissues, motion-induced effects are likely to appear in close proximity to boundaries between different tissue types because the, such as the outer boundaries of ventricles. To reduce head motion in the neuroimaging studies included in this thesis, we stabilized the participants' heads using soft paddings and repeatedly instructed them to lie as still as possible. Head motion is particularly problematic in resting-state fMRI where motion leads to altered correlations of BOLD signal (Power et al., 2014, 2012). Additional processing steps for reduction of motion-induced effects in the data were done in **Study III**, as discussed above. Motion can also have strong effects on task-based fMRI, particularly if the motion is correlated with the specific task investigated. This makes it difficult to separate the cognitive process of interest and motion-induced effects. Therefore, in **Study IV**, we refrained from using a speeded response task, as was done in the behavioral version of the task in **Study I**. Because the participants responded with a button press, it could be assumed that small motion effects (as well as activation in motor cortex) could be induced. In addition to study design, individual motion as measured by the realignment parameters was included in the statistical model to account for motion. Importantly, the data processing steps aiming to reduce the effects of motion can, at best, substantially reduce the effects, but cannot completely remove them. Therefore, group

comparisons of motion, assessed using Power's framewise displacement (Power et al., 2012), were done in **Study III** and **IV** to ensure that potential group differences of interest were not likely to be induced by group differences in motion.

Of particular importance to the studies included in this thesis, and to others investigating the orbitofrontal regions of the brain, are susceptibility artifacts. Common fMRI sequences, as the ones used in **Study III** and **IV**, are highly sensitive to distortions of the magnetic field due to air-tissue boundaries. These types of problems occur in regions in close proximity to the sinuses, often leading to signal distortion and signal loss in orbitofrontal regions when acquiring fMRI data (Ojemann et al., 1997). To ensure that there was not extensive signal loss in the ROIs in **Study III**, raw signal amplitude was visually compared between the included ROIs and two additional regions, for which susceptibility artifact would not be expected.

Despite the discussed drawbacks, MRI still provides us with a unique way to study brain structure and function in vivo and has been invaluable to advancements made in the understanding of the human brain. Specifically, the majority of studies investigating structural and functional cerebral reorganization in sensory deprivation reviewed in this thesis, as well as the ones investigating olfactory processing and multisensory integration, are based on MRI. They are the basis upon which the hypotheses in the studies in this thesis are built, and the three neuroimaging studies in this thesis all use MRI.

3.5 STATISTICAL SUPPORT FOR NULL-EFFECTS

In both **Study II** and **III**, effects were hypothesized that we could not find support for using the planned statistical analysis methods. It is, however, important not to confuse a lack of evidence sufficient to reject the null hypothesis (no group differences in mean value) with support for the null hypothesis. Testing whether there is in fact support for the null hypothesis can be done in different ways. Equivalence tests in the form of the two one-sided tests procedure can be used to test whether there is statistical support for an effect smaller than the minimum effect size of interest (Lakens, Scheel, & Isager, 2018; Lakens, 2017). An upper and lower equivalence bound around the null-effect are set, based on the minimum effect size of interest, and two directed hypothesis tests are then performed to assess whether an effect larger than the upper equivalence bound or smaller than the lower equivalence bound can be rejected. If that is the case, the test has provided statistical support of an effect smaller than the minimum effect size of interest. This approach was used in **Study II**, and the smallest effect size of interest was based on the effect size the study provided 80 % power to detect. Support for null-effects can also be provided using Bayesian statistics, as done in **Study III**. In contrast to the two one-sided tests procedure, in which the hypotheses are either rejected or not, the Bayesian approach provides a ratio of the support for the null and alternative hypothesis.

3.6 ETHICAL CONSIDERATIONS

For all studies in this thesis, participants are informed that participation is on a strictly voluntary basis and that they are allowed, at any given point prior to or during the study, to cancel or abort their participation. No invasive methods known to cause physical suffering or harm to

the participants are used, and the risk of serious injury is very small. However, there are some important ethical aspects that need to be considered.

3.6.1 Working with a rare subject group

As mentioned earlier, the participating individuals with anosmia are not a patient group, e.g. recruited by treating healthcare personnel or from healthcare facilities, and are therefore not put in a position in which they have to consider whether their choice of participating would affect their future healthcare.

This project does not have the objective to directly prevent, diagnose, or treat the studied group (individuals with anosmia). The hope is that the knowledge gained can lead to an increased understanding of our brain's capacity for change in general and, more specifically, a better understanding of changes associated with olfactory sensory deprivation, providing a stable foundation for future research focused on more clinical areas. A concern from an ethical perspective is that part of the studied subject group is hoping for help or a treatment, which they do not receive by participating in this research. It is made clear prior to entering the study that this is a need we cannot meet and that individual help is not offered. Participants are informed about the study goals (both verbally and in written form) and, as long as the purposes of the research is clear, we must trust our participants autonomy and that they are able to decide themselves whether they think it is worth participating or not.

3.6.2 Privacy

During the studies, personal demographic information (and in some cases relevant medical history) as well as neuroimaging data is collected. All data belonging to one individual are saved under a unique participant number on a server which only authorized researchers have access to. Data are further almost exclusively presented on group level in publications to ensure that individuals cannot be identified; when individual data points are presented, identifiable links between individuals and data are never included. This is particularly important when working with a rare subject group, because the knowledge of age and sex could potentially be sufficient to identify an individual.

3.6.3 Olfactory testing

All participants (individuals with anosmia and controls) perform an olfactory test to confirm anosmia or normosmia, depending on subject group. This step creates the possibility of discovering unexpected olfactory problems in controls. In these types of studies, the researcher is often neither trained for, nor allowed to, render clinical diagnoses. If hyposmia or anosmia is suspected in a control participant, the only possible action is to exclude the participant from the study and suggest that the individual contact the primary care provider, if worried. It is also important to inform participants that olfactory ability can fluctuate due to e.g. nasal congestion or other temporary issues. Regarding individuals with anosmia, there is the possibility to come to the conclusion that they are hyposmic or normosmic, which would be expected to be perceived as positive.

Individuals with anosmia, and particularly those with a congenital condition, might experience discomfort, feeling questioned or even ridiculed, when asked to do a full olfactory ability test in spite of the fact that they don't have a working olfactory sense and might not even have a concept of what an odor is. It is important that the researcher performing the test is aware of this fact and warns participants that it might feel strange to perform a sensory test for a sensory modality you do not have. The researcher should further explain that this is an important validation of the individual's condition and is needed in order to confirm results within the research community given that we often do not have access to a full medical anamnesis documenting the sensory deprivation.

3.6.4 Neuroimaging

Although the participants are asked if they suffer from claustrophobia at the earliest stages of recruitment, there is always the risk that a participant might react negatively and panic in the MRI scanner. There is also a slight risk of physical discomfort (lying still in a supine position, being instructed to keep the head as still as possible) during the collection of MRI data. However, these risk factors are very small, something that the participants are informed of and given the opportunity to reflect on prior to participation.

When running an MRI study, it is important to consider the risk involved with the strong constant magnetic field from the scanner as well as the fluctuating fields while collecting data. Already during the recruitment, we combine our own specific questions with the same questionnaire that the hospital uses to make sure that we don't include participants who, e.g., have a pacemaker or are pregnant. Although no risk factors associated with pregnancy are known, we follow the principle of caution.

There is always a small risk for incidental findings when participating in a neuroimaging study, i.e. that signs of abnormalities or disease in the central nervous system are found. The fact that a problem is found could lead to preventive care, but there is also the possibility that the finding is incurable. All participants are informed that a radiologist will inspect the images and that they will be contacted if something is found. Importantly, it is also made clear that the research study is not a full medical examination and that the imaging sequences used are for our study purposes and not optimized for identifying clinical issues. After this information, the participants again have the opportunity to reconsider participation.

4 RESULTS

In this section, an overview of the results and conclusions for each of the four studies included in this thesis is presented. For further details, the reader is referred to the full-length studies provided at the end of the thesis as separate numbered appendices.

4.1 STUDY I: SENSORY LOSS ENHANCES MULTISENSORY INTEGRATION PERFORMANCE

The integration of input from more than one sensory modality, multisensory integration, has been linked to behavioral gains such as increased accuracy and faster responses (Murray et al., 2016; Stein & Stanford, 2008; Stevenson, Ghose, et al., 2014). Although complete sensory deprivation has repeatedly been linked to altered, often compensatory, abilities in certain aspects of the spared senses (Frasnelli et al., 2011), the integration of sensory information is rarely studied in sensory deprived individuals. Still, for the individual, an enhanced ability to integrate information from the spared senses would be of great benefit when lacking one sense, thereby taking the best possible advantage of the remaining available sensory input. It is possible that the sparse study of multisensory integration in sensory deprivation is, at least partially, based on the fact that both research fields have put a lot of attention on the auditory and visual sensory modalities, with either blind or deaf individuals in sensory deprivation studies, while many established multisensory integration paradigms use audio-visual stimuli.

Although complete olfactory sensory deprivation, anosmia, is much more prevalent than visual and auditory deprivation, potential compensatory processing in anosmia is rarely studied. By studying potential multisensory compensatory mechanisms in individuals with anosmia, we are provided with an excellent opportunity to both include larger subject groups, relative to sizes commonly used in studies of sensory deprived individuals, and to use established experimental audio-visual integration paradigms. Accordingly, in **Study I**, audio-visual integration was assessed in individuals with isolated, non-traumatic functional anosmia (both congenital and acquired; N=37) and matched controls (N=37), with the hypothesis that olfactory sensory deprivation leads to multisensory compensatory abilities. Specifically, two different integration tasks were used to assess the integration: one with simple perceptual stimuli assessing temporal integration and one with more complex, dynamic, degraded stimuli assessing integration based on inverse effectiveness (see chapter 3.3.1-3.3.2).

4.1.1 Study I Results and conclusions

In the first experimental task, we asked whether olfactory sensory deprivation enables better temporal binding of simple audio-visual stimuli. The temporal binding of simple auditory and visual stimuli was tested in a simultaneity judgement task. The auditory (a short beep) and visual (a flash in form of a white circle) stimuli were presented either simultaneously or with a temporal separation ranging from ±25 ms to ±300 ms. A significant difference between individuals with anosmia and controls in perceived simultaneity of the auditory and visual stimuli over the span of asynchronies was demonstrated as a main effect of Group in a repeated-measures analysis of variance (rmANOVA). Because an individual's temporal binding of

stimuli is often measured by the temporal binding window, i.e., the range of temporal asynchronies for which the stimuli are still perceived as simultaneous (Stevenson & Wallace, 2013; Stevenson, Zemtsov, & Wallace, 2012), the temporal binding window was used for further group comparisons. Here, we used the common definition of the binding window as the span of temporal asynchronies during which at least 75 % of the individual peak perceived simultaneity is reached. Individuals with anosmia demonstrated significantly narrower temporal binding windows as compared to controls, a reduction independent of whether the anosmia was congenital or acquired (Figure 8A).
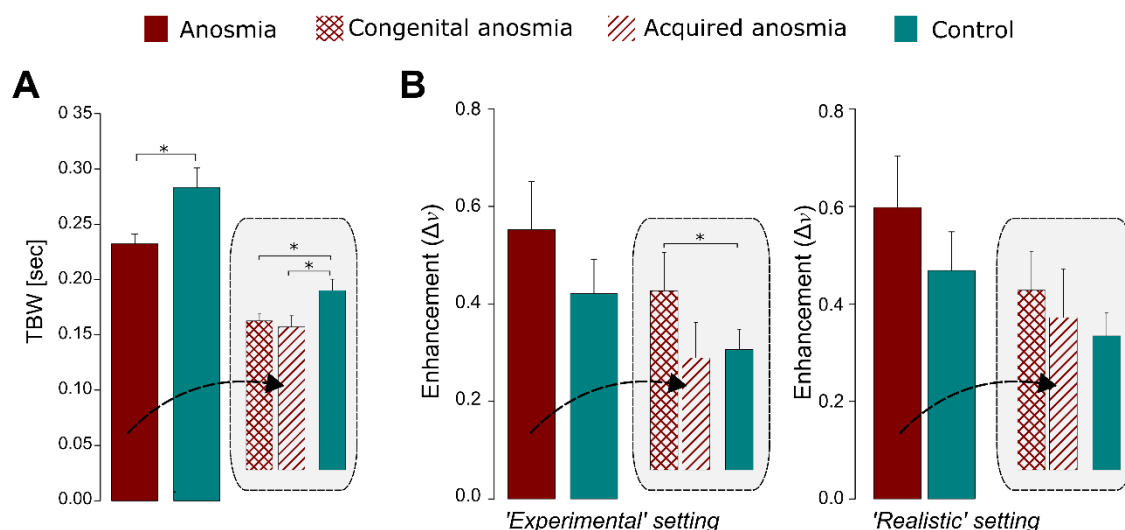

Figure 8 A) Simultaneity judgement task. *Individuals with anosmia demonstrated a significantly narrower audio-visual temporal binding window relative to controls. This narrowing was significant for individuals with congenital as well as acquired anosmia (inserted gray box).* **B) Object identification task**. *No significant group differences in multisensory enhancement between individuals with anosmia and controls were demonstrated in either the 'experimental' setting, when comparing informative bimodal to informative unimodal stimuli, or in the 'realistic' setting, when comparing bimodal to unimodal object information in bimodal stimuli. However, individuals with congenital, but not acquired, anosmia demonstrated a significant increase in multisensory enhancement relative to controls in the 'experimental' setting (inserted gray box). Error bars indicate standard error of the mean. TBW = temporal binding window, Δv = difference in drift rate.*

In the second experimental task, we wanted to assess the effects of olfactory sensory deprivation on multisensory enhancement effects in the processing of more complex and dynamic sensory information. In accordance with an established experimental paradigm (Regenbogen et al., 2018, 2016), video and audio clips depicting moving objects were degraded with individually determined levels of noise to increase the multisensory integration effects based on the principle of inverse effectiveness. Noise levels were based on a thresholding procedure performed for auditory and visual stimuli separately. In the multisensory integration task, the object stimuli were presented either unimodally (only audio clip/only video clip) or bimodally (matching audio and video clips). Specifically, two different versions of unimodal object stimulus presentation were included: the clips were either presented completely unimodally or combined with pure noise in the non-informative sense (e.g., a video clip depicting an object combined with auditory noise). The first approach is commonly adopted in experimental paradigms investigating multisensory integration, whereas the second approach mimics a more realistic setting, in which we often get input from multiple senses simultaneously, regardless of whether or not the input is informative. Participants were asked to identify the presented object with speeded responses. Performance was analyzed using a drift

diffusion model that has the analytical benefit of combining measures of accuracy and response time with drift rate as the performance measure of interest (for additional information, see chapter 3.3.3). Before assessing multisensory integration effects, a number of control measures were taken. No group differences relating to decision style (threshold separation), response execution (non-decision time), or attention (response time) were found. To assess whether potential overall group differences in performance, as indicated by drift rate, were demonstrated, a group comparison over the five conditions (bimodal and auditory/visual unimodal for both 'experimental' and 'realistic' setting) was done with a rmANOVA. No significant group differences in drift rate were demonstrated, although there was an interaction effect of group and condition.

A significant multisensory enhancement in drift rate, i.e., the performance improvement when provided with bimodal information as compared to the best performance when provided with unimodal information, was demonstrated over groups for both the 'experimental' and 'realistic' setting. This confirms that the experimental manipulation worked. However, in contrast to the hypothesis, no group differences in multisensory enhancement were demonstrated in either setting. When splitting the anosmia group into subgroups based on a congenital or acquired sensory deprivation, statistical evidence supporting greater multisensory enhancement for individuals with congenital anosmia, as compared to controls, was demonstrated. This was only true in the 'experimental' setting, however, and not in the 'realistic' setting; no differences between individuals with acquired anosmia and controls were demonstrated (Figure 8B).

In conclusion, individuals with anosmia, independent of onset of sensory deprivation, demonstrated a significantly narrower audio-visual temporal binding window relative to matched control participants with a normal sense of smell. A narrow temporal binding window is linked to lower levels of multisensory illusion perception (Stevenson et al., 2012), whereas a wide temporal binding window is linked to neurodevelopmental conditions, such as autism spectrum disorders (Wallace & Stevenson, 2014). Together, this suggests that the narrower temporal binding window demonstrated by individuals with anosmia is linked to improved multisensory abilities. In contrast to the significant group differences in temporal binding window, only individuals with congenital anosmia demonstrated increased multisensory enhancement, relative to controls, and only in one out of the two settings. These results suggest that absence of olfactory input is linked to improved discovery of simultaneity violations of simple perceptual stimuli, and that congenital anosmia might further be associated with better utilization of bimodal, as compared to unimodal, complex, degraded information; a potential multisensory compensatory effect of the sensory deprived.

4.2 STUDY II: MORPHOLOGICAL CHANGES IN SECONDARY, BUT NOT PRIMARY, SENSORY CORTEX IN INDIVIDUALS WITH LIFE-LONG OLFACTORY SENSORY DEPRIVATION

Based on the effects of congenital visual deprivation (A. Jiang et al., 2015; Noppeney et al., 2005) and the results from olfactory deprivation studies (Reichert & Schöpf, 2018), a lifelong absence of olfactory input could be assumed to alter the morphology of cerebral olfactory

sensory regions. However, only a handful of studies investigating brain morphology in congenital anosmia exists, and the majority of these studies focus purely on the olfactory bulb and/or the depth of the olfactory sulcus (Abolmaali et al., 2002; Huart et al., 2011; Yousem et al., 1996). The two existing studies that include statistical morphological comparisons throughout the brain both indicate atypical morphology in, amongst others, regions important for olfactory processing. This includes a volumetric gray matter increase in unilateral piriform (primary olfactory) cortex reported in both studies, albeit in opposite hemispheres. These results contrast the atrophy demonstrated in early visual regions in both congenital and acquired blindness. Furthermore, both studies indicated atypical morphology in the orbitofrontal (secondary olfactory) cortex: decreased volume in left olfactory sulcus was reported in one study, whereas a lack of volumetric differences, but increased cortical thickness in bilateral anteromedial orbitofrontal cortex, was reported in the other (Helena Gásdal Karstensen et al., 2018; Frasnelli et al., 2013). Although both studies indicate similar regions, the lack of overlap requires further studies to determine the effects of lifelong olfactory absence on the human brain. It could be hypothesized that discrepancies in results between studies originate from working with a rare condition, which naturally leads to small sample sizes. Thus, to determine whether isolated congenital anosmia is associated with atypical gray matter morphology, and thereby elucidate which of the previous results we could replicate, **Study II** assessed gray matter morphology in isolated congenital anosmia based on structural MRI from a considerably larger group of subjects than previously assessed. Specifically, atypical gray matter morphology, beyond the established olfactory bulb and olfactory sulcus depth measures, was compared between individuals with isolated congenital anosmia (N=33) and matched normosmic controls (N=34) using complimentary volumetric and surface based analysis methods. We hypothesized that atypical morphology would be demonstrated in both piriform and orbitofrontal cortex.

4.2.1 Study II Results and conclusions

First, to assess whether individuals with isolated congenital anosmia demonstrate atypical gray matter volume, voxel-wise comparisons of gray matter volume between individuals with congenital anosmia and controls were done. This analysis revealed four large clusters of altered morphology in the orbitofrontal cortex in individuals with congenital anosmia (Figure 9A). Specifically, gray matter atrophy in individuals with congenital anosmia, as compared to controls, was demonstrated around the bilateral olfactory sulci. Interestingly, bilateral clusters of gray matter volume increases were also demonstrated in close proximity to the atrophied regions, namely in the medial orbital gyri. To determine potential mediating effects of these volumetric alterations, complimentary surface based analysis in form of vertex-wise group comparisons of cortical thickness, area, and curvature were done. The volumetric atrophy around the olfactory sulci was supported by decreased surface area and curvature in the bilateral olfactory sulci and medial orbital gyri. Further, increased cortical thickness was shown in the left medial orbital gyrus (a result also reflected in the right hemisphere when using a more liberal statistical threshold; Figure 9B). Additionally, a small cluster of increased curvature in

the left superior temporal sulcus was demonstrated by individuals with anosmia; a result that was not reflected by the other morphological measures.
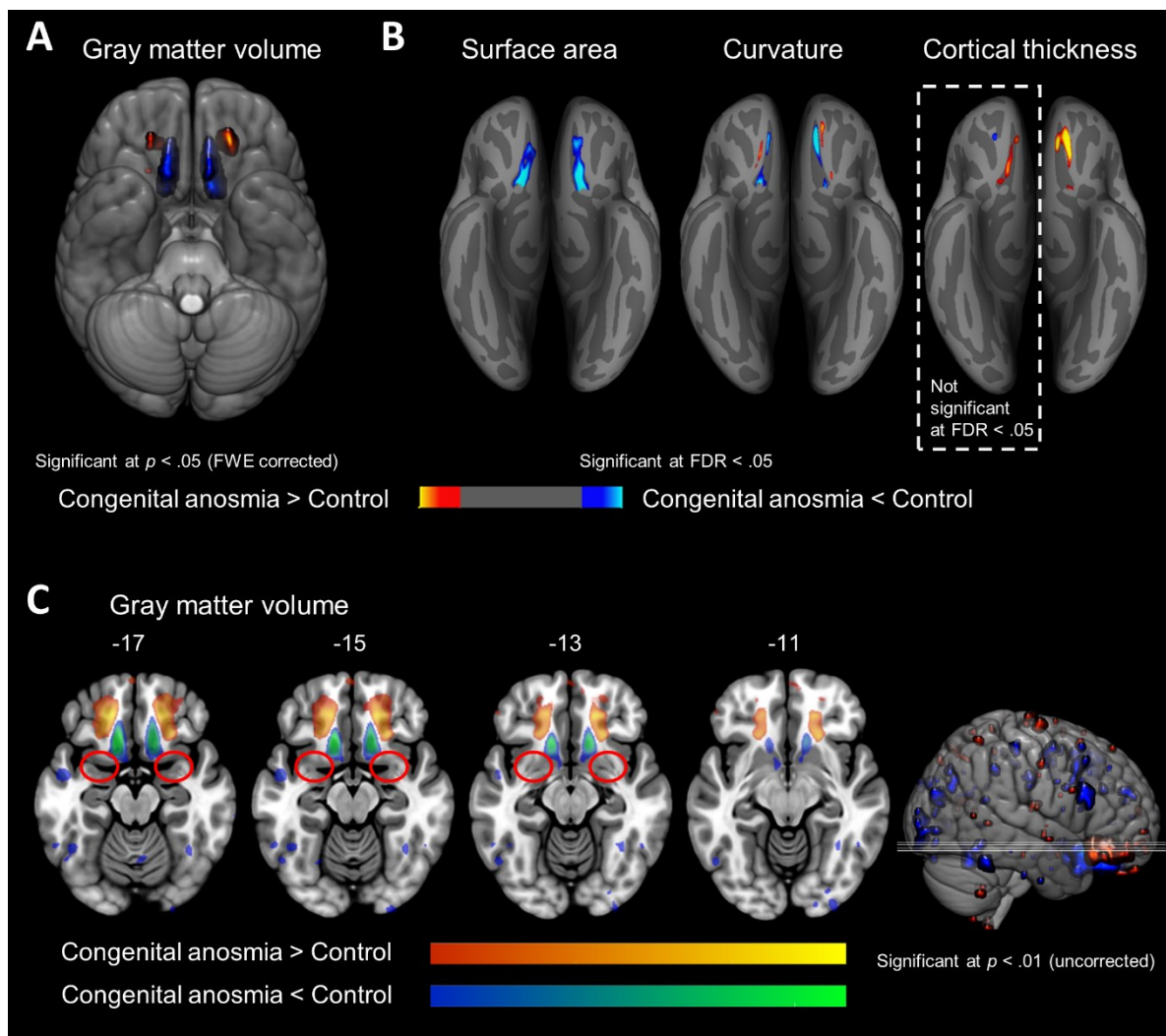

Figure 9 Morphological reorganization in the orbitofrontal cortex. *Individuals with isolated congenital anosmia, relative to normosmic controls, demonstrated **A)** gray matter volume decreases along the olfactory sulci and gray matter volume increases in the medial orbital gyri, and **B)** decreased surface area and curvature and increased cortical thickness along the olfactory sulci. Note that the curvature measure has opposite signs for gyri and sulci; all clusters indicate a flatter cortex for individuals with congenital anosmia. **C)** No group differences in gray matter volume were demonstrated in piriform cortex at the liberal statistical threshold of p < .01 (uncorrected). Numbers in white above axial slices indicate z-coordinate in MNI-space and the red circles indicate the position of piriform cortex. Slice positions are displayed on the brain in the lower right corner. FWE = family-wise error, FDR = false discovery rate.*

Interestingly, in contrast to the hypothesis and to results from previous studies, none of the morphological measures indicated group differences in piriform cortex. To ensure that this was not simply a result of conservative statistical thresholds applied to correct for multiple comparison based on all gray matter voxels in the brain, more liberal thresholds were used. However, the lack of evidence for atypical morphology in piriform cortex remained (Figure 9C). Finally, to determine whether the data actually supports a lack of group differences in piriform gray matter volume, rather than merely lacking support for any group differences, analysis in form of equivalence testing based on the two one-sided tests procedure was performed post-hoc (Lakens, 2017). Gray matter volume in both left and right piriform cortex of both groups could be viewed as equivalent, based on the set equivalence bounds, meaning

that there was statistical support for a lack of an effect of the size we had statistical power to detect.

Additionally, the repeatedly reported decrease in olfactory sulcus depth in individuals with isolated congenital anosmia, as compared to controls, was replicated in our sample. There was substantial overlap in sulcus depth, however, between the two groups. Therefore, it can be concluded that the previously suggested use of olfactory sulcus depth measures as a part of clinical diagnosis of congenital anosmia should not be recommended (Huart et al., 2011).

Because morphological differences were restricted to the orbitofrontal cortex, specifically in, or in close proximity to, the bilateral olfactory sulci, it could be assumed that a link between these measures and the demonstrated decreased olfactory sulcus depth exists. Therefore, potential indications of a linear relation between sulcus depth and the main morphological results were investigated with Pearson's correlation analysis. Albeit the correlation analyses yielded ambiguous and mainly non-significant results, a positive association between olfactory sulcus depth and surface area in the olfactory sulcus, as well as a negative association between sulcus depth and cortical thickness in the medial orbital gyrus, was demonstrated in both groups. Noteworthy is that significant correlations between olfactory sulcus depth and all types of included morphological measures were demonstrated; however, not consistently demonstrated over groups and individual clusters. These analyses show at least partial support for the idea that the morphological reorganization in the orbitofrontal cortex could be a congenital abnormality linked to cortical folding around the olfactory sulci, potentially based on absent olfactory bulbs.

In conclusion, a striking lack of evidence for atypical morphology in piriform (primary olfactory) cortex was demonstrated in individuals with isolated congenital anosmia. However, both cortical increases and decreases were demonstrated, albeit restricted to the orbitofrontal (secondary olfactory) cortex, except a small cluster in the left superior temporal sulcus. These unexpected results suggest the existence of different reorganization processes as a consequence of lifelong olfactory inexperience in which both congenital abnormalities and plastic sensory-dependent reorganization may have contributed. Importantly, based on the discrepancy between congenital olfactory deprivation and congenital visual deprivation, we conclude that sensory deprivation-dependent morphological cerebral reorganization is sensory-specific.

4.3 STUDY III: NORMAL OLFACTORY FUNCTIONAL CONNECTIVITY DESPITE LIFELONG ABSENCE OF OLFACTORY EXPERIENCES

Effects of lifelong sensory deprivation on the function of cerebral regions that normally process the deprived sense is difficult to determine because the normal way of studying a sensory processing region is by presenting the associated sensory stimuli. However, using functional MRI, previous findings have demonstrated that the functional connectivity during rest, both within and from cortical regions normally processing visual input, is altered in blind individuals (Bauer et al., 2017; D. Wang et al., 2014), indicating an alternative way of studying functional effects of sensory deprivation. In particular, the regional homogeneity in visual regions, i.e.,

the similarity of signals between nearby voxels, is higher in blind individuals than sighted controls (A. Jiang et al., 2015), and the homotopic connectivity, i.e., the connectivity between the same location in opposite hemispheres, is decreased in blind relative to sighted individuals (Hou et al., 2017). Importantly, these abnormalities in functional connectivity suggest that the lack of visual sensory input interrupts the normal development because a decrease in regional homogeneity and increase in homotopic connectivity are demonstrated during development (Anderson et al., 2014; Zuo et al., 2010).

In **Study III**, the resting-state functional connectivity within the olfactory system was compared between individuals with isolated congenital anosmia (N=33) and matched normosmic controls (N=33). First, functional connectivity between core olfactory processing regions was compared between groups, under the hypothesis that a lifelong lack of olfactory input would lead to decreased connectivity. Thereafter, based on the unexpected indication of normal morphology in primary olfactory cortex from **Study II**, the regional homogeneity and voxel-mirrored homotopic connectivity within primary olfactory cortex was compared between groups. Based on the known developmental trajectory for sensory processing regions and the demonstrated alterations in blind individuals, an increased homogeneity and decreased homotopic connectivity in individuals with congenital anosmia, as compared to normosmic controls, was hypothesized.

4.3.1 Study III Results and conclusions

To investigate whether the resting-state functional connectivity between core olfactory processing regions is affected by lifelong olfactory inexperience, olfactory functional connectivity was compared between individuals with isolated congenital anosmia and controls. In contrast to the hypothesis, no statically significant differences between the individuals with anosmia and normosmic controls in connectivity between core olfactory processing regions were demonstrated; not even at liberal statistical thresholds uncorrected for multiple statistical tests were group differences found. It should be noted, however, that in neither group were the functional connections between the core olfactory regions particularly strong, except for between bilateral regions (Figure 10).

To assess potential effects of lifelong anosmia on the connectivity within the primary olfactory cortex, voxel-mirrored homotopic connectivity and regional homogeneity was compared between groups. Adding to these unexpected lack of group differences in connectivity between core olfactory regions, and contradictory to the stated hypotheses, no group differences in either voxel-mirrored homotopic connectivity or regional homogeneity were demonstrated. To estimate whether the lack of group differences should be interpreted as indications of group similarities, post-hoc analysis in form of Bayesian independent samples t-tests were used for group comparisons of connectivity between core olfactory processing regions as well as regional homogeneity and homotopic connectivity. All Bayesian analysis yielded anecdotal to

moderate support for the null hypothesis (no group difference); no support for the alternative hypothesis was demonstrated.
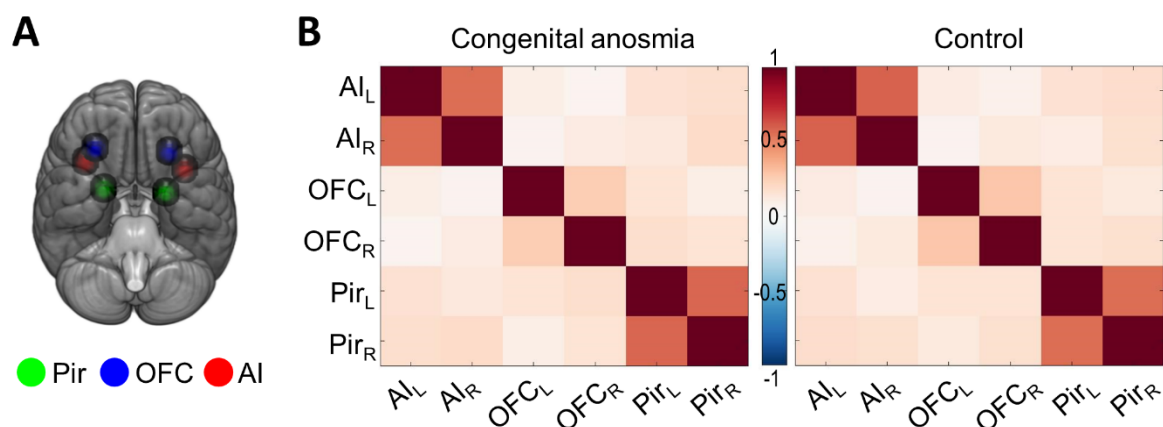

*Figure 10 Functional connectivity between core olfactory regions. **A)** The core olfactory regions of interest: piriform cortex, orbitofrontal cortex, and anterior insula. **B)** Correlation matrices for individuals with congenital anosmia and controls displayed separately. No significant group differences in functional connectivity between any of the regions were demonstrated at p < .05 uncorrected for multiple comparisons. Pir = piriform cortex, OFC = orbitofrontal cortex, AI = anterior insula.*

All in all, the results indicate that despite a lifelong absence of olfactory processing, individuals with congenital anosmia demonstrate typical resting-state functional connectivity within primary olfactory cortex as well as between core olfactory regions. We conclude that olfactory experience seems to have a remarkably low impact on the development of functional connectivity in the olfactory system, at least during rest.

4.4   STUDY IV: SEEING BEYOND YOUR NOSE? THE EFFECTS OF LIFELONG OLFACTORY SENSORY DEPRIVATION ON CEREBRAL AUDIO-VISUAL INTEGRATION

In **Study I**, indications of a potential multisensory compensatory effect in individuals with anosmia were demonstrated in the form of enhanced audio-visual integration performance; more clearly so in individuals with congenital as compared to acquired olfactory deprivation. Compensatory abilities in individuals with complete sensory deprivation, such as enhanced auditory spatial abilities in blind individuals, has been linked to cross-modal processing and morphological reorganization in cortical regions normally devoted to the deprived sensory modality (see chapter 1.4.1). Whether the previously demonstrated multisensory abilities in anosmia are mediated by altered cerebral multisensory processing had not been established. In particular, potential cross-modal multisensory compensatory processing in olfactory regions is relevant to explore as it could contribute to an understanding of the absence of morphological (**Study II**, however see Frasnelli et al., 2013; Karstensen et al., 2018) and functional connectivity (**Study III**) abnormalities in primary olfactory (piriform) cortex. Alternatively, the multisensory behavioral benefit demonstrated by individuals with anosmia could be mediated by enhanced processing within established multisensory integration regions.

To investigate whether the cerebral processing and integration of audio-visual stimuli differs between individuals with isolated congenital anosmia (N=33) and matched normosmic controls (N=33), the neural processing and integration of dynamic audio-visual stimuli was studied

using functional MRI. Specifically, we hypothesized that individuals with congenital anosmia would either demonstrate increased cross-modal processing in the piriform or orbitofrontal cortex, or increased processing in the multisensory intraparietal and superior temporal sulcus.

4.4.1 Study IV Results and conclusions

The processing and integration of audio-visual stimuli was studied using fMRI while presenting short audio and video clips depicting dynamic objects to the participants. The stimuli were part of the same stimulus set used in the second experimental task in **Study I**, but were overlaid with the same noise level for all participants (as opposed to having been individually adjusted in **Study 1**). The stimuli were presented either unimodally (only audio/video clip) or bimodally (matching audio and video clip). First, we assessed whether individuals with congenital anosmia demonstrated altered audio-visual processing or integration, compared to controls, in olfactory or multisensory regions. Group comparisons of multisensory processing (activity linked to audio-visual stimuli) and multisensory integration (as indicated by the maximum criterion, see chapter 1.5.2) were done for four ROIs: the piriform and orbitofrontal cortices to assess potential cross-modal takeover of olfactory regions, and the intraparietal and superior temporal sulci to assess potential functional reorganization in multisensory regions. Contrary to the hypothesis, the results demonstrated no statistically significant group differences in audio-visual processing or integration in any of the ROIs (Figure 11).
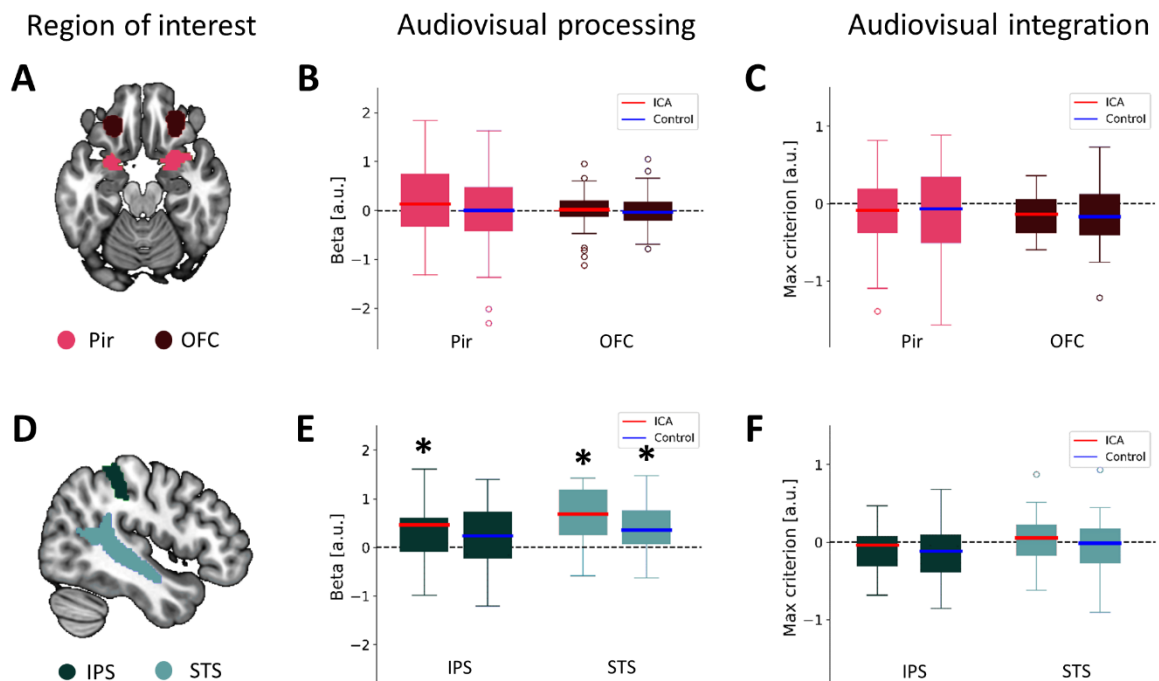

Figure 11 Region of interest analysis*. **A)** The two olfactory ROIs displayed on an axial view of the brain: Pir = piriform cortex, OFC = orbitofrontal cortex. **B)** Beta values for audio-visual processing in the olfactory ROIs were not significantly different from baseline or different between groups. **C)** The maximum criterion, i.e., the difference in beta values for audio-visual processing and the largest beta for auditory/visual processing, was not significantly different from baseline, or different between groups, in the olfactory ROIs. **D)** The two multisensory ROIs displayed on a sagittal view of the brain: IPS = intraparietal sulcus, STS = superior temporal sulcus. **E)** Beta values for audio-visual processing in the multisensory ROIs were significantly greater than baseline in both groups, except for the IPS in the control group. No significant differences between groups were demonstrated. **F)** The maximum criterion contrast was not significantly different from baseline, or different between groups, in the multisensory ROIs. For boxplots: the boxes delineate the first and third quartile, the red (congenital ansomia) and blue (control) horizontal lines indicate the median, and the whiskers stretch to the furthest data points within 1.5 interquartile range above/below the boxes. ICA = isolated congenital anosmia, a.u. = arbitrary units, * = significantly different from baseline.*

As a control measure, we assessed whether audio-visual processing or integration was significant within the ROIs in both groups. No indications of cross-modal audio-visual processing or integration in the two olfactory regions were demonstrated in either group, whereas audio-visual processing in the multisensory regions were indicated in both groups (except for the intraparietal sulcus in the control group).

To explore whether isolated congenital anosmia is associated with altered audio-visual integration or processing outside the predefined ROIs, whole-brain voxel-wise group comparisons were performed. When using a conservative statistical threshold, correcting for the multiple statistical tests performed, no group differences in either audio-visual processing or integration were discovered. However, after applying a more liberal threshold for further exploration, the maximum criterion revealed enhanced multisensory integration for individuals with congenital anosmia, as compared to controls, in both cortical (the left superior temporal sulcus) and subcortical (the superior colliculus) multisensory regions (Figure 12). Furthermore, increased integration processing was indicated in the left precuneus, a region also showing increased audio-visual processing for individuals with anosmia, along with regions around the central sulcus, parahippocampal, and cingulate regions, when applying the more liberal statistical threshold. No indications of decreased audio-visual integration or processing were demonstrated in individuals with congenital anosmia.
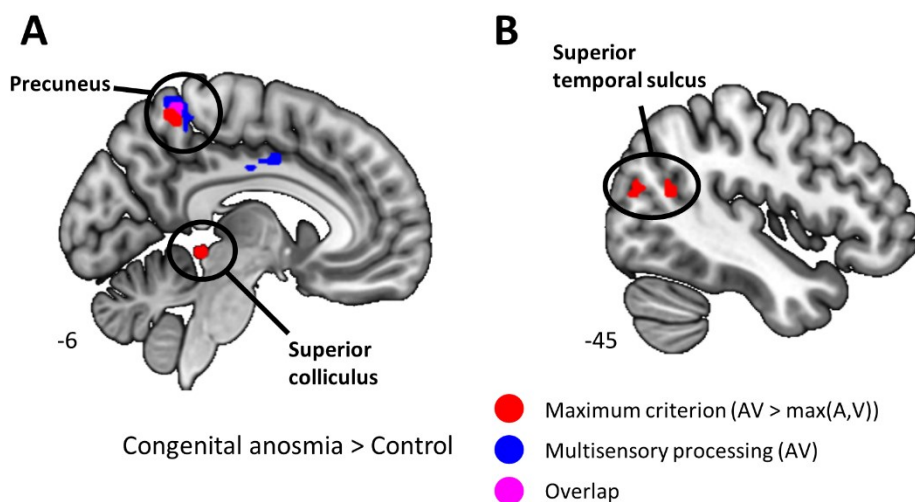
Figure 12 Exploratory analysis. *A) Individuals with congenital anosmia demonstrated increased activity related to multisensory integration, as indicated by the maximum criterion, in the superior colliculus, relative to controls. Furthermore, individuals with anosmia demonstrated increased multisensory processing as well integration in the precuneus. B) Individuals with congenital anosmia demonstrated increased activity related to multisensory integration in the superior temporal sulcus. Results are displayed at an uncorrected threshold of p > .001 and a minimum cluster size of 10 voxels. A = auditory, V = visual, AV = audio-visual.*

Taken together, these results show no support for any cross-modal multisensory processing or integration in olfactory regions in individuals with isolated congenital anosmia. The results do, however, indicate increased multisensory integration processing in both cortical and subcortical established multisensory regions in congenital anosmia. Although consistent with the hypothesis of altered processing in multisensory regions, the regions indicated are not in

the *a priori* defined regions of interest and are based on liberal statistical thresholds, thereby limiting the strength of the evidence for altered multisensory integration processing. We conclude that there are indications of enhanced, potentially compensatory, processing in multisensory regions in individuals with a lifelong absence of olfactory experience, but that this notion must be confirmed in future studies.

5 DISCUSSION

The overall aim of this thesis was to increase the understanding of the effects of complete olfactory sensory deprivation on the human brain. In particular, this thesis focused on assessing morphological and functional reorganization in brain regions normally associated with olfactory processing. Moreover, I aimed to assess potential multisensory compensatory abilities and associated cerebral processing caused by olfactory sensory deprivation. All in all, the included studies have yielded support for part of the hypotheses, demonstrating morphological reorganization in the orbitofrontal cortex in individuals with isolated congenital anosmia (**Study II**), altered multisensory integration performance (**Study I**), and indications of altered multisensory integration in multisensory regions (although not within the *a priori* hypothesized ROIs; **Study IV**). However, results contradicting the *a priori* hypotheses were also obtained; some of which can be viewed as controversial. Specifically, the lack of morphological reorganization in piriform cortex in individuals with isolated congenital anosmia (**Study II**) was unexpected and inconsistent with the literature (Frasnelli et al., 2013; Helena Gásdal Karstensen et al., 2018). Additionally, the lack of observed differences in olfactory functional connectivity between individuals with normal olfactory abilities and those with a lifelong inexperience with olfaction were not the anticipated effects (**Study III**).

In this chapter, I will discuss how the findings from the four studies included in this thesis can be interpreted, but also their limitations and, importantly, their potential implications for future research and outstanding questions.

5.1 IS PIRIFORM CORTEX UNAFFECTED BY A LIFELONG ABSENCE OF OLFACTORY EXPERIENCES?

In contrast to our hypotheses, none of the studies included in this thesis show any indications of alterations in piriform cortex in individuals with isolated congenital anosmia when compared to matched normosmic individuals. **Study II** demonstrates absent morphological differences in piriform cortex and **Study III** indicates normal functional connectivity in form of regional homogeneity and homotopic connectivity within primary olfactory cortical regions (piriform cortex, anterior olfactory nucleus, and olfactory tubercle), as well as normal functional connectivity between piriform cortex and both the orbitofrontal cortex and anterior insula. Additionally, **Study IV** shows no indication of either cross-modal audio-visual processing or audio-visual integration in piriform cortex. These findings do not agree with the structural and functional reorganization demonstrated in sensory processing regions associated with the deprived sense in deaf and blind individuals (for more details, see chapter 1.4.1), nor with past publications indicating gray matter atrophy within piriform cortex in individuals with congenital anosmia (Frasnelli et al., 2013; Helena Gásdal Karstensen et al., 2018). However, despite their controversial nature, it is reasonable to believe that the obtained results are reliable and valid. The lack of morphological group differences in piriform cortex in **Study II** persisted although liberal statistical thresholds for voxel-wise comparisons were applied, and equivalence testing yielded statistical evidence for an absence of group differences, which, with respect to the effects sizes, we had sufficient statistical power to detect (Lakens et al., 2018;

Lakens, 2017). Importantly, based on the considerably larger sample of individuals with congenital anosmia included in **Study II** (N=33), compared to the two previously published studies of whole-brain gray matter morphological alterations using similar analysis methods (N=17, Frasnelli et al., 2013; N=11, Helena Gásdal Karstensen et al., 2018), we argue that the statistical power in **Study II** should be sufficient to find the effects presented in the previous literature, if indeed present in our sample. Further support for the notion that our studies were sufficiently powered to detect effects previously reported is the fact that we did replicate several past findings. These included cortical increases in the orbitofrontal cortex, reported by Frasnelli et al. (2013), and cortical decreases along the olfactory sulci, as reported by Helena Gásdal Karstensen et al. (2018). Still, the altered morphology in piriform cortex could not be replicated.

To the best of our knowledge, **Study III** is the first study assessing resting-state functional connectivity in isolated congenital anosmia. Therefore, hypotheses in **Study III** were based on a literature of sensory deprivation in other sensory modalities, developmental studies, and olfactory functional neuroimaging studies. We hypothesized that a life-long absence of olfactory input would change the intrinsic connectivity from, and within, olfactory processing regions. This was not the case. Results from **Study III** demonstrated normal functional connectivity within the piriform cortex and between piriform cortex and both the orbitofrontal cortex and anterior insula. Because olfactory processing regions are located in parts of the brain prone to susceptibility artifacts when using BOLD fMRI, which might conceal potential effects (Ojemann et al., 1997), the raw BOLD signal amplitude was assessed in the ROIs as well as in additional regions less vulnerable to susceptibility artifacts. Comparable signal amplitudes, however, were demonstrated for all regions, except for the anterior olfactory nucleus, a subregion of the primary olfactory ROI. Furthermore, as an additional quality control measure, we established that our control group data could be used to replicate a previous publication of an olfactory resting-state network (Tobia et al., 2016). Together, this indicates that we have sufficient signal in our ROIs and that our data processing steps to, e.g., reduce motion-induced noise, have not distorted the data, as previous results can be replicated. Similar to **Study II**, the lack of differences between groups in **Study III** remained despite the application of very liberal statistical thresholds. Therefore, Bayesian analysis were applied post-hoc and resulted in support for the null hypotheses. However, for the post-hoc applied analysis in **Study II** and **III**, it is important to note that neither the equivalence test nor the Bayesian statistics provided undisputable evidence of null-effects. For **Study II**, we have statistical support for a lack of effect of the size that can be detected given at least 80 % statistical power, and for **Study III**, the evidence for the null hypothesis is anecdotal to moderate, not strong. In **Study IV**, the evidence for altered cross-modal audio-visual processing and audio-visual integration in piriform cortex in individuals with congenital anosmia was absent in the ROI-based analysis. Additionally, no voxels indicated group differences in either audio-visual processing or audio-visual integration in piriform cortex in the exploratory whole-brain voxel-wise analyses. Because these results are less controversial than the lack of structural and functional

connectivity alterations in **Study II** and **III**, no post-hoc analysis to assess evidence for the null-hypothesis was done.

Combined, the three neuroimaging studies communicate that we were unable to isolate any differences with respect to the function and morphology of the piriform cortex in individuals with isolated congenital anosmia. However, this does not necessarily mean that no differences in the structure or function of piriform cortex exist. In fact, a complete absence of abnormalities in cortical regions normally receiving direct bulbar input would be remarkable. When interpreting the results presented in the studies included in this thesis, the limitations of the methods used in relation to the questions asked must be taken into account. For example, the piriform cortex is a comparably small cortical regions with complex folding, spanning the medial frontotemporal junction. This could potentially lead to suboptimal normalization of individual brains into the MNI space, and thereby attenuating potential abnormalities in this regions in individuals with congenital anosmia. Additionally, MRI has restricted spatial and temporal resolution, meaning that the data upon which the null results are based are on a different temporal and spatial scale than the underlying neurons and their activity. Therefore, what we conclude regarding the structure of piriform cortex, based on the results in **Study II**, is that if individuals with isolated congenital anosmia have a structurally different piriform cortex than individuals with a normal sense of smell, the effects are smaller than what can be expected based on the effects of other sensory deprivations. Group differences could potentially be identified using a much higher spatial resolution than the 1 mm^3 used in **Study II** and, if possible, even larger samples.

Although no indication of differences in resting-state functional connectivity between individuals with congenital anosmia and normosmic individuals were found in **Study III**, it could be speculated that some form of functional connectivity alterations based on a lifelong lack of olfactory sensory input exist. Assuming that is the case, we must consider whether the failure to discover these differences in **Study III** could be caused by either the analysis approach adopted or by the type of data collected. With respect to analysis choices, it could be discussed whether the ROIs were optimally chosen and whether a data driven approach to define resting-state networks, such as independent component analysis, would have generated different results. Additionally, it could be hypothesized that by looking at changes in functional connectivity during the 9 minutes of rest using dynamic functional connectivity analysis rather than a static measure over the whole 9 minute time series, subtle group differences in functional connectivity could be discovered. Although these alternative analysis approaches should be investigated in the future, the ROIs in **Study III** were chosen based on the hypothesis that the potential connectivity alterations caused by absent olfactory input would be strongest in core olfactory regions. Furthermore, although it is plausible to find dynamic connectivity alterations despite a lack of differences in static connectivity, it is unlikely (Hutchison et al., 2013). Therefore, it is more feasible to assume that if group differences in connectivity exist, the absence of findings in **Study III** is based on the type of data used rather than the chosen analysis approach. A vital question to ask based on the results in the study is whether resting-state is appropriate for the study of olfactory connectivity. The connectivity between piriform cortex,

orbitofrontal cortex, and anterior insular cortex was low even in the control group consisting of individuals whose normal olfactory abilities were experimentally confirmed. Although these regions have previously been used as seeds for olfactory resting-state networks (Karunanayaka, Tobia, & Yang, 2017; Lu et al., 2019; Tobia et al., 2016), which we in **Study III** could replicate, our analysis identified that the overlap in connectivity from these regions is not large, therefore challenging the use of them to establish an olfactory resting-state network (discussed in the supplementary material of **Study III**). Furthermore, the fact that an olfactory network is not among the established resting-state networks, despite the existence of clear visual and auditory resting-state networks (J S Damoiseaux et al., 2006; Power et al., 2011) present early in life (Fransson et al., 2007), suggests that further investigation of the existence of an olfactory resting state network is called for. Specifically, this indicates that resting-state might be suboptimal to assess olfactory functional connectivity. In addition to the specific problems related to olfactory resting-state connectivity, we also have to consider the possibility that even if group differences in connectivity between individuals with anosmia and controls exist, we might not be able to discover them based on the limited spatial and temporal resolution of fMRI.

So far, I have discussed the lack of clear olfactory deprivation-dependent effects on piriform cortex morphology and function based on the assumption that effects do exist. Although it is difficult to imagine that lifelong olfactory inexperience has little to no effect on the piriform cortex, we should consider whether the very essence defining this patient group, the lifelong inexperience of odor sensations, is contributing to the lack of effects. Rodent studies investigating how piriform cortex is affected by olfactory bulb ablation, i.e., a complete removal of the olfactory bulb and thereby the olfactory afferent signals, indicate that if the olfactory bulb is removed closely after birth, the effects on piriform cortex are small. Specifically, if the bulb is removed right after birth, thereby partly mimicking a congenital deprivation, the cortical thickness in piriform cortex is practically unaffected; in contrast, a later removal of the olfactory bulb causes a marked cortical thinning (Friedman & Price, 1986a, 1986b; Westrum & Bakay, 1986). The sustained piriform cortical thickness in animals with this early removal of afferent input is likely based on the fact that intracortical association fibers extend into the outer cortical layer in which the afferents normally reside (Friedman & Price, 1986b). Interestingly, beyond the extension into outer cortical regions, no indications of altered organization of the association fibers were demonstrated. This suggests that the structural connectivity remains essentially unaltered, with the obvious exception being the afferent connections from the non-existing olfactory bulb. Although structural connectivity, as studied in the rodents, and functional connectivity, as assessed in **Study III**, are measures that do not overlap completely even if studied in the same species, the measures are intertwined (Jessica S Damoiseaux & Greicius, 2009). We cannot determine whether the preservation of cortical thickness and connectivity demonstrated in these studies of bulb ablation can be directly translated to humans with isolated congenital anosmia; however, these studies do provide a potential explanation for the lack of structural as well as functional effects in piriform cortex in **Study II-IV**.

If the same cortical reorganization principles as those observed in the rodent bulb ablation studies also apply in humans with anosmia, a redistribution of cells in the cortical layers of piriform cortex, but no strong effect on cortical size, would be expected in individuals with congenital anosmia. This could potentially be confirmed using a much higher spatial resolution than the 1 mm^3 used in **Study II**, or in post-mortem histology samples. The bulb ablation studies furthermore support a clear morphological alteration in piriform cortex when the afferent input is lost at a later developmental stage than directly after birth. In humans, this would suggest that a morphological reorganization in piriform cortex in individuals with acquired anosmia would be evident. This notion has some support in the human literature, with gray matter volume decreases in piriform cortex demonstrated in individuals with acquired anosmia compared to controls (Bitter et al., 2010; Peng et al., 2013; Yao et al., 2014; however see Yao et al., 2017). The combined results from the studies include in this thesis, the studies on brain morphology in acquired anosmia, and the rodent bulb ablation studies, suggest that the concept of an early critical period with high plasticity, during which the strongest effects of sensory deprivation occur, might not hold for olfactory deprivation. In fact, it has been argued that no critical period exists in olfaction, at least not in the same sense as in the other sensory modalities (Coppola & White, 2019). Coppola and White argue that except for an early, brief period of high synaptic plasticity of bulbar input to the rat piriform cortex, a plasticity that remains high for associational synapses throughout life, no clear signs of a typical critical period are present. Coppola reasons that because olfaction does not share the temporal and spatial dimensions visual and auditory processing are dependent on, olfactory processing does not have to adjust for body growth or align with the other senses based on these attributes. This is indeed an interesting distinction between sensory modalities, which I will return to below (chapter 5.3).

Given that piriform cortex naturally does not process olfactory input in individuals with congenital anosmia, the obvious question to ask is what the functional role of these regions are in individuals with a lifelong absence of olfactory experience. Unfortunately, none of the studies in this thesis is able to provide much help answering that question because none of them provide any indications of functional or structural reorganization in piriform cortex. We can, however, speculate that because the piriform cortex is not solely processing olfactory input in individuals with normal olfactory abilities, the non-olfactory processing might be preserved, despite olfactory deprivation, upholding the macroscopic structure and connectivity of piriform cortex. A relevant example of the non-olfactory processing is the piriform cortex activity induced by the mere act of sniffing without odor present (Sobel et al., 1998). Naturally, nose breathing and sniffing is present also in individuals with congenital anosmia, and tentative evidence (not peer reviewed) suggest that the sniff-induced activation of piriform cortex is in fact also present in individuals with congenital anosmia (Weiss et al., 2016). However, the sniff-induced activity is still much lower than the odor-induced activity (Kareken et al., 2004), and it has furthermore been indicated that the nasal airflow linked to the sniff-induced processing is sensed by the olfactory sensory neurons (OSN) (Grosmaitre, Santarelli, Tan, Luo, & Ma, 2007). Because individuals with congenital anosmia often lack olfactory epithelium, in

which the OSNs reside (Jafek et al., 1990; Leopold et al., 1992), the potential sniff-induced activity in individuals with congenital anosmia needs to be further investigated, and alternate potential explanations for the function of piriform cortex in the absence of olfaction should be considered.

Similar to higher-order association cortices, the piriform cortex has reciprocal connections with a wide network of brain regions and demonstrates associative memory properties (Dade, Zatorre, & Jones-Gotman, 2002; Gottfried, 2010; Kay, 2011). The distributed activation patterns demonstrated in piriform cortex in response to stimuli seem to be strongly linked to the odor or odor-object identity, with little alteration under associative learning paradigms when paired with reward or punishment (but see Li, Howard, Parrish, & Gottfried, 2008). This has been demonstrated both when the learned behavior is linked to an actual odor stimulus (P. Y. Wang et al., 2020) and when arbitrarily selected neuron populations in piriform cortex are stimulated in learning paradigms (Choi et al., 2011). Still, the stable activation patterns are directly linked to behavioral outcomes. Of particularly high relevance for the work in this thesis is the fact that stimulation of piriform neurons in anosmic mice led to conditioned behavior, just as it did for non-anosmic mice (Choi et al., 2011). This confirms that activation of neurons in the piriform cortex, independent of the existence of olfactory sensory input, is sufficient to elicit learned behavioral responses. Furthermore, it has been demonstrated that plasticity within piriform cortex induced by input from association fibers remains throughout life (Best & Wilson, 2003) and that the synaptic plasticity in piriform cortex is more strongly affected by descending input from the orbitofrontal cortex than afferent input from the olfactory bulb (Strauch & Manahan-Vaughan, 2017). In line with the task-selective organization of the brain discussed in (discussed in chapter 1.4.3), it could therefore be hypothesized that the memory-like function displayed by the piriform cortex is retained in individuals with congenital anosmia based on non-olfactory input.

A limitation of the investigation of potential structural and functional group differences in olfactory cortex in **Study II-IV** is that different ROIs were used in the three studies. **Study II** was based on whole-brain voxel-wise analysis where the piriform ROI was solely used for post-hoc equivalence testing because no group differences were detected in this hypothesized region using voxel-wise comparisons. Specifically, the piriform ROI was based on a recent publication in which the primary olfactory cortex was manually delineated based on an anatomical atlas (Zhou et al., 2019). Based on the null-results in piriform cortex in **Study II**, an extended version of the same piriform ROI, also including the two primary olfactory regions the anterior olfactory nucleus and olfactory tubercle, was used in **Study III** to investigate functional connectivity differences during rest. In **Study IV**, a different piriform ROI than the one used in **Study II** and **III** was used, so as to be consistent in the manner of defining ROIs across all four ROIs included in **Study IV**; a combination of activation- and atlas-based definitions of regions were used to create all four ROIs. Additionally, the piriform ROI used in **Study IV** is the one in which Porada et al. (2019) indicated multisensory integration effects, which suited the purpose of **Study IV** well. Although the discrepancy between studies does not facilitate direct comparisons of results between studies, all three studies also included voxel-

wise comparisons using quite liberal thresholds, hence assuring that effects, or in this case, the lack thereof, are not strictly dependent on ROI definition.

5.2 PLASTIC REORGANIZATION VERSUS CONGENITAL ABNORMALITIES

Plasticity is a term adopted to describe a variety of structural and functional alterations in the brain. As briefly discussed in chapter 4, views differ on when plasticity is an appropriate term to use; in the title of this thesis, it is used in one of the widest senses, originating from between-group differences. Compared to a title, this discussion leaves more room to elaborate on how demonstrated group differences might arise, i.e., whether they stem from plastic reorganization processes or not. The atypical morphology demonstrated within the orbitofrontal cortex in individuals with isolated congenital anosmia in **Study II** will be theoretically examined. In particular, I will address the question of whether the atypical morphology results from a plastic cortical reorganization or whether it is a congenital effect, unrelated to plastic reorganization.

Study II revealed two different types of atypical morphology in the orbitofrontal cortex in individuals with congenital anosmia: volumetric decreases in and around the bilateral olfactory sulci and volumetric increases in the bilateral medial orbital gyri. These results were supported by surface-based measures of cortical thickness, curvature, and area, and replicate and extend the previously reported orbitofrontal cortical thickness increase (Frasnelli et al., 2013) and gray matter volume decrease (Karstensen et al., 2018). A potential explanation of this distinctively different morphology in the orbitofrontal cortex in individuals with congenital anosmia is the hypothesis of congenital abnormal cortical folding presented in the discussion in **Study II**. In essence, the hypothesis states that an absence of olfactory bulbs during development would cause abnormal development of the olfactory sulci because the formation of the olfactory sulci depends on the projection of the olfactory tracts, which, in turn, depends on the olfactory bulbs (Abolmaali et al., 2002; Huart et al., 2011; Turetsky, Crutchley, Walker, Gur, & Moberg, 2009). Hence, a congenital lack of olfactory bulbs is linked to a significantly decreased olfactory sulcus depth, and the atypical morphology demonstrated around the olfactory sulci naturally follows upon this abnormal cortical folding. This hypothesis could be directly tested by assessing anosmic individuals assumed to have congenital or a very early onset of anosmia, who also demonstrate olfactory bulbs of typical size. An absence of morphological abnormalities around the olfactory sulci in these individuals would indicate that the deviating morphology around the olfactory sulci demonstrated in individuals with congenital anosmia in **Study II** indeed are of a congenital origin, rather than being a secondary effect of lifelong olfactory deprivation. Unfortunately, this type of study would be very difficult to perform because the majority of individuals with congenital anosmia demonstrate a complete lack of olfactory bulbs; none of the 33 individuals with isolated congenital anosmia included in **Study II-IV** demonstrated clearly visible bulbs. An alternative approach would be to investigate whether atypical orbitofrontal morphology is present very early in life in individuals with congenital anosmia, which would suggest a congenital origin. This would, however, require olfactory screening of young children which is typically not done, reflected by the fact that congenital anosmia is typically not diagnosed until the early teens.

In contrast to the morphological decreases around the olfactory sulci in individuals with isolated congenital anosmia, the volumetric increases in the medial orbital gyri cannot as effortlessly be explained by the hypothesized congenital abnormal cortical folding. If we assume that the size of the cortical surface remains essentially unaltered despite alterations in cortical folding, the flattening of the olfactory sulci should lead to altered morphology in surrounding regions because of a location shift of the cortical surface normally residing in the olfactory sulci. However, **Study II** indicated decreased cortical surface area in the bilateral olfactory sulci in individuals with congenital anosmia without demonstrating any increases elsewhere. Consequently, a suggested shift of cortical surface from the flattened olfactory sulci to the medial orbital gyri cannot be substantiated and does not provide a reasonable explanation for the volumetric increases in the medial orbital gyri. Additionally, if the gray matter volume increases in the medial orbital gyri were directly caused by the atypical cortical folding in the olfactory sulci, the clusters of increased volume would be expected to appear along the clusters of decreased volume in the olfactory sulci. Instead, the clusters of gray matter volume increase have a more spherical shape than the elongated clusters of gray matter decrease in the olfactory sulci. The clusters of gray matter volume increase are located lateral to the anterior part of the clusters of decrease, further challenging a link between a congenital abnormal cortical folding and the gray matter volume increases. Altogether, the results in **Study II** do not provide any evidence supporting the hypothesis of a congenital abnormality in the olfactory sulci as the cause of the volumetric increases in the medial orbital gyri.

If we, based on above arguments, assume that the gray matter volume increases within the medial orbital gyri in individuals with isolated congenital anosmia are not of congenital origin, the increases must be a result of sensory deprivation-induced plastic cortical reorganization. The regions with increased gray matter volume in congenital anosmia demonstrate a partial overlap with the regions that, next to piriform cortex, demonstrate the most reliable activation when presented with olfactory stimuli (Seubert, Freiherr, Djordjevic, et al., 2013). However, the orbitofrontal cortex is a highly multimodal region (see chapter 1.1.3), which complicates interpretations of its cortical alterations. We can speculate about a significant decrease in processing due to the absence of olfactory input, but also about a potential increase in non-olfactory processing based on the multimodal nature of the orbitofrontal cortex. If the orbitofrontal regions linked to olfactory processing are assumed to be deprived of most input in the absence of olfactory input, the cortical increases might be explained based on the same principle used to explain the counterintuitive cortical increases within visual cortex in congenitally blind individuals, namely a lack of synaptic pruning during development (J. Jiang et al., 2009; Park et al., 2009; Frasnelli et al., 2013). In short, the lack of relevant sensory input during early development leads to an absence of the normally-occurring pruning of redundant

synapses, which leads to a subsequent increase in cortical thickness in comparison to individuals going through the normal, developmental pruning process[1].

Potential atypical functional processing within the regions that demonstrate atypical morphology in individuals with isolated congenital anosmia could help explain their atypical morphology. However, as of today, no evidence of altered functional processing within the orbitofrontal cortex in individuals with isolated congenital anosmia has emerged. **Study III** revealed normal resting-state functional connectivity between the orbitofrontal cortex and both the piriform and insular cortices. Furthermore, no altered processing or integration of audio-visual stimuli were in **Study IV** demonstrated in the orbitofrontal cortex. Bell et al. (2019) suggested that sensory-induced compensatory processing only occurs for functions that both the absent and remaining senses can perform, such as spatial processing performed using both audition and vision. The notion of a task-selective rather than sensory-selective organization of the brain aligns quite well with this theory (Amedi et al., 2017). The theory postulates that cortical regions with a specific function will continue to perform this function despite being deprived of input from the sense normally providing the major part of input if it receives relevant input from other sensory modalities. Based on these views, the function orbitofrontal cortex plays in olfactory processing could help create hypotheses of potential functional reorganization associated with the structural increases. Because the orbitofrontal cortex is associated with flavor processing by integrating olfactory, gustatory, trigeminal, and somatosensory signals (Price, 2008; Rolls, 2005), it could be hypothesized that compensatory processing of the non-olfactory flavor components occur in the orbitofrontal cortex. Congenital anosmia is associated, however, with neither enhanced gustatory nor enhanced trigeminal abilities; if anything, these abilities are diminished (Frasnelli et al., 2010; Gagnon et al., 2014; Gudziol et al., 2001). A link between the cortical alterations and increased processing of the non-olfactory components of the flavor percept is therefore unlikely.

Alternatively, one of the more prominent functions of the orbitofrontal cortex is reward processing (Gottfried & Zald, 2005; Kringelbach & Rolls, 2004), with demonstrated involvement in olfactory value prediction and learning (Gottfried & Zelano, 2011; Howard et al., 2015; P. Y. Wang et al., 2020). Clearly, reward-related processing is a function that is not solely reserved for olfaction but highly relevant in relation to input from all sensory modalities. Hence, reward processing in healthy individuals is a function performed with input from the olfactory sense as well as other sensory modalities, and reward is processed in the orbitofrontal cortex, a region demonstrating structural reorganization in isolated congenital anosmia. It could therefore be hypothesized that altered reward processing is a consequence of congenital anosmia. Although this hypothesis is speculative, exploring whether the processing of reward

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[1] The pruning of redundant synapses based on sensory input is a plastic process. Arguably, a lack of this process in individuals with congenital sensory deprivation, resulting in altered brain morphology as compared to individuals with intact senses, should not be considered a plastic reorganization but instead a lack of the plastic reorganization occurring during normal development.

could be connected to regions demonstrating atypical morphology in individuals with congenital anosmia might be an interesting future research avenue.

It should be noted for future studies assessing potential functional alterations related to the clusters of volumetric increase in individuals with congenital anosmia that these clusters reside in a region of the orbitofrontal cortex that is strongly affected by susceptibility artifacts of the BOLD signal. In the functional neuroimaging data sets included in this thesis (**Study III and IV**), the BOLD signal amplitudes were found to be adequate in the orbitofrontal ROIs used (based on neuroimaging meta-analysis). However, when assessing the signal in ROIs based on the clusters that demonstrate gray matter volume increases in individuals with congenital anosmia, the BOLD signal was clearly distorted and some participants had insufficient coverage. Measures should be implemented to ensure good data quality in these regions, and potential discrepancies between structural and functional images should be considered when interpreting results within artifact prone regions. All in all, difficulties in functional imaging of the regions demonstrating structural abnormalities in congenital anosmia suggests that the functional role of these clusters might be difficult to determine using standard BOLD fMRI sequences.

5.3 AUDIO-VISUAL INTEGRATION IN OLFACTORY SENSORY DEPRIVATION

The results in **Study I** indicate that individuals with anosmia, and in particular those with congenital anosmia, demonstrate enhanced audio-visual integration performance. Both individuals with acquired and congenital anosmia demonstrated a significant narrowing of the audio-visual temporal binding window in comparison to matched controls. The narrowing of the temporal binding window is arguably interpreted as an enhanced ability, with increased detection of small temporal asynchronies associated with, e.g., enhanced performance in problem solving tasks (L. Zmigrod & Zmigrod, 2016). In contrast, a broader temporal binding window has been associated with neurodevelopmental disorders where problems with multisensory integration is a disease characteristic, such as autism spectrum disorders, schizophrenia, and dyslexia (Stevenson, Siemann, et al., 2014; Wallace & Stevenson, 2014). Furthermore, individuals with congenital, but not acquired, anosmia demonstrated increased multisensory enhancement, compared to controls, in a task with degraded dynamic stimuli. However, this increased multisensory enhancement was only demonstrated when comparing performance based on multisensory informative stimuli to unisensory informative stimuli; no significant group differences were demonstrated when comparing multisensory informative stimuli to multisensory stimuli with unisensory information (i.e., unisensory informative stimuli with pure noise in the non-informative sensory modality). The fact that more evident behavioral benefits were demonstrated by individuals with congenital anosmia resonates with the literature on deprivation-dependent behavioral and neural reorganization in other sensory modalities which generally demonstrates stronger effects for congenital than acquired sensory deprivation (see chapter 1.3.1 and 1.4.1). It should, however, be noted that the subgroup of individuals with acquired anosmia included in **Study I** was small (albeit the number of participants with acquired anosmia is comparable to the sample sizes in many studies of sensory

deprivation; for further discussion on this topic, see chapter 5.4). Results based on analyses of this subgroup should therefore be interpreted with caution.

From a compensatory point of view, it could be argued that the enhanced multisensory integration abilities demonstrated by individuals with anosmia are a compensatory consequence of the olfactory deprivation, allowing the deprived individuals to extract as much useful information as possible from the remaining sensory input. However, for auditory and visual sensory deprivation, the existence of multisensory compensatory abilities are not as evident as those demonstrated in **Study I** for individuals with anosmia. In particular, congenitally blind individuals appear to demonstrate a lower degree of integration of inputs from different sensory modalities (further discussed in chapter 1.5.3). Although this might appear like a disadvantage, it also implies that these individuals are better at ignoring distracting input from an irrelevant sensory modality when focusing attention on the input from one sense. It has been suggested that the sensory separation demonstrated by blind individuals is caused by a lack of alignment between an internal space (experienced by tactile sensory input) and an external space (experienced by auditory sensory input). In contrast to the visual, auditory, and tactile senses that all provide spatial and temporal information, olfactory input does not contribute information about these dimensions. This suggests that while the absence of visual input might impede the alignment of auditory and tactile input, thereby hindering optimal sensory integration, olfaction is not required to calibrate how the auditory and visual senses align. Congenital olfactory deprivation should therefore not have a detrimental effect on audio-visual integration, a notion confirmed by **Study I**.

Based on the behavioral results in **Study I**, **Study IV** aimed to assess potential neural differences in audio-visual processing and integration between individuals with isolated congenital anosmia and matched normosmic individuals. An experimental paradigm assessing integration of dynamic multisensory stimuli, similar to the paradigm used in **Study I** where individuals with congenital anosmia demonstrated greater multisensory enhancement, was used in **Study IV**. Contrary to the hypotheses of increased multisensory cross-modal processing in olfactory regions or in established multisensory regions, no differences were demonstrated between individuals with congenital anosmia and controls in the *a priori* selected ROIs. However, support for increased multisensory integration in established multisensory regions in individuals with congenital anosmia was found based on exploratory whole-brain voxel-wise group comparisons. Specifically, higher audio-visual integration activity was demonstrated in the left posterior superior temporal sulcus and in the superior colliculus; however, this was not significant at a conservative statistical threshold corrected for multiple comparisons. Based on the exploratory character of these results, in combination with the non-conservative statistical threshold, replication is called for. Nonetheless, if we assume that both the fMRI-based results indicating enhanced multisensory integration activity within multisensory regions in individuals with congenital anosmia and the behavioral results suggesting enhanced multisensory integration performance by the same group are reproducible and valid, a link between these results is probable. It can be hypothesized that an olfactory deprivation-induced facilitation of audio-visual integration occurs in established multisensory

regions, thereby enabling improved integration performance. Although the mechanisms are unknown, it could be speculated that a lifelong absence of olfactory input to the superior temporal sulcus, a region implicated in visuo-olfactory integration (Gottfried & Dolan, 2003), could facilitate integration of the remaining senses processed in this region. This speculation is partially supported by the non-human animal literature demonstrating that the absence of input from a sensory modality regulates the neuronal compositions within multisensory regions. Specifically, a congenital absence of visual input has, in multisensory regions, been associated with an increased proportion of neurons responding to a spared sensory modality (Hyvärinen, Hyvärinen, & Linnankoski, 1981) as well as a preserved or slightly increased number of multisensory neurons responding to bimodal input from two spared senses (Carriere et al., 2007; Wallace, Perrault, Hairston, & Stein, 2004). It is, however, unclear if this altered neural composition leads to enhanced integration performance.

A potential facilitation of multisensory integration of spared sensory modalities in regions normally integrating olfactory input would, however, not explain the demonstrated increase in **Study IV** in integration activity within the superior colliculus. The superior colliculus receives and integrates auditory, visual, and somatosensory input. However, although the superior colliculus is strongly related to audio-visual integration, the region has not previously been linked to olfactory processing and was therefore not included among the *a priori* hypothesized regions. The superior colliculus is one of the most well-studied multisensory regions in the animal literature and is associated with integration of basic stimulus qualities, such as the temporal and spatial aspects of stimuli. It is noteworthy that the multisensory performance benefit most clearly demonstrated by individuals with anosmia in **Study I** was the narrowing of the temporal binding window, demonstrated in an experimental paradigm based on temporal integration (or separation) of simple perceptual stimuli. In light of the imaging results from **Study IV**, it plausible that the superior colliculus is mediating this perceptual alteration in individuals with anosmia, although temporal integration has also been linked to cortical multisensory regions, namely the superior temporal and intraparietal sulci (Powers, Hevey, & Wallace, 2012; S. Zmigrod & Zmigrod, 2015). It would be relevant to assess the temporal binding window in individuals with anosmia while simultaneously doing neuroimaging with high temporal resolution, such as magnetoencephalography. We would then be able to determine not only whether the behavioral multisensory benefit can be replicated, but also start to delineate processing mechanisms linked to these perceptual differences, potentially in the superior colliculus.

In contrast to the indications of increased multisensory integration processing within multisensory regions in individuals with congenital anosmia, the absence of statistically significant group differences in olfactory processing regions demonstrated by our ROI analysis remained absent also in the exploratory whole-brain analysis. Hence, no support for the hypothesized cross-modal processing as a basis for altered behavioral performance was found in **Study IV**, despite the link between cross-modal processing and behavior demonstrated in blind individuals (Collignon et al., 2007; Gougoux et al., 2005). However, if we assume that the main purpose of processing in olfactory regions reflects the previously suggested functions,

namely memory-like processing in piriform cortex and reward-related processing in the orbitofrontal cortex, audio-visual integration would not be considered the most likely functional takeover of these regions, based on the reasoning of a task-selective organization of the brain. So far, the functional roles of these regions in individuals with a lifelong absence of olfactory input remain unknown.

5.4   ON THE IMPORTANCE OF GROUP IN SENSORY DEPRIVATION STUDIES

The absence of support for structural and functional differences within piriform cortex in individuals with congenital anosmia can be perceived as striking, especially when compared to the clear effect on functional connectivity and spontaneous activity demonstrated as a result of a short-term disuse of an arm by wearing a cast for two weeks (Newbold et al., 2020). Why does a lifelong absence of olfactory experiences not affect the functional connectivity in olfactory cortex in a similar manner? Although I cannot provide a satisfactory answer to this question, there are differences between the studies included in this thesis and the study by Newbold *et al.* that help explain the differences in results. One clear difference between the studies is the fact that in the study of short-term disuse of an arm, there is an abrupt alteration in function, and therefore in processing, in related cortical regions. In contrast, absence of olfactory processing is the normal state for individuals with congenital anosmia. I specifically want to highlight a second important difference between the studies, as it is an inherent problem in (human) sensory deprivation studies. When studying rare conditions that we are unable to reverse and ethically cannot induce in humans, we rely on comparisons between individuals rather than within individuals. The large between subject variability in most measures of interest leads to large amount of noise in the data, thereby reducing the probability of finding effects. In these types of studies, the general assumption is that the control group serves as a baseline measure against which the rare subject group is compared. Potential group differences are then intuitively interpreted as an effect dependent on the sensory deprivation. However, because all individuals differ, so do different constellations of control groups. A clear example of how this can be problematic is the study by Alary et al. (2009) in which tactile performance of blind individuals was compared to two different sighted control groups. The blind group only demonstrated enhanced performance in comparison to one of the two control groups. If only one control group had been included, the performance of blind individuals would either have been interpreted as a clear enhancement in abilities or as normal performance. The fact that the control group constellation affects the results of studies, and thereby the interpretation of the subject group studied, emphasizes the importance of choosing an appropriate control group. To limit confounding variables that might inflate (or reduce) group differences, as close a match as possible on relevant parameters between individuals in the control and sensory deprivation groups is therefore preferred. However, the specific qualities upon which the matching should be based depends on the particular phenomenon studied.

In addition to the importance of selecting an appropriate control group, the heterogeneity within sensory loss groups can also be a potential confounder (Merabet & Pascual-Leone, 2010). As discussed in chapter 3 and 4, there are differences between individuals with a congenital

sensory deprivation and those with a late-onset loss, and these groups are often separated in studies. However, individuals who were deprived of a sense early in life are often grouped together with individuals with congenital sensory deprivation. Combined with the fact that the definition of when a deprivation should be considered as early-onset varies greatly between studies, this leads to large differences in group constellations between studies (P. Voss, 2013). Additionally, the cause and duration of sensory deprivation further contributes to the heterogeneity. In **Study I**, both individuals with congenital and acquired anosmia participated. To keep the homogeneity in the acquired anosmia group relatively high, we restricted the recruitment of participants based on, e.g., the duration and cause of sensory deprivation (e.g., only non-traumatic cause). However, this resulted in a much smaller subgroup of individuals with acquired anosmia than that of individuals with congenital anosmia, although an acquired olfactory sensory deprivation is much more common. The results of **Study I** suggest that there are both similarities and differences between the two anosmia subgroups. However, the small sample size creates the drawback that no strong conclusions can be made. We decided to restrict our sample to only include individuals with isolated congenital anosmia in **Study II-IV**, to build a solid ground to stand on by keeping the sample homogeneous. The results from these studies call for future assessment of individuals with acquired anosmia to provide more information on cortical reorganization (or the lack thereof) as a result of complete olfactory sensory deprivation.

Albeit the studies in this thesis have quite large sample sizes in comparison to the majority of studies on complete sensory deprivation, the included sample sizes would not be considered large in most other contexts in which the results are based on between-group comparisons. The generally small sample sizes in studies of sensory deprivation are a natural consequence of the rarity of complete sensory deprivation. Small samples lead to low statistical power to detect small effects. For example, the equivalence test comparing piriform cortex gray matter volume between individuals with congenital anosmia and normosmic controls in **Study II** could only demonstrate statistical support for an absence of group differences larger than the effect size we had sufficient power to detect, as discussed above. Although there are exceptions, studies of sensory deprivation commonly include less than 20 sensory deprived individuals, and samples smaller than 10 are not unusual. Publishing null-effects is likely very difficult with these small sample sizes given that the lack of statistically significant effects in studies with low statistical power do not provide much knowledge. At best, results might provide support for a lack of a very large effect but will be insufficient to give further insight about smaller effects. Therefore, it is imaginable that the published literature is biased, suggesting that effects of sensory deprivation are greater than they actually are. This is probably not caused by an intent to publish inflated effects, but more likely because null-results often remain unpublished when based on small samples. One thing that can be done to counteract this effect is to increase sample sizes through research collaboration by initiating multi-site studies (as done in **Study II-IV**). These types of studies do, however, come with their own inherent drawbacks related to differences between data collection sites. Study protocols should remain as consistent as possible for all sites, and it should be a particular priority to always include a matched control

to a sensory deprived individual at the same site. This way, potential between-group effects are not confounded by site differences. Although the increased within-group variance in multi-site studies potentially can disguise effects, the increase in sample size should more than compensate for this problem.

5.5   CONCLUSIONS

This thesis aimed to assess how complete olfactory sensory deprivation affects the human brain and behavior. The results presented suggest that anosmia is associated with enhanced audio-visual integration performance and increased audio-visual integration activity in established multisensory integration regions. However, although anticipated morphological alterations in the orbitofrontal cortex were demonstrated in individuals with congenital anosmia, the results presented in this thesis demonstrate that congenital olfactory sensory deprivation does not have the expected effects on the human brain based on evidence from sensory deprivation in other sensory modalities. Absence of evidence for reorganization of the piriform cortex, the cerebral region that receives most of the input from the olfactory bulb, stands in sharp contrast to the expected alterations in morphology, functional connectivity, and potential cross-modal processing, based on the existing literature. The clear discrepancies between the effects of deprivation in different senses stress the importance of not using deprivation in one sensory modality as a model for how sensory deprivation affects our brain in general. The notion that that there are common principles of how the brain copes with sensory deprivation in all sensory modalities (Merabet & Pascual-Leone, 2010) should be adopted with caution. Studies included in this thesis only scratch the surface of how complete olfactory sensory deprivation affects the human brain and behavior. Nonetheless, I hope that this thesis can be used as a stepping stone towards further research trying to answer some of the questions it has raised.

5.6   FUTURE DIRECTIONS

The studies in this thesis have provided both expected and unexpected results with varying degrees of statistical support. Presented results have led to some clear conclusions but also raised many new questions. Based on the results presented in this thesis, I believe there are three main directions future research should take.

First, the question I find most critical is to determine what functional role piriform cortex has in individuals with isolated congenital anosmia. The surprising and clear lack of evidence for any alteration in this region makes the question of reorganization particularly compelling because the delineation of the region's functions has the potential of shedding light upon the reasons behind these null-results.

Second, further research is needed on multisensory integration in individuals with anosmia. The studies included in this thesis support the idea that audio-visual integration is affected by anosmia on a behavioral performance level as well as on a neural processing level. However, the demonstrated effects require replication and should not be considered as unquestionable evidence for behavioral and neural compensatory plasticity. Nonetheless, the notion that there

are potential positive aspects of losing one's sense of smell is a very powerful and positive message to many individuals with sensory loss.

Third, the mechanisms behind the deviating morphology in the orbitofrontal cortex demonstrated by individuals with isolated congenital anosmia, and its potential functional implications, should be determined.

Finally, the research presented in this thesis is basic research aiming to increase our understanding of the neural and behavioral effects of a total absence of olfactory input; here with a specific focus on individuals with a lifelong olfactory inexperience. Therefore, the results presented here have no direct clinical relevance. However, increasing our understanding of the olfactory brain, and particularly how olfactory deprivation affect its organization, could serve as a basis for research that is clinically oriented. The hope is that the results provided in this thesis can be a small contribution to that increase in knowledge. To this point, a salient notion derived from results presented here is whether the absence of discernible alterations in piriform cortex is a sign of preserved structural and functional organization that could, potentially, facilitate a recovery of olfactory abilities if future clinical advances enables a cochlear implant-like solution for the olfactory system. That could potentially be of relevance for a vast amount of people suffering from partial or complete olfactory sensory deprivation.

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