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AN OBJECT'S SMELL IN THE MULTISENSORY BRAIN

HOW OUR SENSES INTERACT DURING
OLFACTORY OBJECT PROCESSING

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An Object's Smell in the Multisensory Brain

How Our Senses Interact During Olfactory Object Processing

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Für meinen Onkel Bewo

POPULAR SCIENCE SUMMARY OF THE THESIS

Imagine yourself waking up in your bed in the morning. It is quite early and you still need another minute to properly wake up. You turn over again. But, what is this smell that breezes past your nose? Is it coffee? Is it really true that your partner is already preparing coffee? You are not quite sure. Maybe it is just wishful thinking. That is why you get out of your bed and walk towards the kitchen. The closer you get to the kitchen the stronger the smell gets, and in addition, you can hear the sound of the coffee machine brewing coffee. You are now pretty sure that it is the smell of freshly brewed coffee that fills the apartment. You have evidence from two senses at the same time: your sense of smell and your sense of hearing. Although you already feel quite certain about what you perceive, as soon as you enter the kitchen and also see the coffee machine brewing coffee, you are completely convinced. Now three of your senses are simultaneously telling you that what you perceive is coffee. You do not, however, have three separate sensory impressions. Instead your brain does the magic of taking the different sensory inputs and fusing them into one percept. This magic is called multisensory integration.

The ability to integrate different sensory impressions appears to be especially important and beneficial when we perceive an object's smell. That is because we generally have difficulty recognizing an object based on its smell alone. For example, consider the situation when you were lying in bed and merely perceived the smell of coffee. You were not able to identify, without doubt, what the smell was. But as soon as you received help from your sense of hearing, it became more apparent what you were smelling. And it was fully apparent when you finally also saw where the smell was coming from. The present thesis tries to shed some light on what happens in your brain in these three different situations.

The studies involved in this thesis aimed to answer three main questions: 1. Where and how is information about an object's smell processed in the brain when we face a situation in which we merely perceive a smell and try to identify what it is? 2. Which brain regions are generally involved in combining object-related information from different senses, regardless of whether we perceive an object through two or three senses? 3. What happens in brain regions that are attributed to the sense of smell when we perceive an object's smell and additionally receive assisting input from one or two other senses?

Taken the results of all studies together, we show that when we perceive an object's smell, not only brain regions that belong to the sense of smell but also areas belonging to the sense of vision and other distributed brain regions are additionally involved. Let us reconsider the coffee example and apply our findings to the three different situations described.

Our results indicate that in a situation like the first setting described above, where the individual were lying in bed, trying to identify what they were smelling, brain regions usually concerned with processing information about objects that are seen, now process information about the object that is smelled. While doing so, these regions are not merely active but show a specific pattern of activation. This pattern is specific to the object currently processed. This means that

by looking at the brain's activation pattern one can read out that it is the smell of coffee that is perceived.

Let us continue with the next setting where the individual additionally heard the sound of the object that they were smelling. We show that in such situations, two brain regions play an important role; one located in the lower posterior half of the brain's left hemisphere and one being part of the brain's smell system. The first region is called the left inferior parietal cortex and appears to be responsible for establishing a relationship between what is, for example, smelled and heard. This function is an essential sub-process of multisensory integration. First, it has to be evaluated whether the incoming signals are related, meaning whether they carry information about the same object. Only if they do so they should be integrated into a fused percept. That is, although the inferior parietal cortex does not seem to fuse different sensory inputs, it plays a key role in the magic process. Our results indicate that actual integration of an object's smell and, for example, the corresponding sound is performed by the brain region that is part of the brain's smell system and is responsible for processing the object information that is carried in a smell. This region is called the posterior piriform cortex. We found that it does not only receive information about an object's smell but also about its sound and look; if what is heard matches what is smelled, it integrates the signals. Applied to the example scenario above, it means that because the sound of the coffee machine and the smell of freshly brewed coffee are both associated with the object coffee, the posterior piriform cortex takes the two incoming signals and merges them. Thereby, the processing of the smell gets boosted. It is likely that this boosting is what improves the perception of the smell.

Finally, let us consider the last situation where the individual smelled, heard and saw the object coffee at the same time. We observed that in such a setting where an object is perceived through three senses, the inferior parietal cortex is more active compared to a situation where only two senses are involved. This likely indicates that here the process of establishing a relationship between the incoming signals is more demanding because more senses need to be related to each other. We further observed that the more senses provide helpful input about the smelled object, the more the posterior piriform cortex is active. This continuous increase in activation from one situation to the other is probably what makes the percept of the object coffee become clearer and clearer.

Taken together we found that the perception of an object's smell is a very complex process that requires the teamwork of a widespread network of brain regions. If we encounter ourselves in a multisensory situation where we smell an object and simultaneously see and hear it, the different sensory impressions are probably first related to each other in the inferior parietal cortex, and if they match they are then combined in the posterior piriform cortex to improve processing of the object's smell. But not only multisensory situations elicit engagement of other brain regions than the ones in the smell system. Even when we merely smell an object, without seeing, feeling tasting, or hearing it, far more brain regions than just the ones belonging to the brain's smell system are recruited. But why? It is likely that the brain is wired to work as efficient as possible by spreading computational demands across several sensory systems. This

can be viewed as an analogy to grid computing where workload is distributed across several nodes in the network. Instead of overwhelming the brain's smell system with the task of identifying an object based on its smell, it appears very beneficial to additionally involve other sensory systems that are highly qualified and effective to process object information. We can thus conclude that the perception of an object's smell is a multisensory process, even if it does not obviously involve other senses.

ABSTRACT

Object perception is a remarkable and fundamental cognitive ability that allows us to interpret and interact with the world we are living in. In our everyday life, we constantly perceive objects—mostly without being aware of it and through several senses at the same time. Although it might seem that object perception is accomplished without any effort, the underlying neural mechanisms are anything but simple. How we perceive objects in the world surrounding us is the result of a complex interplay of our senses.

The aim of the present thesis was to explore, by means of functional magnetic resonance imaging, how our senses interact when we perceive an object's smell in a *multisensory* setting where the amount of sensory stimulation increases, as well as in a *unisensory* setting where we perceive an object's smell in isolation. In **Study I**, we sought to determine whether and how *multisensory* object information influences the processing of *olfactory* object information in the posterior piriform cortex (PPC), a region linked to olfactory object encoding. In **Study II**, we then expanded our search for integration effects during multisensory object perception to the whole brain because previous research has demonstrated that multisensory integration is accomplished by a network of early sensory cortices and higher-order multisensory integration sites. We specifically aimed at determining whether there exist cortical regions that process multisensory object information independent of from *which* senses and from *how many* senses the information arises. In **Study III**, we then sought to unveil how our senses interact during olfactory object perception in a unisensory setting. Other previous studies have shown that even in such unisensory settings, olfactory object processing is not exclusively accomplished by regions within the olfactory system but instead engages a more widespread network of brain regions, such as regions belonging to the visual system. We aimed at determining what this visual engagement represents. That is, whether areas of the brain that are principally concerned with processing visual object information also hold neural representations of olfactory object information, and if so, whether these representations are similar for smells and pictures of the same objects.

In **Study I** we demonstrated that assisting inputs from our senses of vision and hearing increase the processing of olfactory object information in the PPC, and that the more assisting input we receive the more the processing is enhanced. As this enhancement occurred only for matching inputs, it likely reflects integration of multisensory object information. **Study II** provided evidence for convergence of multisensory object information in form of a non-linear response enhancement in the inferior parietal cortex: activation increased for bimodal compared to unimodal stimulation, and increased even further for trimodal compared to bimodal stimulation. As this multisensory response enhancement occurred independent of the congruency of the incoming signals, it likely reflects a process of relating the incoming sensory information streams to each other. Finally, **Study III** revealed that regions of the ventral visual object stream are engaged in recognition of an object's smell and represent olfactory object information in form of distinct neural activation patterns. While the visual system encodes information about both visual and olfactory objects, it appears to keep information from the

two sensory modalities separate by representing smells and pictures of objects differently. Taken together, the studies included in this thesis reveal that olfactory object perception is a multisensory process that engages a widespread network of early sensory as well higher-order cortical regions, even if we do not encounter ourselves in a multisensory setting but exclusively perceive an object's smell.

LIST OF SCIENTIFIC PAPERS

- I. **Porada, D. K.**, Regenbogen, C., Seubert, J., Freiherr, J., Lundström, J. N. (2019). Multisensory Enhancement of Odor Object Processing in the Primary Olfactory Cortex. *Neuroscience*, 418, 254-265.
doi: 10.1016/j.neuroscience.2019.08.040
- II. **Porada, D. K.**, Regenbogen, C., Freiherr, J., Seubert, J., Lundström, J. N. (2021). Trimodal processing of complex stimuli in inferior parietal cortex is modality-independent. *Cortex*. doi: 10.1016/j.cortex.2021.03.008
- III. **Porada, D. K.**, Kietzmann, T. C., Seubert, J., Lundström, J. N. (2021). Seeing what you smell: An object's smell is manifested as multi-voxel activation pattern in the ventral visual pathway. *Manuscript*.

LIST OF ADDITIONAL SCIENTIFIC PAPERS

Publications by the author that are not included in this thesis.

- I. Regenbogen, C., Axelsson, J., Lasselin, J., **Porada, D. K.**, Sundelin, T., Peter, M. G., Lekander, M., Lundström, J. N., Olsson, M. J. (2017). Behavioral and neural correlates to multisensory detection of sick humans, *PNAS*, 114(24), 6400-6405. doi: 10.1073/pnas.1617357114
- II. Arshamian, A., Laska, M., Gordon, A. R., Norberg, M., Lahger, C., **Porada, D. K.**, Jelvez Serra, N., Johansson, E., Schaefer, M., Amundin, M., Melin, H., Olsson, A., Olsson, M. J., Stensmyr, M., Lundström, J. N. (2017). A mammalian blood odor component serves as an approach-avoidance cue across phylum border - from flies to humans. *Scientific Reports*, 7(1), 13635. doi: 10.1038/s41598-017-13361-9
- III. 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
- IV. Gerhardsson, A., **Porada, D. K.**, Lundström, J. N., Axelsson, J., Schwarz, J. (2020). Does insufficient sleep affect how you learn from reward or punishment? Reinforcement learning after two nights of sleep restriction. *Journal of Sleep Research*, e13236. doi: 0.1111/jsr.13236

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LIST OF ABBREVIATIONS

A1	Primary Auditory Cortex
ACC	Anterior Cingulate Cortex
ANOVA	Analysis of Variance
APC	Anterior Piriform Cortex
BOLD	Blood Oxygen Level Dependent
fMRI	Functional Magnetic Resonance Imaging
FWE	Family-Wise Error
FWHM	Full-Width at Half Maximum
GLM	General Linear Model
hAC	Higher-order Auditory Cortices
HRF	Hemodynamic Response Function
IFG	Inferior frontal Gyrus
IPC	Inferior Parietal Cortex
IPS	Intraparietal Sulcus
ISI	Inter Stimulus Interval
LOC	Lateral Occipital Complex
MCC	Middle Cingulate Cortex
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
MTG	Middle Temporal Gyrus
MVPA	Multivariate Pattern Analysis
PPC	Posterior Piriform Cortex
PRh	Perirhinal Cortex
RDM	Representational Dissimilarity Matrix
ROI	Region of Interest
SC	Superior Colliculus
SFG	Superior Frontal Gyrus
smPFC	Superior Medial Prefrontal Gyrus
STS	Superior Temporal Sulcus
SVM	Support Vector Machine
TMS	Transcranial Magnetic Stimulation
V1	Primary Visual Cortex
V2	Visual Area 2
V3	Visual Area 3
V4	Visual Area 4

1 INTRODUCTION

We are living in a world that is rich with sensory information. In our everyday life, we are constantly bombarded with sensory information. It is seldom only one sense that is stimulated at a time, but rather, many of our senses receive input simultaneously. We can feel, hear, see, smell, and taste at the same time. What and how we perceive the world surrounding us is the result of a complex interplay of our senses.

Each of our senses allows us to perceive another facet of the world we are living in. However, only the combination of information from several sensory modalities provides us with a holistic and unique experience of our environment, and thereby allows us to react and interact appropriately with the world. Imagine you are going for a walk in the woods and you suddenly see a barking furry animal with four legs approaching you. Is it a dangerous animal? What is the appropriate reaction? Although you have never seen this exact animal before and it is still at a too great distance to see it clearly, you are instantly able to recognize it as a dog, and thus know that you do not need to act particularly cautiously but can keep walking without being afraid. What enables you to almost instantly recognize the animal as a dog is the process of integrating the information from several senses. Not only seeing the animal but also simultaneously hearing it barking facilitates and improves your perception of a dog and thereby allows you to adjust your behavior accordingly (Andreassi & Greco, 1975; Diederich & Colonius, 2004; Gielen, Schmidt, & Van den Heuvel, 1983; Newell, 2004).

This interplay of the senses appears to be especially important and beneficial during olfactory object perception. Olfactory object perception is the process that allows us to perceive, for example, the object “wet dog” when smelling wet dog smell. Perceiving and recognizing an object based on its smell alone might seem like a breeze to do but actually constitutes a challenge for us. Although you might think that you would easily be able to identify common smells, such as banana, coffee, or onion, you would probably have a hard time and fail in roughly 70% of the cases (Desor & Beauchamp, 1974; Engen & Ross, 1973). But, if you, in addition to the smell, received assisting input, such as seeing the color yellow when perceiving the smell of banana, you would more easily correctly identify the smell as the smell of banana (Davis, 1981; Zellner, Bartoli, & Eckard, 1991). These findings indicate that olfactory object perception is highly susceptible to, and highly dependent on, input from our other senses.

While many studies have investigated behavioral aspects of how other sensory inputs facilitate and modify our perception of a smell, the underlying neural mechanisms have remained mostly unexplored. The aim of the present thesis was to explore this knowledge gap by addressing the neural aspects of how our senses interact during olfactory object perception. **Study I** focused on revealing whether processing of object information that is carried in a smell is modulated by object information that reaches our brain through other senses. That is, does complementary input from our sense of vision or hearing support the processing of olfactory object information in brain regions that are associated with the sense of smell? Moreover, does more assisting information help more? **Study II** investigated where else in the brain object information that

reaches our brain through several senses at the same time converges and links together. Are there brain regions that are engaged in multisensory processing independent of the type and number of senses involved? Finally, as previous studies have indicated that the processing of olfactory object information is not limited to brain regions that are associated with the sense of smell but also engages areas attributed to the visual domain, **Study III** unveiled how olfactory object information is processed in areas of the brain that are principally concerned with the processing of visual object information.

In this thesis, I will take you on the journey of discovering multisensory interactions during olfactory object processing. The journey will begin with some introduction into the basics of how our sense of smell works—from inhaling chemical molecules that constitute a smell, to the formation of an object percept. Afterwards, we will dip into the field of multisensory integration, which then allows us to consider olfactory object perception from a multisensory perspective. After having given you an understanding of what forms the basis of my research, I will delve more into details of the individual studies and present aims and methodological aspects of my studies. The journey will then continue with an overview of the obtained results and their implications, followed by a section where I summarize the findings and relate them to each other as well as to other research in the field. At the close of the journey, I will conclude with a take-home message and provide insights into where future research could lead us.

2 LITERATURE REVIEW

2.1 OLFACTORY OBJECT PERCEPTION

Object perception is a remarkable and fundamental cognitive ability that allows us to interpret and interact with the world we are living in. In our everyday life, we constantly perceive objects—mostly without being aware of it. Although it might seem that object perception is accomplished without any effort, the underlying neural mechanisms are anything but simple.

When we see an object, light in form of electromagnetic waves enters our eyes and activates photoreceptors in the retina (Bear, Connors, & Paradiso, 2015). The shape of the light wave is characterized by its wavelength, which carries information about the object's color hue, and by its amplitude, which conveys the color intensity of the object. As the specific shape of the light wave leads to a distinct activation of the photoreceptors in the retina, and this activation is converted into a neural signal that is transferred to the brain, there exists a direct link between retinal activation and the final percept of the object. Such a direct link between receptor activity and final percept also exists for our sense of hearing. When hearing an object, sound is conveyed via pressure waves into the ear (Bear et al., 2015). The characteristics of the sound are conveyed by the frequency, amplitude, and temporal variation of the sound pressure wave. The frequency of the wave carries information about the pitch of the sound and the amplitude of the wave represents the loudness of the sound. In the middle ear, the sound wave is then converted into mechanical vibrations that are subsequently applied to the cochlea. The resulting vibratory pattern of the cochlea evokes a neural signal that is then transferred to the brain. As the shape of the sound wave defines the characteristics of a sound and the vibratory pattern of the cochlea is particular to the shape of the sound wave, a direct link between sound receptor and final sound percept is given. Contrary to this, our sense of smell works differently and is much more complex. While we humans can perceive only a limited spectrum of light and sound, the range of perceivable odors is essentially infinite and the individual odors in this enormous odor space cannot be classified along a single physical dimension such as wavelength (Bushdid, Magnasco, Vosshall, & Keller, 2014; Keller et al., 2017). Hence, the olfactory system is left with the vast challenge to distinguish and make sense of nearly infinitely diverse odors.

When smelling an object by inhaling air through the nose, air containing odorants enters the nasal cavity through the nostrils. Odorants are small volatile chemical compounds that carry an odor. Odors in our everyday life are usually a composite of tens or even hundreds of odorants. The odor of roasted coffee, for example, can, in some compositions, be composed of more than 800 odorants (Flament, 2002). None of them in isolation smells like coffee but all have their own individual odor. Only in combination, do they give rise to the typical coffee aroma. Hence, when smelling an object, a multitude of different odorants is transmitted into the nasal cavity where they bind to olfactory receptors in the upper part of the nasal epithelium (Figure 1) (L. Buck & Axel, 1991). The human olfactory system possesses around 400 different olfactory receptors (Olender et al., 2012; Trimmer et al., 2019; Zozulya, Echeverri, & Nguyen, 2001),

each located on a separate receptor cell. These receptors are not specific to one specific molecule but rather a molecular feature, which means that they can bind different odorants (Firestein, Picco, & Menini, 1993; Malnic, Hirono, Sato, & Buck, 1999; Raming et al., 1993; Sato, Hirono, Tonoike, & Takebayashi, 1994; Sicard & Holley, 1984). Moreover, one type of odorant can bind to multiple receptors (Firestein et al., 1993; Malnic et al., 1999; Sicard & Holley, 1984), with the combination of receptors being specific to the odorant (Malnic et al., 1999) and each receptor cell exhibiting its own unique response profile (Sicard & Holley, 1984). In other words, no two odorants have the same “receptor code”. Although it might seem that one could predict what an odor smells like from the composition of its odorants and their molecular structure, it is at the present time impossible to precisely determine the resulting odor percept (Ravia et al., 2020). Odorants that possess a similar molecular structure can smell different while odorants being structurally unrelated can smell alike (Cain & Polak, 1992; Polak, 1973). Only a minor change in the odorant’s molecular structure changes the receptor code, which in turn leads to a profound change in the odor percept (Beets, 1970; Malnic et al., 1999; Polak, 1973). Moreover, it is not only the molecular structure that determines the final odor percept but also the odorant’s concentration (Gross-Isseroff & Lancet, 1988; Malnic et al., 1999), as well as prior experiences and expectations (Wilson & Stevenson, 2006). Additionally, the repertoire of olfactory receptors is not the same for everyone but varies among individuals (Malnic, Gonzalez-Kristeller, & Gutiyama, 2010). This means that not all individuals can bind the same type of molecular features and, as a result, we perceive odors differently. Hence, in stark contrast to our visual and auditory sense, there is no known direct link between the chemical features of an object’s odor, the subsequent receptor activity, and the final object percept.

How the brain creates a stable olfactory object percept from this deconstructed and at the same time highly complex and variable input, has challenged researcher for many years. However, recent studies have advanced our knowledge profoundly. When olfactory receptor cells are activated by inhaled odorants, they send electrical signals to relay stations in the olfactory bulb, a small brain structure located just above the nasal cavity. The relay stations inside the olfactory bulb are called glomeruli. All receptor cells that express the same type of receptor project to the same glomerulus, leading to a spatial ordering of the olfactory input into an odotopic map (Freiherr, 2017; Grabe & Sachse, 2018; B. A. Johnson & Leon, 2007; L. M. Kay, 2011; Mombaerts et al., 1996; Ressler, Sullivan, & Buck, 1994). But this odotopic map breaks down again when the olfactory signal is seemingly randomly redistributed during projection to the next processing stage (L. M. Kay, 2011; Stettler & Axel, 2009).

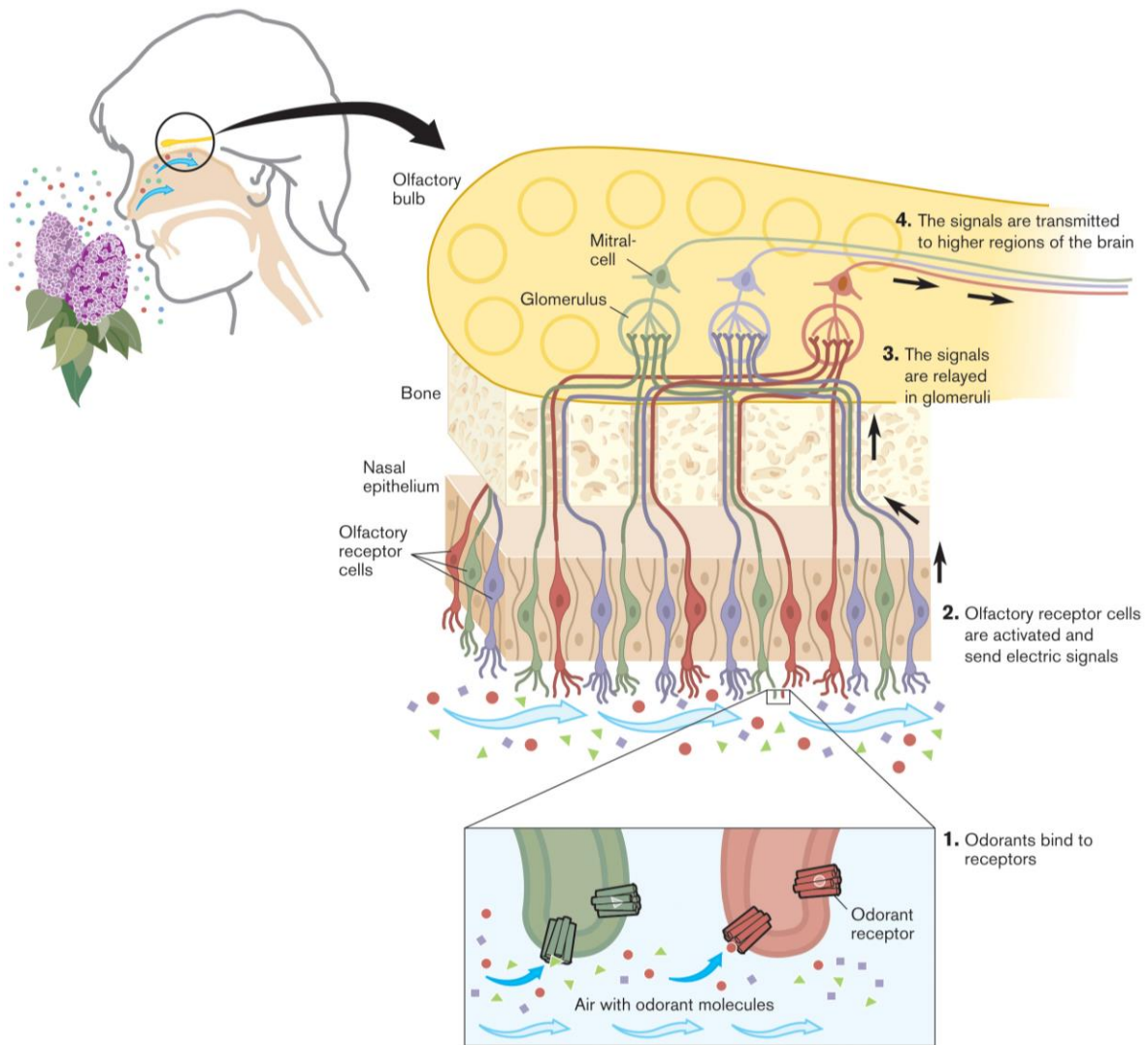


Figure 1. Odorant receptors and the organization of the olfactory system. Odorants bind to olfactory receptors located on receptor cells in the upper part of the nasal epithelium. Each olfactory receptor cell expresses one type of odorant receptor. Binding of odorants activates olfactory receptor cells, which send electrical signals to glomeruli in the olfactory bulb. Receptor cells expressing the same type of receptor project to the same glomerulus, leading to a spatial ordering of the signal, before it is projected to higher-order brain regions. Reprinted from Press release. NobelPrize.org. Nobel Media AB 2021. <https://www.nobelprize.org/prizes/medicine/2004/press-release/> © The Nobel Assembly at Karolinska Institutet. Reprinted with permission.

The olfactory signal is transmitted from the olfactory bulb via the lateral olfactory tract to several brain regions within the same hemisphere, including the anterior olfactory nucleus, olfactory tubercle, anterior and posterior piriform cortices, amygdala and rostral entorhinal cortex (Gottfried, 2010). All these areas that receive direct input from the olfactory bulb are usually considered as constituting the primary olfactory cortex (this is, however, an ongoing debate with opposing views considering the olfactory bulb as primary olfactory cortex (Haberly, 2001)). The vast majority of bulbar projections terminates, however, in the anterior piriform cortex (APC), a region that is associated with processing of the chemical features of an odor. The APC presumably reconstructs an odorant's identity from the deconstructed features by "reading" an odorant's receptor code from the bulbar output, and integrating the

information from the different receptors that is preserved in the glomerular pattern (L. B. Buck, 2004; Malnic et al., 1999). It is further assumed that the distinct odor of coffee, for example, arises from merging the receptor codes of the component odorants. Merging the codes results in one composite representation of an odor's chemical constituents that is different from the representations of the individual components. This composite representation allows us to perceive the odor of coffee as one whole instead of individual components (Malnic et al., 1999; Wilson, 2003). The APC does, however, only encode the chemical identity of an odor, not its perceptual quality. That is, the APC does not "know" that the perceived odor represents the object coffee, it only "knows" which chemicals it is composed of. Which object the composite of chemicals depicts is only encoded at the subsequent processing stage, the posterior piriform cortex (PPC) (Gottfried, Winston, & Dolan, 2006). While the APC differentiates between odors based on their molecular structure regardless of whether they represent the same object or not, the PPC differentiates odors based on the object they represent whether or not they are structurally related (Gottfried et al., 2006; Howard, Plailly, Grueschow, Haynes, & Gottfried, 2009; Kadohisa & Wilson, 2006b). This hierarchical dissociation between the APC's and PPC's function complies with their anatomical connectivity: while the APC receives the majority of its input from the olfactory bulb, the PPC is highly interconnected with several higher-order brain structures, allowing past experiences, semantic associations, and the current context to shape the formation of an object percept (Wilson & Stevenson, 2006). The PPC encodes this object information as a spatially distributed activation pattern (Howard et al., 2009). Each odor is represented by a unique pattern that is independent of the chemical structure of the odor but defined by the odor's perceptual quality. Hence, odors that are structurally similar but depict different objects are represented by dissimilar activation patterns while structurally-dissimilar odors that belong to the same object category (such as "minty") are represented by similar activation patterns. Such a generalization across multiple instances of the same object category is a fundamental property of object recognition. Being able to categorize objects allows us to reduce the complexity of our world and to structure it. By grouping items with similar properties into categories, we can use previous information obtained from other category members to identify an object, make predictions, and adjust our behavior (Rosch, Lloyd, & Social Science Research Council (U.S.), 1978). The ability of grouping similar objects into one category needs, however, to be kept in balance with the ability to discriminate between individual objects of the same category. Being able to differentiate objects that belong to the same category allows us to adjust our behavior to each instance individually. Reacting to all instances in the same way, instead, could have disastrous consequences. If we, for example, would carelessly eat all berries that we grouped into the category "berry", such as blackberries and blueberries but also rowan berries, we would end up having stomachache and being nauseous because rowanberries should not be eaten uncooked. The PPC is therefore not only capable of object categorization but also object discrimination on a fine-grained level. By altering the neural representations of olfactory objects through learning and experience, objects of the same category can be discriminated despite their high similarity (W. Li, Luxenberg, Parrish, & Gottfried, 2006). Object categorization and object discrimination are, however, not the only mechanisms that are

fundamental to olfactory object recognition. The separation of an object's odor from background odors is another fundamental mechanism. Such odor-background segmentation appears to occur already at the level of the APC (Kadohisa & Wilson, 2006a; Linster, Henry, Kadohisa, & Wilson, 2007). When sitting in your favorite coffee shop, waiting for your coffee, you are exposed to a mixture of odors composed of your friend's hot cup of tea, the odor of freshly baked buns, the perfume of the customer next to you, and much more. After a while the APC habituates to this mixture of odors that forms the background odor and only reacts to newly occurring odors (Kadohisa & Wilson, 2006a; Linster et al., 2007). Thereby, when your much longed-for cup of coffee arrives, you can easily segregate the odor of freshly brewed coffee from the background odor. This odor-background segmentation mechanism is presumably supported by the way we inhale through our nose: The persistent presentation of a background odor leads to high-frequency sniffing and thereby reduces the responsiveness of olfactory receptor cells to the odorants that compose the background odor (Verhagen, Wesson, Netoff, White, & Wachowiak, 2007). When a novel odor is then presented together with the background odor, only receptors binding odorants that are different from the background odorants are activated, which means that the background odor is filtered out from the olfactory signal (Verhagen et al., 2007).

Together, the here presented mechanisms represent the cascade of events that is fundamental to our ability to transform chemical molecules into perceptual wholes. The APC and PPC play a key role in olfactory object perception, with the APC encoding the chemical identity and the PPC encoding the object quality of an odor. Through the PPC's high connectivity with higher-order brain structures, object representations are shaped and modified by learning and experiences. Hence, which object we perceive an odor as, varies according to our experiences, current context, and expectations.

2.2 MULTISENSORY INTEGRATION

In everyday life, we constantly perceive and identify objects in our environment. Often, information about an object reaches our brain through different senses at the same time: we might see an object, hear, and smell it. All these different sensory impressions are then seemingly effortlessly combined into one single percept. This process of combining sensory information is commonly referred to as multisensory integration. Our brain matches and combines the different sensory impressions that all carry information about the *same* object but from distinct "sensory viewpoints" and with various amount of environmental noise mixed into the signal. As a result, we are better able to separate object-related information from object-unrelated noise and can establish a more reliable object percept than any of the contributing senses could generate alone (Ernst & Banks, 2002). Referring to the previous example of your favorite coffee shop, when queueing during rush hour waiting for your coffee, each of your senses is exposed to a mixture of signals. You hear the sound of the coffee machine mixed into a quite noisy combination of various chatting customers and music playing in the background. You only partially see the coffee running out of the machine into a cup because the barista preparing your coffee is obscuring your view. And the odor of coffee is embedded in the odor

of freshly baked buns and the perfume of the customer next to you. Although each of these sensory impressions is a composite of high amount of noise that is unrelated to the object coffee and a rather weak object-related signal, you are able to generate a holistic percept of the object coffee by filtering out the noise and integrating the relevant object-related information. By either smelling, hearing, or seeing alone, you would not have been able to form such a reliable object percept.

Multisensory integration does not only allow for a percept that is of a holistic nature, but it also facilitates and improves our perception and lets us react faster to external stimuli (Andreassi & Greco, 1975; Diederich & Colonius, 2004; Gielen et al., 1983; Gottfried & Dolan, 2003). It is defined as the process that combines input from two or more sensory modalities, and results in a response that is significantly different from the response evoked by the most effective modality alone (Stein & Meredith, 1993; Stein, Stanford, Ramachandran, Perrault, & Rowland, 2009). This holds true for behavioral as well as neural responses (Stein, Stanford, & Rowland, 2014).

On a neural level, multisensory integration was first detected in the cat superior colliculus (SC), a subcortical brain structure where visual, auditory, somatosensory, vestibular and proprioceptive information converges, and which is crucially involved in detecting, localizing, and orienting to external stimuli (Meredith & Stein, 1986b). Single cell recordings revealed that neurons in the SC increased their response substantially when a combination of stimuli (visual-auditory, visual-somatosensory, auditory-somatosensory) was presented compared to when one of the stimuli was presented alone (Meredith & Stein, 1986b; Wallace, Meredith, & Stein, 1998). Despite the possibility of a response *decrease* to multisensory stimulation, response *enhancement* is considered the most reliable indication of multisensory integration (Stein et al., 2014). Such multisensory enhancement can either be sub-additive, additive, or super-additive, meaning that the response to the multisensory stimulus combination is either less than, equal to, or greater than the summed responses to the individual unisensory stimuli (Stein et al., 2009).

Since the first discovery of multisensory neurons in SC, multisensory neurons have been detected in various other brain regions and species (Bizley, Nodal, Bajo, Nelken, & King, 2007; Brett-Green, Fifková, Larue, Winer, & Barth, 2003; Driver & Noesselt, 2008; Ghazanfar & Schroeder, 2006; C Kayser, Petkov, & Logothetis, 2008; Nagy, Eördegh, Paróczy, Márkus, & Benedek, 2006; Stein & Meredith, 1993), as well using population-based neuroimaging techniques (Andreassi & Greco, 1975; Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004; Beauchamp, Lee, Argall, & Martin, 2004; Beauchamp, Yasar, Frye, & Ro, 2008; Beauchamp, 2005; Calvert, Hansen, Iversen, & Brammer, 2001; Foxe et al., 2000, 2002; Ghazanfar, Maier, Hoffman, & Logothetis, 2005; C Kayser et al., 2008; Molholm et al., 2006; Noppeney, 2012; Ohla, Höchenberger, Freiherr, & Lundström, 2017; Regenbogen et al., 2017, 2018). Furthermore, the observed neural effects of multisensory integration could be directly linked to behavioral effects (Frens & Van Opstal, 1998; Sella, Reiner, & Pratt, 2014; Wang, Celebrini, Trotter, & Barone, 2008; Werner & Noppeney, 2010a, 2010b).

On a behavioral level, multisensory integration is usually assessed using response time and accuracy measures as well as measures of perceptual fusion. The integration of multisensory signals leads to faster and more accurate responses (Sella et al., 2014; Stein, Huneycutt, & Meredith, 1988; Stevenson et al., 2014; Werner & Noppeney, 2010b) and fused percepts. Such perceptual fusion can be advantageous but can also lead to perceptual illusions. Advantageous effects are especially evident in object (as described in the coffee example above) or speech perception. As an example for the latter, seeing your dialogue partners' mouth moving while hearing their voice makes it much easier for you to understand what they are talking about. Even more when you are in a noisy environment or they are speaking a foreign language (Ross, Saint-Amour, Leavitt, Javitt, & Foxe, 2007; Sumbly, 1954; Xie, Yi, & Chandrasekaran, 2014). A striking example of a perceptual illusion that is generated by multisensory integration is the so called McGurk effect (McGurk & MacDonald, 1976). McGurk and MacDonald showed that the fusion of semantically incompatible visual and auditory speech information can lead to an audiovisual illusion. When listening to a speaker pronouncing the syllable "ba" while watching him uttering the syllable "ga", the visual "ga" and auditory "ba" are integrated and you perceive the speaker as saying "da". You report hearing something that was neither provided by the voice nor by the speaker's face alone. The fused percept is unique. This example nicely illustrates that the brain constantly tries to make sense of the incoming signals. For efficient integration, our brain needs to evaluate whether the different sensory signals arise from a common source and should be integrated, or whether they arise from different sources and should instead be processed separately. Signals matching in their spatial and temporal co-occurrence, as well their cross-modal correspondence and meaning, are more likely to be integrated than signals that are spatially and/or temporally further apart or are mismatching regarding their correspondence or meaning (Meredith, Nemitz, & Stein, 1987; Meredith & Stein, 1986a; Parise & Spence, 2009; Spence, 2011). Although the visual and auditory signals do not match semantically in the presented McGurk effect, they are still integrated because they occur at the same time and location, and further match regarding the speaker's identity—the brain made the most sense out of the diverse signals.

Apart from temporal, spatial and semantic congruency, also the clarity of the individual sensory inputs determines the effectiveness of multisensory integration (Stein & Meredith, 1993). Objects in our environment are rarely clear and distinct but are mostly embedded within a noisy surrounding. This means that it is seldom that we encounter, for example, a bird sitting on a white background, making it easy for us to detect it as a bird. Instead, we often find ourselves in a situation where the bird is hiding deep within a tree and there are leaves and branches obscuring our view. In addition, we hear the bird singing while we simultaneously hear the wind rattling the leaves of trees. Here, the combination of visual and auditory input that both carry information about the bird helps us to locate and detect the bird. The perceptual benefits of integrating the two information streams follow the principle of inverse effectiveness (Stein & Meredith, 1993). This principle states that the benefit of multisensory integration is greater when the unisensory inputs, here visual and auditory, are degraded (Christoph Kayser, Petkov, Augath, & Logothetis, 2005; Perrault, Vaughan, Stein, & Wallace, 2003; Regenbogen,

Johansson, Andersson, Olsson, & Lundström, 2016; Regenbogen et al., 2018; Senkowski, Saint-Amour, Höfle, & Foxe, 2011; Stanford, Quessy, & Stein, 2005; Stevenson & James, 2009; Werner & Noppeney, 2010a). Applied to our example, this means that the more our view is obscured and the more the sound of the wind masks the singing of the bird, the more effective the combination of the two inputs becomes and the more we gain from their integration.

Although our brain is innately wired to process information from different sensory modalities and possesses neurons that respond to various sensory modalities, our ability to integrate multisensory information is not inborn but starts developing during infancy and is shaped by our sensory experiences throughout life (Hillock-Dunn & Wallace, 2012; Jiang, Jiang, & Stein, 2006; Murray, Lewkowicz, Amedi, & Wallace, 2016; Pantev, Paraskevopoulos, Kuchenbuch, Lu, & Herholz, 2015; Wallace & Stein, 1997, 2000; Xu, Yu, Rowland, Stanford, & Stein, 2012). For example, the temporal window that defines which maximum time lag between two occurring signals is acceptable to still integrate them (temporal binding window) can be narrowed by perceptual training (Lee & Noppeney, 2011; Powers, Hillock, & Wallace, 2009; Zerr et al., 2019). Hence, after training, only stimuli occurring very close in time will be integrated while the “natural” time window (without any training) allows for much larger temporal disparities between the signals. The temporal binding window can also adjust according to contextual factors (Cecere, Gross, & Thut, 2016; Hillock, Powers, & Wallace, 2011; Mégevand, Molholm, Nayak, & Foxe, 2013). In a situation where we first perceive a sound and then a visual stimulus, the temporal binding window is usually much more narrow compared to a situation where we first perceive the visual stimulus and then the sound (Cecere et al., 2016; Hillock et al., 2011). This is because light travels faster than sound (we see the lightning before we hear the thunder) and our daily experiences have taught us that under natural circumstances visual signals reach us before auditory signals if they arise from the same source. Hence, if an auditory signal is followed by a visual one, it is rather unlikely that they have one common source and should be integrated. Therefore, the acceptable time lag is very short and only virtually simultaneously occurring signals are integrated. In comparison, we are more generous and allow integration of stimuli with bigger temporal discrepancies if the order is reversed and the visual stimulus comes first, followed by the auditory stimulus. This illustrates that through constant interactions with the world we are living in, we are able to extract statistical information about co-occurrence and learn which events naturally correlate and which do not. Similar to learning that visual signals usually occur before auditory signals through mere exposure to the co-occurring events, we learn already early in life the correspondences between speech sounds and lip movements (Kuhl & Meltzoff, 1982). However, once such associations are learned, they are not rigid. Instead, they are highly plastic across our lifespan and can be modified through new experiences (Flanagan, Bittner, & Johansson, 2008). We are also able to learn new associations between signals that we had previously learned are unrelated (Ernst, 2007). This plasticity demonstrates that our perceptual systems can adapt to the statistics of sensory input by interactively engaging with the environment.

2.3 OLFACTORY OBJECT PERCEPTION FROM A MULTISENSORY PERSPECTIVE

An olfactory object is commonly defined as the distinctive odor that emanates from an object, such as the wet dog odor emitted from a wet dog. That is, an olfactory object constitutes an odor that is associated with a certain object. Usually, such an object has additional other sensory properties, as for instance a distinct visual appearance, a certain surface feel, or a specific associated sound. Thus, an olfactory object is by definition a multisensory entity. Moreover, odors have some immanent associations with other sensory features, such as shape, tone pitch, and silkiness, which cannot be attributed to having emerged from associative learning (Belkin, Martin, Kemp, & Gilbert, 1997; Crisinel & Spence, 2012; Demattè, Sanabria, Sugarman, & Spence, 2006; Deroy, Crisinel, & Spence, 2013; Hanson-Vaux, Crisinel, & Spence, 2013; Seo et al., 2010). In light of these facts, and because in our everyday life we barely perceive an odor in complete isolation without any other sensory input, olfactory object processing should be studied from a multisensory perspective rather than from a unisensory one.

So far, not much established knowledge exists about multisensory interactions during olfactory object perception and particularly, how multisensory stimulation influences olfactory object processing. It is, however, known that olfactory object recognition is a rather difficult task for us; that assisting visual or auditory input allows us to identify an olfactory object more easily; and that olfactory processing in general is highly susceptible to input from other sensory modalities. While it is a fairly simple task for us to identify an object by its visual appearance alone, identifying an object based solely on its odor is very difficult (Cain, 1979; Lawless, 1984; Yeshurun & Sobel, 2010). On average, we are able to correctly identify merely one third of common odors and usually misidentify even such a familiar odor as banana (Desor & Beauchamp, 1974; Engen & Ross, 1973). However, performance improves dramatically when we receive assisting input from another sense: we are able to identify an odor more quickly and more accurately when it is presented together with a color or sound that matches its quality (e.g., red for strawberry odor or Christmas carol for cinnamon odor) (Davis, 1981; Seo, Lohse, Luckett, & Hummel, 2014; Zellner et al., 1991). The high susceptibility of the olfactory sense to other sensory signals can be attributed to its low intrinsic effectiveness. This means that olfactory object information can be considered degraded even in its most precise version. As a result, it is difficult for us to identify an object based on its odor alone, and makes olfactory object perception greatly benefiting from assisting input from other sensory modalities.

Apart from the beneficial effects on olfactory object recognition, visual and auditory inputs have a strong influence on olfactory processing in general. They can, for example, increase and facilitate odor perception. As a few examples, the odor of a flavored drink is perceived as more intense and more pleasant when its color matches the odor (red for strawberry) (Zellner et al., 1991; Zellner & Kautz, 1990); the perceived pleasantness of an odor can be increased by either a pleasant sound such as a laughing baby, a congruent eating sound such as the sound of eating potato chips when smelling potato chips, or congruent background music such as Christmas carols when smelling cinnamon (Seo & Hummel, 2011; Seo et al., 2014); and lastly, detecting the presence of an odor or discriminating between two odors can be facilitated by simultaneous

visual input. For instance, we can detect the presence of an odor more easily if we simultaneously see a picture of an object that matches the odor's quality (e.g., picture of oranges for orange odor) (Gottfried & Dolan, 2003), and we can better discriminate two odors when we are concurrently presented with a color or shape matching one of the presented odors' quality (e.g., red when discriminating between strawberry and lemon odor). This works, even when we are instructed to ignore the visual input (Demattè, Sanabria, & Spence, 2009). The downside of the high susceptibility of olfactory processing is that co-occurring signals from other sensory modalities can also deteriorate odor perception and even lead to olfactory illusions. For example, discriminatory performance is decreased when a disturbing background noise is presented at the same time (Seo, Gudziol, Hähner, & Hummel, 2011), and olfactory illusions can occur by artificially coloring a drink in a different color than its natural color. Here, the odor of a cherry-flavored drink might be mistaken as orange flavor if the drink is colored orange (DuBose, Cardello, & Maller, 1980), and coloring a white wine red leads to a description of the wine's odor as if it was a red wine (Morrot, Brochet, & Dubourdieu, 2001).

Although the behavioral effects of an additional sensory input on odor perception are well established, the underlying neural mechanisms are poorly understood. Does additional sensory input alter odor perception by *directly* modulating the neural processing of the odor? Until the early 2000s this question would have been negated. For decades, scientists believed that individual sensory inputs were processed in strictly segregated sensory systems in the brain, each processing input from one specific sensory modality only. Following this, the olfactory system would be exclusively dedicated to olfactory input while the visual system would process only visual information. Processing within each sensory system, but also within the cortex in general, was further believed to be hierarchically organized: from simple to more complex features and from simple to more complex processes. Hence, the sensory streams would build up separately and then interact and merge at a later processing stage in higher-order multisensory regions, which are not dedicated to one single sensory modality but respond to information from various senses and are especially engaged in integrating various sensory inputs. Commonly assumed cortical multisensory integration hubs are the superior temporal sulcus (STS), regions within prefrontal and premotor cortices, as well as intra- and temporoparietal areas (Barraclough, Xiao, Baker, Oram, & Perrett, 2005; Driver & Noesselt, 2008; Ghazanfar & Schroeder, 2006; Macaluso & Driver, 2005; Molholm et al., 2006; Sugihara, Diltz, Averbeck, & Romanski, 2006).

Today, the picture of a segregated and strictly hierarchically organized brain has changed. Especially in the last 20 years, we have gotten to know that sensory signals are not exclusively processed in a strictly serial manner (Lamme & Roelfsema, 2000; Lamme, Supèr, & Spekreijse, 1998; Sikkens, Bosman, & Olcese, 2019; Sillito, Cudeiro, & Jones, 2006) and that interactions between senses can occur already at an early stage of perceptual processing, in originally assumed unisensory areas (Fuxe & Schroeder, 2005; Giard & Peronnet, 1999; Schroeder & Fuxe, 2005). These areas have been shown to possess multisensory responsiveness in terms of cross-modal activation and exhibit multisensory integration in terms of multisensory enhancement. For example, the auditory cortex does not solely respond to

auditory signals but also to visual or tactile stimulation alone (Bizley et al., 2007; Brosch, Selezneva, & Scheich, 2005; Fu et al., 2003; Schroeder & Foxe, 2002; Schroeder et al., 2001); the somatosensory cortex can be activated by auditory or visual stimuli (Y. D. Zhou & Fuster, 2000; Y.-D. Zhou & Fuster, 2004); olfactory regions respond to visual, auditory, and taste stimuli (Gnaedinger, Gurden, Gourévitch, & Martin, 2019; Gottfried, Smith, Rugg, & Dolan, 2004; Maier, Wachowiak, & Katz, 2012; Varga & Wesson, 2013); and lastly, auditory, tactile, and olfactory responses can be observed in visual regions (A Amedi, Malach, Hendler, Peled, & Zohary, 2001; James et al., 2002; Pietrini et al., 2004; Poremba et al., 2003; Qureshy et al., 2000; Royet et al., 1999; Sathian & Zangaladze, 2002; von Kriegstein, Kleinschmidt, Sterzer, & Giraud, 2005). Besides processing signals from other sensory modalities, some “unisensory” cortices have also been shown to integrate multisensory signals. For example, auditory regions show an increased response to combined audio-visual or audio-tactile input compared to mere auditory stimulation (Bizley et al., 2007; C Kayser & Logothetis, 2007; C Kayser, Petkov, Augath, & Logothetis, 2007; Christoph Kayser et al., 2005; Lakatos, Chen, O’Connell, Mills, & Schroeder, 2007; Pekkola et al., 2006), and activity in the visual object-responsive area (lateral occipital complex, LOC) is increased during combined visual and haptic exploration of objects compared to when the object is only seen (Naumer et al., 2010). Together, the here presented observations of multisensory responsiveness and integration provide profound evidence for an early interaction between our senses and suggest that multisensory information converges early in the cortical hierarchy. One might, therefore, be tempted to answer our previous question, whether additional sensory input alters odor perception by *directly* modulating the neural processing of the odor, with yes. This would, however, be too far of a stretch. Knowing that our senses share some characteristics, such as multisensory responsiveness, does not allow us to imply that they share all characteristics of multisensory processing and are all equally capable of integrating multisensory signals.

To truly understand olfactory object perception, it is important to consider not only multisensory interactions occurring in olfactory areas but also how olfactory object information is processed in other sensory cortices. Visual areas, for example, are activated during higher-order olfactory tasks, as for instance, olfactory object identification, or judging whether an odor represents an eatable or uneatable object (Qureshy et al., 2000; Royet et al., 1999). Such odor-induced activations in visual areas have further been demonstrated to reflect actual engagement in processing of the odor instead of mere correlated activation: olfactory object discrimination improves when the neural processing of the primary visual cortex is artificially increased by transcranial magnetic stimulation (TMS), (Jadauji, Djordjevic, Lundström, & Pack, 2012). These and other results (Vasconcelos et al., 2011) indicate that areas belonging to the visual object processing stream are also functionally involved in non-visual object recognition. A potential explanation for such engagement of the visual system in non-visual object recognition could be that the human brain is wired to take advantage of the sophisticated object recognition properties of our visual system. Regions within the ventral visual object pathway are specialized for the recognition of objects (Kravitz, Saleem, Baker, Ungerleider, & Mishkin, 2013), with each region having its own specialized function. As one moves along the pathway

from posterior to anterior regions, the representations of object features increase in complexity. The computations associated with object recognition are best accomplished using visual input (which is why these areas appear to be “visual”) but previous studies have shown that they can also be performed using non-visual information, such as tactile or auditory input (Erdogan, Chen, Garcea, Mahon, & Jacobs, 2016; Man, Damasio, Meyer, & Kaplan, 2015; Murray, Thelen, et al., 2016; Pietrini et al., 2004; Snow, Strother, & Humphreys, 2014; Vetter, Smith, & Muckli, 2014). This means that especially the LOC, a key region for object recognition, does not only encode visual but also non-visual (tactile and auditory) objects and represents them in form of distinct neural activation patterns. The activation patterns for visual and haptic objects have further been shown to be modality-independent, meaning that a similar neural activation pattern can be observed independent of whether an object is visually or haptically explored (Erdogan et al., 2016). These observations indicate that the ventral visual object stream is capable of processing *non-visual* object information and that it is recruited in an object-specific manner by other senses. Such cross-modal recruitment of the efficient and rapid visual object recognition system could be especially advantageous when the normally related sensory system performs rather poorly in recognizing objects. This arguably applies to the olfactory system, which receives only degraded object information and creates unreliable object percepts.

Together, the here presented findings illustrate that olfactory object perception presumably relies on a complex interplay between our senses. When perceiving only the odor of an object and trying to recognize it, we appear to engage not only the olfactory but also the visual system. When perceiving an olfactory object in a multisensory context, the PPC, the key region for olfactory object processing, might play a crucial role in integrating the object-related information from different senses. That the PPC is interconnected with other sensory systems (Budinger, Heil, Hess, & Scheich, 2006; Cooper, Parvopassu, Herbin, & Magnin, 1994); that it responds to non-olfactory stimuli (Gottfried & Dolan, 2003; Maier et al., 2012; Varga & Wesson, 2013); and that its activity can be modulated by other sensory input (Gnaedinger et al., 2019; Maier, Blankenship, Li, & Katz, 2015) suggests that multisensory object information converges and conjoins at the level of the PPC. Alternatively, higher-order multisensory integration hubs could constitute the actual locus of convergence and integration. Feedback projections from those hubs could then account for potential multisensory effects in the PPC (Driver & Noesselt, 2008).

3 RESEARCH AIMS

The general aim of this thesis was to explore how our senses interact during olfactory object processing. More specifically, we sought to determine whether the olfactory cortex acts as a multisensory integration site, and which other higher-order brain regions are engaged in combining object information from different senses. Moreover, as past research indicated that olfactory object information processing is not limited to brain regions that are associated with the sense of smell but also engages areas attributed to the visual domain, we aimed to further assess what exactly constitutes this engagement.

Study I aimed at determining whether assisting input from our sense of vision or hearing enhances processing of olfactory object information in brain regions that are commonly associated with the sense of smell, and whether the enhancement depends on the number of senses that provide information about the to-be-processed object.

Study II aimed at revealing whether there are brain regions that process multisensory object information independent of from which sense the information arises and independent of the number of senses that provide object information.

Study III aimed at assessing whether areas of the ventral visual stream that are specialized to process visual object information also hold neural representations of olfactory object information and, if so, whether these representations are similar for odors and pictures of objects.

4 MATERIALS AND METHODS

4.1 PARTICIPANTS

Study I and **Study II** are based on the same data collection; therefore, the sample of participants as well as the stimulus set and experimental procedure are identical. Sixteen volunteers (7 women, mean age 26.9 years, SD 3.2 years) participated in the study. In **Study III**, 29 volunteers were initially recruited. However, data from thirteen participants was excluded from analysis due to one of the four following reasons: equipment failure during data collection (n=5), insufficient number of completed experimental runs (n=3), insufficient activation in visual areas during the functional localizer experiment (n=4), or identified cerebral abnormalities (n=1). Therefore, the remaining sample consisted of 16 participants (11 women, mean age 26.9 years, SD 4.8 years). All participants were right-handed, did not take any prescription medication, had no history of functional sensory impairments (i.e. anosmia, hearing, or vision deficits), reported normal hearing, and had normal or corrected-to-normal vision [confirmed by a Snellen's visual acuity evaluation, (Snellen, 1862)], and an intact sense of smell [confirmed by a Sniffin' sticks odor identification test, (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997)]. They furthermore complied with any restrictions for participating in a magnetic resonance imaging (MRI) study. Before participation, all participants gave their informed written consent and were naive to the purpose of the experiment.

4.2 EXPERIMENTAL STIMULI

The stimulus material of **Study I** and **Study II** consisted of odors, sounds, and videos of six familiar objects with clear and distinct features for all three sensory modalities and one control stimulus: 'Coffee brewer', 'Wood fire', 'Lawn mower', 'Popcorn', 'Flopping fish', 'Flushing urinal', and 'nothing' (clean air, no sound, fixation cross). The odors, sounds, and videos were presented in combinations that formed unimodal (object-related information in one modality, control stimulation in the others), bimodal (object-related information in two modalities, control stimulation in the other), trimodal (object-related information in all three modalities), or control (object-related information completely absent, control stimulation in all three modalities) stimuli. This resulted in the following eight combinations: 3x unimodal stimulation (odor, sound, video), 3x bimodal stimulation (odor-sound, odor-video, sound-video), 1x trimodal stimulation (odor-sound-video), 1x control stimulation (Figure 2). Bimodal and trimodal combinations could further be either congruent (modalities receive object information associated with the same object), or incongruent (modalities receive object information associated with different objects). However, in **Study I** and **Study II** only the congruent conditions were of major interest, the incongruent conditions served primarily as control.

The stimulus set of **Study III** consisted of odors and pictures depicting four familiar objects with clear and distinct features for both sensory modalities: 'Banana', 'Lemon', 'Soap', and 'Whiteboard Marker'. The odors and pictures were either presented individually or as congruent combinations (Figure 3A). The combined presentation of odors and pictures was

included for mere exploratory reasons but was not of interest for the research question of **Study III**.

For all studies, odors were presented birhinally with an MRI-compatible computer controlled olfactometer (Lundström, Gordon, Alden, Boesveldt, & Albrecht, 2010). The sounds were presented via headphones at a volume that allowed clear audibility of the objects inside the scanner and participants viewed the visual stimuli via an angled mirror mounted on the head coil.

4.3 EXPERIMENTAL DESIGN AND PROCEDURE

Study I and **Study II** are based on the same data and differ only in their research question and focus of analysis. The functional MRI (fMRI) experiment consisted of two sessions, separated by two days. In Session 1, participants were familiarized with the scanning environment, tasks, and stimuli. Session 2 was the actual experimental session, which was conducted inside an MRI scanner (Siemens 3T). During each experimental trial (Figure 2) participants were first signaled to get ready to sniff (4.33 s on average), and afterwards exposed to one type of stimulation (unimodal, bimodal, or trimodal) for 3s. Following this, participants were asked to indicate the number of stimulated sensory modalities during a 3s long response window. Each type of stimulation was repeated 18 times in total.

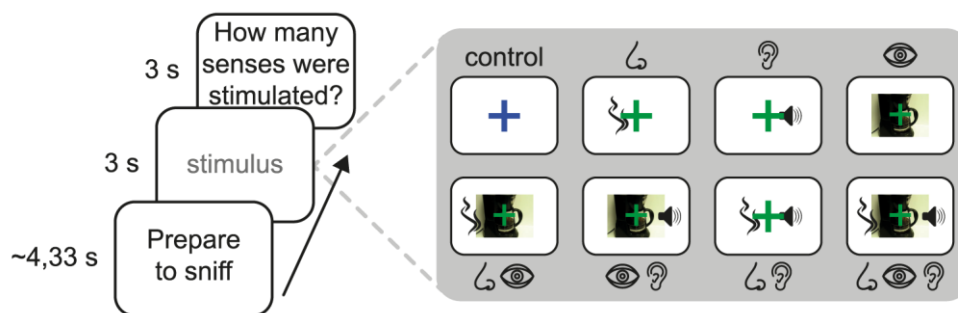


Figure 2. Illustration of the trial sequence and stimulus combinations used in Study I & II. During each trial, participants were exposed to a unimodal, bimodal or trimodal stimulus presentation or a blank control condition. After each trial they were asked to indicate how many senses were stimulated. Cartoon nose indicates olfactory stimulation, eye indicates visual stimulation, and ear indicates auditory stimulation.

The fMRI experiment conducted in **Study III**, consisted of two seemingly identical scanning sessions of approximately 60 minute each, separated by a break of 70 minutes. Each scanning session was split into short runs providing the opportunity to individually adjust the total duration of the experiment. An experimental trial (Figure 3A) started with a black fixation cross displayed on a white background for 4s. Afterwards, a stimulus (odor, picture, or combined odor and picture) was presented for 2s. Participants were instructed to inhale through the nose as soon as a stimulus appeared on the screen or the fixation cross changed color from black to blue (indicating an odor only trial). Following this, participants were asked to indicate which object they had perceived during a 4s long response window. Each stimulus was repeated three

times per experimental run, resulting in 36 trials per run. The number of completed runs varied among subjects (min n=6, max n=12).

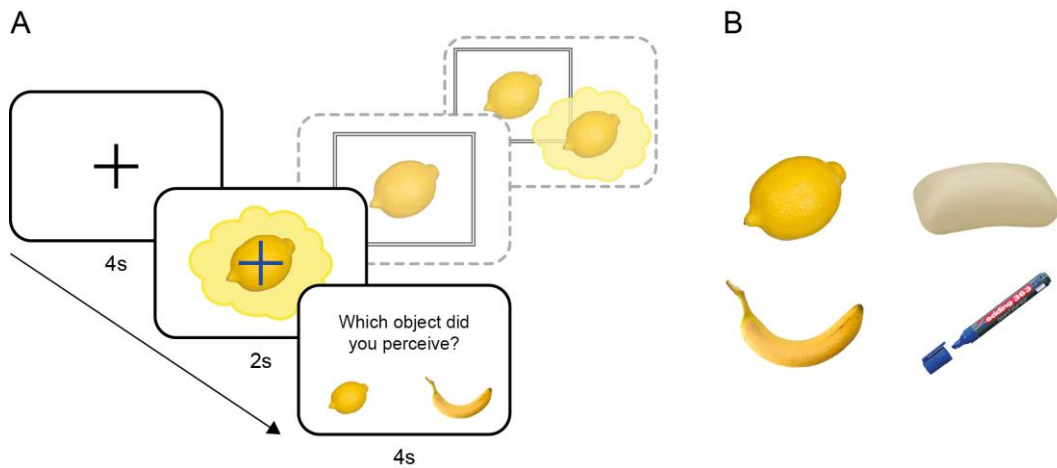


Figure 3. Illustration of the trial sequence and visual stimuli used in Study III. A) During each trial, participants were presented with either an odor, a picture, or a combination of odor and picture of a common object. After the stimulus presentation, participants were asked to indicate which object they had perceived. B) Illustration of the visual stimuli: lemon, banana, soap, whiteboard marker.

4.4 FUNCTIONAL MAGNETIC RESONANCE IMAGING

Functional magnetic resonance imaging is a non-invasive technique to measure and visualize physiological aspects of brain activity using an MRI scanner. An MRI scanner utilizes a combination of a static magnetic field and radiofrequency pulses to measure the magnetic spin of hydrogen protons in body tissue (Huettel, Song, & McCarthy, 2014). Under normal circumstances, all protons in the body are randomly positioned and spin around their own axes. When lying in the MRI scanner, the protons twist their spinning axes so that they all align with the strong static magnetic field of the scanner. This generates a weak magnetization of the body tissue in the direction of the scanner's magnetic field. Detecting the generated magnetization is, however, impossible because it overlaps with the scanner's strong magnetic field. This problem is solved by the application of a radio frequency pulse that matches the protons' spinning frequency: energy is transferred from the pulse to the protons, thus enabling the protons to temporarily flip their spinning axes away from the scanner's magnetic field and synchronize in phase so that the generated magnetization can be detected. The flipped spins act like a rotating magnetic and induce an electric signal in a receiving coil. This electrical current constitutes the MR signal. The stronger the tissue magnetization, the stronger the MR signal. The signal starts to decay immediately after the radio frequency pulse is turned off again because the protons gradually re-align with the scanner's magnetic field. How fast protons re-align with the static magnetic field varies among different types of body tissue. This variation allows for a detailed depiction of the density and shape of different body tissues. Functional MRI uses the properties of the MRI scanner to go beyond depicting anatomical structures and indirectly measure brain activity. fMRI is based on the observation that an active brain region consumes more oxygenated blood (Roy & Sherrington, 1890) and the fact that deoxygenated

and oxygenated hemoglobin in blood have different magnetic properties. This creates a blood oxygenation level dependent (BOLD) signal, which can then be detected. If neuronal activity in a brain region increases, more oxygen is consumed, and as a consequence, the level of deoxygenated hemoglobin increases. Although the regional blood flow increases when neurons become active, the neurons consume slightly more oxygen than new oxygenated blood can flow in, which increases the ratio of deoxygenated to oxygenated hemoglobin temporarily and thereby causes the typical initial dip of the measured BOLD response. About 2s after neuronal activity onset, oxygenated blood starts replacing the deoxygenated blood and the regional blood flow keeps increasing, even above the actual oxygen demand, until it reaches its maximum about 4-6s after neuronal activation onset. As a result, the proportion of oxygenated compared to deoxygenated hemoglobin increases, forming the peak of the BOLD response. Afterwards, the blood flow gradually falls back to the starting level, reaching baseline after around 16 seconds.

4.4.1 Preprocessing of fMRI Data

Preprocessing of the fMRI data was similar for **Study I** and **Study II** and performed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK). The origin of the structural image was manually set to the anterior commissure and each functional image volume was reoriented accordingly. To correct for any head movement during scanning, time-series were first realigned to the run's mean functional image and afterwards to the run's first image. After co-registering the structural image and each run's mean functional image, the mean functional image delivered the priors for a unified segmentation process using non-linear segmentation (Ashburner & Friston, 2005). The structural image was non-linearly segmented into gray matter, white matter, and cerebrospinal fluid. This yielded the normalization parameters that were applied to the structural as well as all functional images. Transforming the individual data into standard Montreal Neurological Institute (MNI) space allowed for statistical analyses across participants. After normalization, the voxel size was 3 x 3 x 3mm for the functional image volumes and 1 x 1 x 1mm for the structural image volume. To reduce the effects of inaccuracies in the normalization procedure and to meet the assumptions of Random Field Theory for subsequent statistical testing, functional images were spatially smoothed using a 6mm full-width at half maximum (FWHM) Gaussian kernel in **Study I** and an 8mm kernel in **Study II**. Different smoothing kernel sizes were used because in **Study I**, we specifically wanted to assess activity within the piriform cortex, a small anatomical area, whereas in **Study II**, we assessed anatomically larger areas and expected a larger within subject anatomical variance.

In **Study III**, preprocessing of the fMRI data was optimized for multivariate analyses and performed using SPM12 software. The structural images were automatically segmented into gray matter and white matter, inflated and parcellated using Freesurfer (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, 2004). Using SPM12, the origin of the structural image was manually set to the anterior commissure and each functional image volume was reoriented accordingly. Time-series were first slice scan time corrected and subsequently

realigned to the first non-discarded volume of the run as reference volume. The slice-time corrected first volume of the first run served as reference image for co-registration of the functional and structural data. As multivariate analyses are typically conducted within-participants in native space, we refrained from any normalization procedure. To improve the signal-to-noise ratio of the data, we applied GLMdenoise (K. N. Kay, Rokem, Winawer, Dougherty, & Wandell, 2013). GLMdenoise is a Matlab toolbox implementing a denoising technique that identifies noise sources, such as head motion, in the data by performing a principal component analysis on the time-series of task-unrelated voxels. These noise sources are subsequently regressed out from the time-series of all voxels to derive a clean BOLD signal. To determine task-unrelated voxels, GLMdenoise needs to be informed about the timing of the stimuli while being kept blind to the experimental conditions upon which subsequent analyses rely.

4.4.2 Regions of Interest

4.4.2.1 Combined functional and anatomical ROI definition

All Regions of Interest (ROIs) used in **Study I** were defined in standard MNI space by using a combination of functional and anatomical images. To avoid circularity in our analysis, the images used to define the ROIs were independent of the data being analyzed.

We defined six bilateral ROIs: olfactory areas: anterior piriform cortex (APC) and posterior piriform cortex (PPC), visual areas: primary visual cortex (V1) and lateral occipital complex (LOC), as well as auditory areas: primary auditory cortex (A1) and a complex of higher order auditory regions (hAC) (Figure 4). The PPC constituted our main region of interest as we were especially interested in investigating processes related to olfactory object perception. The APC was included as a control region to determine whether any potential observed responsiveness is specific to PPC, or potentially permeates even earlier stages of olfactory processing. The visual and auditory areas were selected to correspond to the assumed function of the APC and the PPC, i.e., feature-based versus object-based processing (Gottfried, 2010), in the respective modality.

As functional olfactory ROIs, we used an activation likelihood estimation map of the piriform cortex (comprising both APC and PPC) based on 45 olfactory fMRI studies (Seubert, Freiherr, Djordjevic, & Lundström, 2013). To obtain individual ROIs for APC and PPC, we partitioned and restricted the functional map with anatomical masks of the APC and the PPC. These anatomical masks were defined by manual delineation of each region in each hemisphere on a separate sample of normalized T1 images from 60 participants. When merging the resulting masks across individuals, we preserved only voxels that were present in at least 30% of all images and that did not overlap between the APC and the PPC masks. The APC mask was furthermore restricted with a probabilistic atlas-based anatomical mask of the insula comprising the anterior, middle and posterior short gyri, available at www.brain-development.org (Failletot, Heckemann, Frot, & Hammers, 2017).

For the functional visual ROIs, we retrieved reverse inference maps based on 2,549 studies from the NeuroSynth database (www.neurosynth.org). We included only voxels for which activation above baseline was reported. To restrict the activation map and create bilateral functional-anatomical ROIs similar to the ones created for the olfactory system, we further restricted the functional visual ROIs with probabilistic atlas-based anatomical masks available in the SPM Anatomy Toolbox (Eickhoff et al., 2005). A bilateral mask of the calcarine sulcus served as anatomical mask for V1. A combined bilateral mask of the anterior and posterior hOc4l (region 4 in the lateral part of human occipital cortex) served as anatomical mask for the LOC since these regions are assumed to represent the anatomical equivalent to the functionally defined LOC (Malikovic et al., 2016).

As functional auditory ROIs, we used a reverse inference map based on 1,055 studies retrieved from the NeuroSynth database (www.neurosynth.org). To create the bilateral functional-anatomical ROI for the primary auditory cortex, we restricted the derived functional map with a bilateral anatomical mask consisting of the AAL atlas-based anatomical ROI of Heschl's gyrus and the TE1 (primary auditory cortex) ROI available in the SPM Anatomy Toolbox. The bilateral functional-anatomical ROI for auditory object areas was created by restricting the activation map with a combined bilateral mask of the Brodmann areas 22 and 40, the AAL atlas-based anatomical ROI of the supramarginal gyrus and the probabilistic atlas-based anatomical TE3 (secondary auditory cortex) ROI available in the SPM Anatomy Toolbox (Eickhoff et al., 2005).

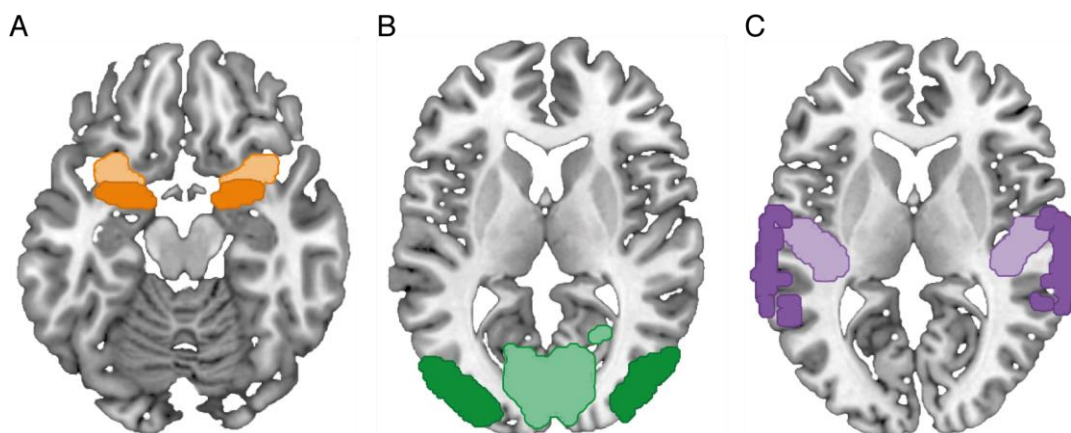


Figure 4. Regions of interest used in Study I. Pre-defined ROIs for the (A) olfactory, (B) visual and (C) auditory modality.

4.4.2.2 Functional ROI definition

In **Study III**, we defined ROIs for each individual in native space. We were especially interested in the LOC, a key area for visual object recognition (Grill-Spector, Kourtzi, & Kanwisher, 2001). Individual LOC ROIs were defined using functional images that were independent of the data being analyzed. The functional localizer data was collected at the beginning of the first and second scanning session. Each of the two localizer runs had a duration of 4.3 minutes and consisted of three blocks showing 20 grey-scale pictures of objects within

a grid, three blocks showing scrambled versions of those objects within a grid and seven blocks showing an empty grid. Each block lasted 20s (stimulus duration 700ms; ISI 300ms). The blocks were presented in interleaved order with empty grid blocks at the beginning and the end of each run. Participants were asked to fixate a small fixation cross displayed in the center throughout the whole run.

To delineate the LOC in each individual's brain, we contrasted activation for complete versus scrambled objects and displayed the result on the participants' flattened cortical representation. We then selected only voxels that showed higher activation ($p < .01$, uncorrected) for complete objects compared to scrambled objects and were located around the lateral occipital cortex and posterior fusiform gyrus, which together constitute the LOC (Grill-Spector et al., 2001). The drawn ROIs were subsequently resampled from surface to volumetric space using a built-in Freesurfer function and then combined across both hemispheres (Figure 5).

4.4.2.3 Anatomical ROI definition

Individual V1 ROIs used in **Study III** were defined on the participants' flattened anatomy in native space. The ROIs were obtained from the automatic cortex parcellation procedure implemented in Freesurfer (Fischl, 2004). The surface-based ROIs were first projected back into volumetric space using a built-in Freesurfer function and then combined across both hemispheres (Figure 5).

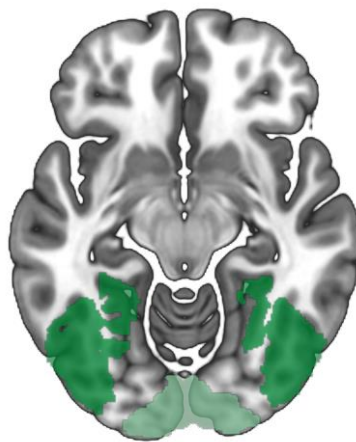


Figure 5. Regions of interest used in Study III. The here shown ROIs depict group averages of the individually defined V1 (light green) and LOC (dark green) ROIs. For illustration purposes only, the ROIs were normalized and merged across participants.

4.4.3 Univariate Analyses

In **Study I** and **Study II**, we were interested in assessing the neural mechanisms underlying multisensory integration. To this end, we acquired BOLD images while participants performed the previously described experiment. To infer whether the measured brain activity is related to the experimental manipulation, we used a General Linear Model (GLM). A GLM tries to explain the time course of the acquired BOLD signal as a linear combination of experimental

manipulations, known confounds such as head motion, and errors (variance that cannot be explained by experimental manipulations or confounds). All experimental manipulations that could explain some variation in the measured brain activity, such as experimental conditions, button presses etc., and all known confounds are considered explanatory variables and represented in the GLM as individual regressors. All regressors together constitute the design matrix. The experimental regressors are subsequently convolved with a simulated BOLD response, the so-called hemodynamic response function (HRF). Thereby one obtains a predicted BOLD signal, which can then be compared to the measured BOLD signal. The activation of each voxel (three-dimensional pixel) in the brain is estimated separately, meaning that the same GLM is used for all voxels but with separate parameter estimation for each voxel. The estimated level of activation is represented by a β value. A GLM analysis results in one β value for each voxel in the brain and for each regressor. This means a whole-brain map of β values is obtained for each regressor. These activation maps can be subsequently statistically compared.

4.4.3.1 ROI-based analyses

The collected BOLD images were used in **Study I** to compare activation in particularly olfactory but also visual and auditory ROIs when participants were presented with a unimodal, bimodal, or trimodal stimulus. We were especially interested in the effect of multisensory stimulation on information processing in the PPC, the other regions served primarily as negative control. As previous studies indicate that olfactory regions respond to sensory stimulation received through other senses (Gottfried et al., 2004; Maier et al., 2012), we first assessed whether our olfactory ROIs would respond to videos or sounds of objects. Subsequently, to determine whether activation in olfactory regions would increase when more information about the to-be-processed object is available, we compared the neural responses when one, two, or three senses were stimulated. As a direct comparison to olfactory regions, we also assessed whether cross-modal responsiveness and a linear activation increase by the number of stimulated senses would equally be observed in visual and auditory regions.

The design matrix used in the GLM to explain the measured signal contained one regressor for each experimental condition where participants gave response (3x unimodal, 3x bimodal congruent, 3x bimodal incongruent, 1x trimodal congruent, 1x trimodal incongruent), one regressor that represented non-response trials, one regressor modelling the response period, and six realignment parameters representing head motion. We additionally added response time measures as parametric modulators for the regressors modeling the experimental conditions to account for potential differences in attention between the conditions. To account for serial correlations in the data, we included a first order autoregressive model. To remove low frequency noise in the signal before estimation of the model, we used a high-pass filter with a cutoff of 128s. The design matrix was subsequently convolved with a standard simulated HRF.

To assess the level of activation in our predefined ROIs when one, two, or three senses were stimulated, we contrasted the activation map for each experimental condition against the control condition on an individual level. By implementing this step, we excluded any activation

that would be merely related to inhalation. From the obtained contrast maps, for each ROI separately, we extracted only the voxels within the ROI and averaged activation across voxels. The activation estimates for all odor-containing bimodal conditions were afterwards averaged to obtain one mean bimodal estimate. The same was done for the bimodal video and the bimodal sound conditions. To determine whether activation in our ROIs increased with an increasing number of stimulated senses, we applied a linear mixed model with type of stimulation as fixed factor (unimodal, bimodal, trimodal) and participant as a random factor for each ROI separately. To establish whether the observed activation pattern was consistent across regions in the olfactory cortex, we contrasted the activation pattern in the PPC to the activation pattern in the APC with a 2 (ROI: APC vs PPC) \times 3 (type of stimulation: unimodal vs bimodal vs trimodal) repeated measures analysis of variance (ANOVA). We further compared activation patterns in the PPC, LOC, and hAC by means of a 3 (ROI: PPC vs LOC vs hAC) \times 3 (type of stimulation: unimodal vs bimodal vs trimodal) repeated measures ANOVA. Finally, we assessed the cross-modal responsiveness of our ROIs by means of one-sample *t* test. We tested whether activation in olfactory regions in response to a video or sound was significantly greater than to control stimulation. We tested the same for odor and sound stimulation in visual regions, as well as odor and video stimulation in auditory regions.

4.4.3.2 Whole-brain analyses

In **Study II**, the collected fMRI data was used to identify regions in the whole brain that exhibited bimodal and trimodal integration effects in terms of super-additivity: bimodal stimulation exceeding the sum of the unimodal components, and trimodal stimulation exceeding the super-additive bimodal integration effects.

We used the same GLM as described in Study I but this time we convolved the regressors with a HRF with time and dispersion derivatives to account for regional differences in the shape of the HRF. For each participant, we contrasted the estimated activation map for each experimental condition against the implicit baseline. These contrast maps were then entered into a group-level flexible factorial design modelling participants as random effects and experimental conditions as fixed effects.

To infer multisensory processing from BOLD responses, several statistical criteria of different stringency have been suggested (Beauchamp, 2005). For the purpose of **Study II**, we decided to characterize multisensory processing as super-additive activation. This means that activation measured during multisensory stimulation was considered to be specific to the neural process of relating sensory components if it was statistically higher than the summed activation measured during separate unimodal stimulation. To determine modality-independent bimodal effects, we first analyzed all possible bimodal combinations of modalities (odor-video, odor-sound, video-sound) separately. This was achieved by contrasting each bimodal condition to the sum of the respective unimodal conditions. Because participants were instructed to sniff during any kind of stimulation, even if there was no odor present, we adjusted for multiple subtraction of activation attributed to sniffing when computing the super-additive contrasts. In other words, we contrasted the sum of bimodal and control condition to the sum of the

respective unimodal conditions (e.g., odor-sound + control > odor + sound, see Table 1). Each contrast revealed brain regions relating specific bimodal information to each other. These contrasts were subsequently entered in a conjunction analysis (conjunction null hypothesis; (Nichols, Brett, Andersson, Wager, & Poline, 2005)) to determine the overlap between all three super-additive bimodal contrasts (see Table 1). This allowed us to exclude brain regions that only processed bimodal information for specific modalities and isolate the brain regions showing super-additive responses across all three possible bimodal combinations. Hence, the resulting isolated regions could be labeled as modality-independent bimodal processing sites.

All conjunction analyses used a voxel-level threshold of $p < .001$ uncorrected for multiple comparisons, for each contrast entering the conjunction analysis. This approach was chosen because significance testing against a conjunction null-hypothesis relies on the simultaneous statistical significance of three contrasts, where a threshold of family-wise error (FWE) $p < .05$ applied to three such tests would yield an extremely conservative overall statistical significance threshold of $p < .05^3 = .000125$ (Fisher's method of estimating the conjoint significance of independent tests (Fisher, 1950)).

Afterwards, we identified brain regions where the response to trimodal stimulation exceeded the sum of bimodal and unimodal responses. Thus, we tested for super-additive effects for trimodal relative to bimodal stimulation. For this purpose, we first computed three separate contrasts, each contrasting the sum of trimodal and control condition to the sum of one bimodal condition and the missing unimodal condition (e.g., odor-sound-video + control > odor-sound + video, see Table 1). We then entered these contrasts into a conjunction analysis to isolate brain regions exhibiting greater responses to trimodal stimulation relative to any combination of bimodal and unimodal sensory input. The identified regions could therefore be labeled as modality-independent trimodal processing sites. Finally, we computed the overlap between modality-independent bimodal and modality-independent trimodal processing sites by means of a conjunction analysis over all bimodal and trimodal contrasts (see Table 1). We thereby isolated brain regions demonstrating multisensory processing independent of the number and type of integrated sensory modalities.

Finally, as an additional exploratory analysis, we aimed to determine whether the observed modality-independent super-additive effects would be sensitive to the congruency of the sensory signals. We therefore assessed whether super-additive activation could also be observed for incongruent bimodal and trimodal stimulation. To this end, we first computed separate contrasts assessing super-additive activation for each incongruent bimodal condition relative to its unimodal counterparts (e.g., odor-sound-*incongruent* + control > odor + sound) and subsequently assessed the overlap between these contrasts. For incongruent trimodal stimulation, we followed the same analysis procedure as for the bimodal conditions. Meaning, we first separately contrasted the incongruent trimodal condition to the sum of activation elicited by each congruent bimodal condition and its respective unimodal complement (e.g., odor-sound-video-*incongruent* + control > odor-sound-*congruent* + video), and afterwards computed a conjunction analysis across all three contrasts. To specifically test for an effect in

the previously identified modality-independent multisensory processing sites, we applied an inclusive mask consisting of a conjunction across the super-additive contrasts for congruent bimodal and trimodal stimulation ($p < .05$, uncorrected).

Table 1. Contrast descriptions of all group-level contrasts for congruent experimental conditions used in Study II.

	Contrasts
Unimodal stimulation	odor > control sound > control video > control
Bimodal processing	odor-sound + control > odor + sound odor-video + control > odor + video sound-video + control > sound + video (odor-sound + control > odor + sound) \cap (odor-video + control > odor + video) \cap (sound-video + control > sound + video)
Trimodal processing	odor-sound-video + control > odor-sound + control odor-sound-video + control > odor-video + sound odor-sound-video + control > sound-video + odor (odor-sound-video + control > odor-sound + video) \cap (odor-sound-video + control > odor-video + sound) \cap (odor-sound-video + control > sound-video + odor)
Super-additive processing independent of the number and type of stimulated modalities	(odor-sound + control > odor + sound) \cap (odor-video + control > odor + video) \cap (sound-video + control > sound + video) \cap (odor-sound-video + control > odor-sound + video) \cap (odor-sound-video + control > odor-video + sound) \cap (odor-sound-video + control > sound-video + odor)

Table 2. Contrast descriptions of group-level contrasts used in Study II to assess the sensitivity of the superadditivity effect to the congruency of the sensory signals. Incongruent stimulus combinations are labeled with *i* (e.g., odor-sound-video-*i*), while congruent stimulus combination are labeled with *c* (e.g., odor-sound-video-*c*).

Contrasts	
Congruency-sensitivity of bimodal processing	$(\text{odor-sound-}i + \text{control} > \text{odor} + \text{sound}) \cap (\text{odor-video-}i + \text{control} > \text{odor} + \text{video}) \cap (\text{sound-video-}i + \text{control} > \text{sound} + \text{video})$ masked with $(\text{odor-sound-}c + \text{control} > \text{odor} + \text{sound}) \cap (\text{odor-video-}c + \text{control} > \text{odor} + \text{video}) \cap (\text{sound-video-}c + \text{control} > \text{sound} + \text{video}) \cap (\text{odor-sound-video-}c + \text{control} > \text{odor-sound-}c + \text{video}) \cap (\text{odor-sound-video-}c + \text{control} > \text{odor-video-}c + \text{sound}) \cap (\text{odor-sound-video-}c + \text{control} > \text{sound-video-}c + \text{odor})$
Congruency-sensitivity of trimodal processing	$(\text{odor-sound-video-}i + \text{control} > \text{odor-sound-}c + \text{video}) \cap (\text{odor-sound-video-}i + \text{control} > \text{odor-video-}c + \text{sound}) \cap (\text{odor-sound-video-}i + \text{control} > \text{sound-video-}c + \text{odor})$ masked with $(\text{odor-sound-}c + \text{control} > \text{odor} + \text{sound}) \cap (\text{odor-video-}c + \text{control} > \text{odor} + \text{video}) \cap (\text{sound-video-}c + \text{control} > \text{sound} + \text{video}) \cap (\text{odor-sound-video-}c + \text{control} > \text{odor-sound-}c + \text{video}) \cap (\text{odor-sound-video-}c + \text{control} > \text{odor-video-}c + \text{sound}) \cap (\text{odor-sound-video-}c + \text{control} > \text{sound-video-}c + \text{odor})$

4.4.4 Multivariate Analyses

In **Study III**, we aimed to determine whether information about an object’s odor is manifested as spatially distributed activation patterns in areas of the ventral visual pathway. To this end, we employed multivariate pattern analyses (MVPA). MVPA relies on systematic differences in the pattern of neural activity across conditions. In contrast to univariate analyses that consider the activation in each voxel separately, multivariate approaches analyze activity in spatially distributed sets of voxels. Thereby patterns of activation can be detected that are linked to an experimental manipulation but do not lead to a significant overall change in activation across voxels and therefore remain undetected in univariate analyses. Besides the experimental manipulations, also variation in pre-stimulus brain activation or random fluctuations in attention can induce trial-to-trial differences, even between trials of the same condition. To account for such response differences across trials of the same condition, and for overlap of the BOLD signals between adjacent trials, we followed the “Least-Squares Separate” approach (Turner, Mumford, Poldrack, & Ashby, 2012) by constructing and estimating a separate GLM for each trial in each run. That resulted in 36 GLMs per run. The GLMs were set up with one regressor of interest corresponding to the onset of the current trial of interest (duration of 2s). All other trials, including response period and button press, were combined into a single nuisance regressor. All regressors were convolved with the canonical HRF. A high-pass filter with a cutoff of 128s removed low-frequency drifts in the signal and serial autocorrelations were accounted for using a first order autoregressive model.

4.4.4.1 ROI-based pattern classification

To validate the location of our predefined ROIs and our analysis approach, we first determined that we could decode visual objects from V1 and LOC. For this purpose, we trained and tested a classifier to differentiate between visual objects based on multi-voxel activation patterns evoked by pictures of different objects. Subsequently, to quantify the sensitivity of each ROI

to olfactory object information, we used the patterns of activity evoked by the odor of different objects for training and testing a classifier to differentiate between olfactory objects. The classifier was based on a linear support vector machine (SVM). To run classification analyses of activation patterns, we applied The Decoding Toolbox (Hebart, Görger, & Haynes, 2014) and used the trial-wise beta-estimates from the above described GLM analysis. Classification analyses were conducted for each individual separately and within native space. For all classification analyses, we employed a leave-one-run-out cross-validation procedure where we trained the SVM classifier on beta-estimates from all runs except one and tested it on the beta-estimates from the left-out run. In each cross-validation step another run served as test data. The number of cross-validation iterations varied among subjects depending on the number of completed experimental runs. The accuracy scores computed in each cross-validation iteration were subsequently averaged resulting in one final decoding accuracy value per classification analysis per subject. These subject-wise accuracy values were later averaged across participants to obtain an average group decoding accuracy for each classification analysis. For all classification analyses, only voxels within the predefined ROIs were considered.

Considering the recent debate about the appropriateness of t-tests to evaluate the significance of decoding accuracies (Schreiber & Krekelberg, 2013), we employed a permutation approach (Stelzer, Chen, & Turner, 2013) to determine the significance of our decoding accuracies on the group level. First, for each of the two classification analyses (1x picture classification, 1x odor classification) in each ROI, we shuffled category labels in 1000 different combinations and performed the decoding with the shuffled labels. Afterwards, we randomly selected (with replacement) one decoding accuracy value per participant and averaged these values to one group average decoding accuracy. This procedure was repeated 10^5 times. Based on the resulting 10^5 average decoding accuracies, we created an empirical chance distribution that we used to determine the significance of our classification results.

4.4.4.2 ROI-based representational similarity analyses

To examine the similarity of multi-voxel activation patterns in our predefined ROIs for odors and pictures of objects, we performed a representational similarity analysis (Kriegeskorte, Mur, & Bandettini, 2008). This analysis allowed us to go beyond investigating *whether* our ROIs represent visual and olfactory object information, and to explore *how* they represent this information. We compared the neural response patterns across experimental conditions by means of representational dissimilarity matrices (RDM). To this end, we first averaged the trial-wise beta estimates for each of the odor and picture conditions (4 odor conditions, 4 picture conditions) across runs within each subject and thereby obtained one mean beta estimate per condition for each participant. From each mean beta estimate, we then extracted the activity estimates for voxels within our predefined ROIs and used the extracted multi-voxel activation patterns to compute an RDM for each ROI separately. To do so, we compared each pair of conditions by computing the correlation distance (1 minus Pearson linear correlation) between the associated activation patterns (0 = perfect correlation, 1 = no correlation, 2 = perfect anticorrelation). The computed dissimilarity values were then combined into an RDM for each

individual. This resulted in an 8 x 8 RDM for each participant, where each row represents the dissimilarities between one condition and all other conditions including itself.

To assess whether the RDMs match across participants in each ROI, we computed the Spearman's rank correlation between the lower-triangular entries of the individual RDMs. The computed correlation coefficients were then combined into a second-order RDM where each row represents the correlation between one participant's RDM and all other participants' RDMs, including itself. By averaging the lower-triangular entries of the constructed matrix, we obtained a mean between-subject RDM correlation coefficient. To evaluate the significance of the between-subject correlation for each ROI separately, we employed a permutation approach. Under the null hypothesis that the RDMs are not correlated across participants, meaning that the neural representations of the experimental conditions are not related between participants, the condition labels can be shuffled without affecting the between-subject correlation. For each pair of participants, we first randomized the condition labels in one of the RDMs by consistently reordering rows and columns and subsequently computed the Spearman's rank correlation between the lower-triangular entries of the two RDMs. We then combined the pairwise correlation coefficients into a randomized second-order RDM and calculated a mean between-subject correlation coefficient by averaging the lower-triangular entries. By repeating this procedure 10^4 times, we obtained an empirical null distribution simulating that the RDMs are not correlated across participants. This distribution was then used to determine the significance of our actual average between-subject correlation coefficient.

After having determined the significant similarity of RDMs across participants, we averaged them into one group RDM for each ROI. To visually explore the similarity structure of activation patterns in each ROI, we performed non-metric multidimensional scaling (minimizing the stress function) on the group RDMs. By transforming dissimilarity metrics into distance measures, multidimensional scaling allows to visualize the dissimilarities of activation patterns as distances in two dimensional space: Dissimilar patterns are placed far apart while similar patterns are placed close together.

Besides visually inspecting the group RDMs, we aimed to statistically determine the similarity of olfactory and visual response patterns in our predefined ROIs. If olfactory and visual object information would be represented in a similar way, odor- and picture-evoked response patterns for the same objects should be more similar (less dissimilar) to each other than response patterns for different objects. To test this, we first extracted the subpart of the group RDM (for each ROI separately) representing pattern comparisons between odor and picture conditions and separated it into diagonal (same objects) and off-diagonal (different objects) dissimilarity values (Figure 6). We then averaged the off-diagonal and diagonal elements respectively and computed their difference (off-diagonal minus diagonal). To assess the statistical significance of this difference, we used a permutation test. To simulate the null hypothesis that the dissimilarity between neural representations is the same for all object comparisons (no difference between same and different objects), we randomly shuffled rows and columns of the subpart of the group RDM and computed the difference between mean off-diagonal and mean

diagonal values. This step was repeated 10^4 times. The randomized differences were combined into an empirical null distribution simulating that odor- and picture-evoked response patterns for the same objects are not more similar to each other than response patterns for different objects.

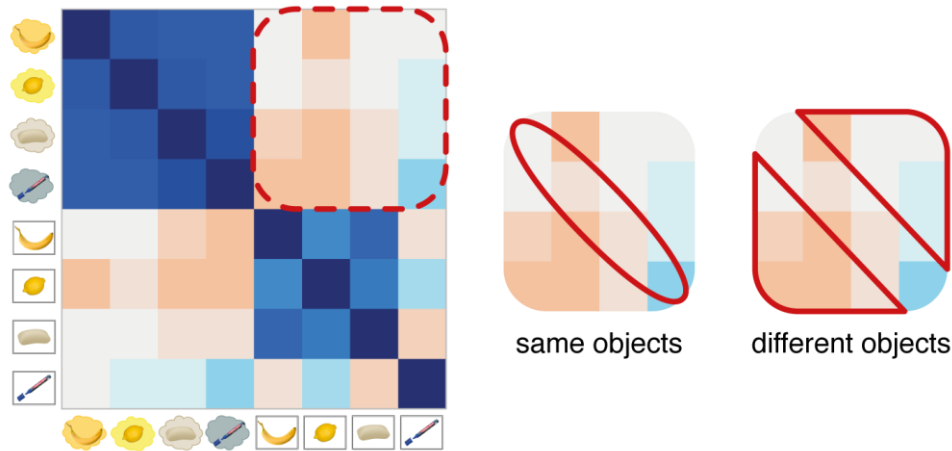


Figure 6. Illustration of the procedure to assess differences between olfactory and visual object representations. First, the subpart of the group RDM (for each ROI separately) representing pattern comparisons between odor and picture conditions was extracted. This subpart was afterwards separated into diagonal (same objects) and off-diagonal (different objects) dissimilarity values. The obtained off-diagonal and diagonal elements were then averaged respectively and their difference was computed (off-diagonal minus diagonal). A permutation test was used to assess the statistical significance of this difference.

4.4.4.3 Whole-brain searchlight analyses

To examine whether also other brain regions than our predefined ROIs are sensitive to olfactory and visual object information, we performed searchlight decoding analyses across the whole brain (Kriegeskorte, Goebel, & Bandettini, 2006). We followed an identical classification procedure as described above for the predefined ROIs, except that this time, we considered all voxels within the brain instead of only within a ROI. Briefly, we conducted two separate leave-one-run-out cross-validation classification analyses (1x odor classification, 1x picture classification) in the whole brain. The size of the searchlight was set to 5mm radius, which means that for each voxel in the brain, a decoding accuracy value was computed based on activation patterns within a spherical neighborhood of 5mm radius surrounding that voxel. The achieved accuracy value (mean accuracy across cross-validation iterations) was assigned to the voxel on which the sphere was centered. To obtain accuracy deviations from chance level, the theoretical chance-level of 25% (the probability of the classifier to decode the correct object identity by chance) was subtracted from each accuracy value. We thereby obtained whole-brain accuracy-minus-chance maps for each subject for each classification. To allow for statistical analyses across participants, the individual accuracy-minus-chance maps were first transformed into standard MNI space and afterwards smoothed with an isotropic 7mm FWHM Gaussian kernel to reduce the effects of inaccuracies in the normalization procedure and to meet the assumptions of Random Field Theory for subsequent statistical testing. Due to computational limitations, we could not employ a permutation approach to identify regions that

exhibited significant above-chance decoding accuracies on the group level. Therefore, for each of the two classification analyses separately, we instead entered the individual normalized and smoothed accuracy maps into a one-sample t test against zero. Significant clusters were defined using a cluster-forming threshold of $p < .001$ and a cluster-level correction at a FWE rate of $p < .05$.

4.5 ETHICAL CONSIDERATIONS

All studies included in this thesis had prior ethical approval. For all studies, participants voluntarily signed up to participate after being informed of the study purpose and were free to cancel their participation or to abort the experiment at any time without the need of stating a reason. We ensured that they did not feel forced at any time. Participants were informed about the procedure and we made sure that they understood it by providing them with as much information as needed to ensure that they were able to consider their participation carefully before giving their informed written consent.

None of the stimuli or measurements used were harmful to the participants. The odors that served as stimuli are all labelled as “Generally Recognized As Safe” according to the U.S. Food and Drug Administration and all methods used are well established and widely used in neuroscience and clinical research. Although no invasive or otherwise harmful stimuli or methods were used, there are still some ethical issues our studies carry with them that should be addressed.

4.5.1 Personal Data

In all studies included in the thesis, we collected personal data such as name, birth date, sex, as well as behavioral and neuroimaging data. To avoid that individuals could be identified based on the collected data, all data were anonymized and stored so that only authorized persons could access them. Moreover, data were either only presented on a group-level or in a way that did not allow the data to be attributed to a specific individual.

4.5.2 Olfactory Performance Test

Because one of the studies’ requirements was a normal sense of smell, we tested each participant’s sense of smell with a well-established testing procedure called the Sniffin’ Stick test (Hummel et al., 1997). With this procedure, we excluded any potential hyposmia (reduced ability to smell and detect odors) which could have confounded our experimental results. Hyposmia could be due to a cold or could have more severe reasons. However, the sniffing test procedure as we used it, is solely for ensuring normal sense of smell. It does not serve as a diagnostic method of hyposmia. If, however, we had to exclude some participants because they did not pass the Sniffin’ Sticks test, we were obliged to inform them about the reason for exclusion. As we are not qualified to set medical diagnoses, we were not allowed to make any diagnostic utterance. Nevertheless, we were obligated to inform the participants that an issue with their sense of smell could exist and that we recommend them to see a medical doctor if they are worried. Because such statement might easily give cause for concern, it is important

to explain that not-passing the test does not indicate any major medical issue but could just be due to a “bad day”, a cold, or other minor non-clinical reason.

4.5.3 Neuroimaging

In all studies included in this thesis, we acquired images of the participants’ brains and could thereby potentially have revealed a medical condition that would have otherwise remained undetected. At the end of each fMRI experiment, we completed a structural scan of the participants’ brain. These images were later examined by a radiologist. If some abnormalities were detected the participant was contacted by a neurologist. Although this standard procedure bears the concern of limiting the participants’ autonomy by requiring them to undergo an examination of their brain as soon as they agree on participating in our study, they were informed about the requirement prior to their participation and were thereby able to refuse it.

Besides the risk of incidental findings when participating in an MRI study, there is also the chance of feeling discomfort while lying in the MRI scanner. This could be due to several reasons. Remaining still in a supine position for a long time, for example, might feel uncomfortable. Moreover, participants might feel closed-in or anxious while in the MRI scanner even though they have previously indicated that they do not suffer from claustrophobia in general. Although we provided participants with ear plugs and headphones, the scanner noise could be perceived as too loud and uncomfortable. Another reason could be the strong static magnetic field causing peripheral nerve or muscle stimulation and thereby inducing a twitching sensation. Although fMRI is considered a non-harmful measurement, participants were informed about any potential risk an MRI study carries with it prior to their participation.

For safety reasons, we generally excluded people with metal material implanted in their body (e.g., braces, implants etc.). People with epilepsy or taking illegal drugs were not allowed to participate in the study as they could react more strongly to the strong magnetic field of the MR-Scanner. Moreover, we excluded pregnant females as we still know little about the effects of strong static magnetic fields on fetal development and wanted to avoid any potential risk.

4.5.4 Exclusion Criteria

To participate in the studies, our volunteers needed to fulfil certain requirements. Some of those requirements were necessary to avoid any harm to the participants (for MR safety reasons as previously discussed). Another exclusion criterion that did not serve the participants’ benefit but rather served the purpose of reducing variance in the study sample, was, for example, left-handedness. However, such an exclusion criterion causes that individuals in the population are not treated equally. As we unfortunately did not have the resources to broaden our study sample to include a representative range of any possible variation, we were forced to restrict participation in our studies to individuals meeting our defined profile.

5 RESULTS

5.1 STUDY I: MULTISENSORY ENHANCEMENT OF OLFACTORY OBJECT PROCESSING

Previous research has shown that our ability to identify an object based on its odor alone is rather poor but improves dramatically when we receive assisting cues from other senses (Davis, 1981; Desor & Beauchamp, 1974; Engen & Ross, 1973; Zellner et al., 1991). In **Study I**, we aimed at revealing the neural processes that might mediate this improved perception of an olfactory object in a multisensory environment. We therefore sought to determine, by means of fMRI, whether and how *multisensory* object information influences the processing of *olfactory* object information in the human PPC, a region linked to olfactory object encoding (Gottfried, 2010; Howard et al., 2009). This region has previously been assumed to be strictly olfaction-specific but there is growing evidence that such presumptive unisensory areas are actually not exclusively unisensory. Instead, they can be affected by interactions between different senses (Fuxe & Schroeder, 2005; Giard & Peronnet, 1999; Schroeder & Fuxe, 2005). Given this growing evidence, we hypothesized that the PPC would process not only olfactory but also other sensory object information. We further hypothesized that assisting input from other senses about the to-be-processed object would enhance the neural processing of the olfactory object information already at the level of the olfactory cortex and not only at a later processing stage of higher-order integration sites. To prove our hypotheses, we first determined whether the PPC responds to object information that is related to an odor but derives from other senses. Subsequently, we tested whether an object's odor and information from other senses about that object are integrated within the PPC, a process that would be expressed as an increased activation level. We additionally examined whether the level of activation is linearly related to the number of senses providing assisting input. Finally, to assess whether the observed activation patterns are specific to the PPC or regions dedicated to the sense of smell, we applied an equivalent testing procedure to the APC, an olfactory region preceding the PPC in the olfactory processing hierarchy, as well as to visual and auditory regions that are assumed to resemble the PPC and APC with respect to their function.

5.1.1 The PPC Responds to Non-Olfactory Object Information

In line with earlier studies (Gottfried et al., 2004), we observed that the PPC responded significantly to mere visual object information (Figure 7A). As previous studies have shown that the PPC responds also to auditory stimulation (Gnaedinger et al., 2019; Varga & Wesson, 2013; G. Zhou, Lane, Noto, et al., 2019), we expected to find PPC activation for auditory stimulation. However, contrary to our expectations, the PPC did not significantly respond above baseline to auditory object information alone (Figure 7A).

5.1.2 The PPC Integrates Multisensory Object Information

Confirming our hypothesis that assisting input from other senses about the to-be-processed object would enhance the neural processing of the olfactory object information, we observed that activation in the PPC increased when participants perceived an object through several

senses, compared to solely smelling it. This activation increase was linear. That is, the more senses provided information about the to-be-processed object the more the activity in PPC increased (Figure 7B). To ensure that the observed activation increase indeed reflected integration of sensory object information and not a mere increase in sensory stimulation, we assessed whether activity would also increase for incongruent multisensory stimulation. Incongruent multisensory input did not lead to an activation increase in the PPC (Figure 7C).

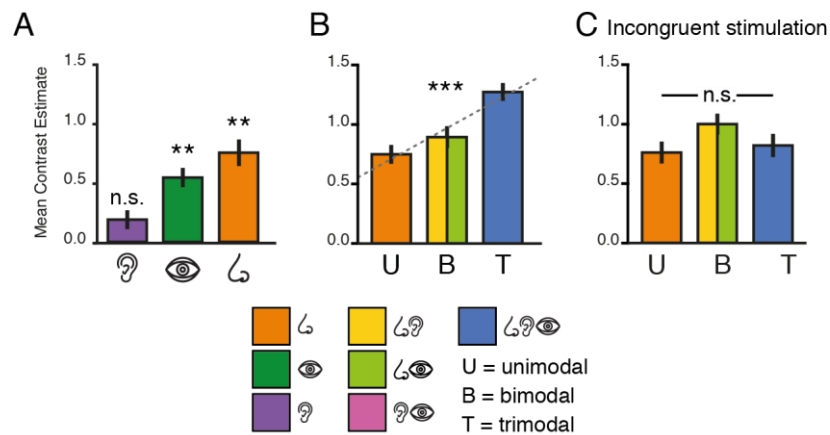


Figure 7. Multisensory response pattern in the PPC in Study I. **A)** Extracted mean contrast values for cross-modal activation in the PPC. Error bars depict SEM. One-sample t tests ($* p < .05$, $** p < .01$, $*** p < .001$) revealed significant cross-modal activation for visual but not for auditory stimulation. **B)** Extracted mean contrast estimates for unimodal (U), bimodal (B), and trimodal (T) stimulation. Bimodal bars reflect averages of the two contributing bimodal conditions. Error bars depict SEM. A linear mixed model revealed a significant ($*** p < .001$) linear increase in activation with incrementing modalities. **C)** Extracted mean contrast estimates for unimodal (U), bimodal (B), and trimodal (T) incongruent stimulation. Bimodal bars reflect averages of the two contributing bimodal conditions. Error bars depict SEM. There was no linear increase in activation with incrementing modalities for incongruent stimulation. Colors denote sensory combinations, cartoon symbols indicate type of sensory stimulation: nose = olfactory stimulation, eye = visual stimulation, ear = auditory stimulation.

5.1.3 Cross-Modal Activation in Other Sensory Cortices

In contrast to the PPC, the APC was not active when participants merely saw or heard an object. In line with previous findings, early visual regions responded significantly to mere odor stimulation (Qureshy et al., 2000; Royet et al., 1999). However, contradicting previous findings, they did not respond to the sound of objects (Poremba et al., 2003; von Kriegstein et al., 2005). Auditory regions, in contrast, were active in response to both, visual and olfactory stimulation. This confirms earlier findings showing visually evoked activation in auditory cortex (Bizley et al., 2007; Schroeder & Foxe, 2002).

5.1.4 Multisensory Response Enhancement in Other Sensory Cortices

Similar to the PPC, also the APC showed a multisensory response enhancement. That is, activation increased linearly with the number of stimulated senses (Figure 8A). This linear increase was, however, lower than the one observed in the PPC (Figure 8B).

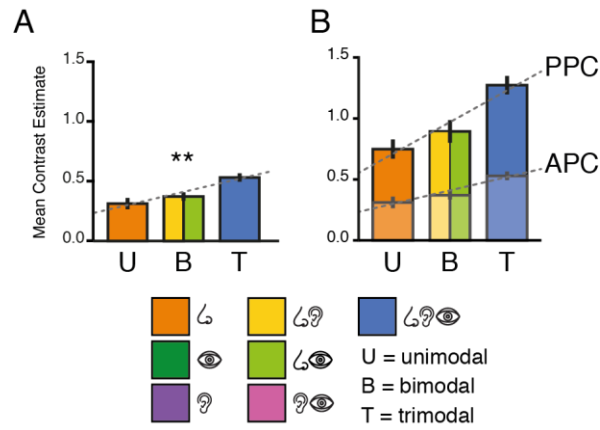


Figure 8. Multisensory response pattern in the APC in Study I. **A)** Extracted mean contrast estimates for unimodal (U), bimodal (B), and trimodal (T) stimulation. Bimodal bars reflect averages of the two contributing bimodal conditions. Error bars depict SEM. A linear mixed model revealed a significant (** $p < .01$) linear increase in activation with incrementing modalities. **B)** Effect of number of stimulated modalities on activation in the APC and PPC. A two-way repeated measures ANOVA revealed a significant interaction between ROI (APC vs PPC) and number of stimulated modalities (unimodal vs bimodal vs trimodal): increasing the number of stimulated senses had a stronger effect on activation in the PPC than in the APC. Colors denote sensory combinations, cartoon symbols indicate type of sensory stimulation: nose = olfactory stimulation, eye = visual stimulation, ear = auditory stimulation.

Subsequently, we assessed whether the observed multisensory response enhancement was a general phenomenon of object perception or specific to the olfactory system. We found that multisensory stimulation did not affect the activation level in either visual or auditory regions. While an increasing number of senses providing congruent object information had an increasing effect on the neural response in regions of the olfactory system, it had no discernible effect on the visual and auditory systems (Figure 9).

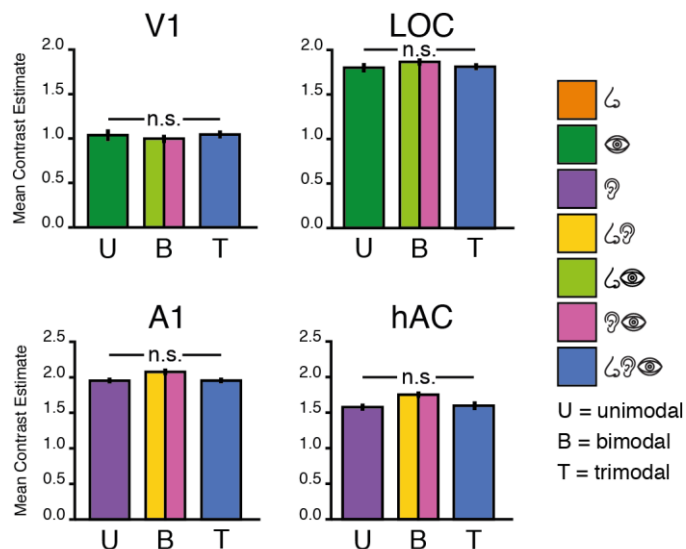


Figure 9. Multisensory response enhancement in visual and auditory ROIs in Study I. Extracted mean contrast estimates for unimodal (U), bimodal (B), and trimodal (T) stimulation in visual ROIs: V1 and LOC, and auditory ROIs: A1, hAC. Bimodal bars reflect averages of the two contributing bimodal conditions. Error bars depict SEM. Linear mixed models revealed no significant linear increase in activation with incrementing modalities for any of the ROIs. Colors denote sensory combinations, cartoon symbols indicate type of sensory stimulation: nose = olfactory stimulation, eye = visual stimulation, ear = auditory stimulation.

5.2 STUDY II: MODALITY-INDEPENDENT PROCESSING IN THE PARIETAL CORTEX

In Study I, we showed that when we perceive an object's odor in combination with its sound and look, the object-related information arising from the different senses is integrated in the PPC. In **Study II**, we then expanded our search for integration effects during multisensory object perception to the whole brain because previous research had demonstrated that multisensory integration is accomplished by a network of early sensory cortices and higher-order multisensory integration sites (Regenbogen et al., 2018). Previous studies on multisensory processes have, however, often used ecologically irrelevant stimuli such as simplified artificial stimuli or only audiovisual combinations. It is, therefore, still a question whether the identified central multisensory processes are generalizable to more complex everyday-life stimuli as well as other and more sensory modalities. In **Study II**, we aimed to assess whether there exist cortical regions that process multisensory object information independent of from *which* senses and from *how many* senses the information arises. We first assessed which brain regions exhibit a super-additive response profile for specific bimodal stimulus combinations only, and which brain regions respond in a super-additive fashion across all bimodal conditions, meaning independent of the combination of stimulated modalities. Subsequently, we identified brain regions exhibiting a modality-independent super-additive response profile for trimodal stimulation. Finally, we examined whether there are brain regions responding in a super-additive fashion for any multisensory stimulus combination, meaning independent of *which* and *how many* senses were stimulated.

5.2.1 Integration of Olfactory and Auditory Object Information

We found increased (super-additive) activation in the right superior medial prefrontal gyrus (smPFC) and the anterior part of the cingulate cortex (ACC) for the combined presentation of odor and sound (odor-sound) compared to the sum of the activations evoked by separate odor and sound stimulation (Table 3).

5.2.2 Integration of Olfactory and Visual Object Information

The left intraparietal sulcus (IPS) exhibited a super-additive response to the combined presentation of olfactory and visual object information (Table 3).

5.2.3 Integration of Visual and Auditory Object Information

The combined presentation of visual and auditory object information evoked a super-additive response the left IPS, middle frontal gyrus (MFG), inferior frontal gyrus (IFG), middle orbital gyrus, and middle cingulate cortex (MCC). In the right hemisphere, superior frontal gyrus (SFG), middle temporal gyrus (MTG) and inferior parietal cortex (IPC)/IPS were activated in a super-additive manner. Additionally, bilateral SFG and MTG responded in a super-additive fashion (Table 3).

Table 3. Significant super-additive activation evoked by odor-sound, odor-video, and sound-video stimulation in Study II. Contrasts resulted from a random-effects GLM ($ts > 4.79$, $ps < .05$, whole-brain-corrected for multiple comparisons (FWE), $k > 10$ voxels). Stereotaxic coordinates of local maxima of activation are expressed as x;y;z values in MNI space. Numbers within parenthesis indicate Brodmann areas (BA).

Contrast	Brain region	Hemisphere	Size	<i>t</i>	x	y	z
odor-sound + control > odor + sound	Superior medial gyrus / Anterior cingulate cortex	R	10	5.7	12	56	28
	Anterior cingulate cortex	R	11	5.6	15	47	13
odor-video + control > odor + video	Intraparietal sulcus	L	22	5.5	-51	-40	43
sound-video + control > sound + video	Superior frontal gyrus (BAs 6, 44, 45)	R	800	7.7	18	53	28
	Middle temporal gyrus	L	158	7.8	57	-43	-2
	Intraparietal sulcus	L	405	7.6	-51	-58	43
	Middle temporal gyrus	R	117	7.3	-57	-37	-8
	Middle cingulate cortex	L	12	5.5	-3	-19	37
	Middle frontal gyrus	L	37	6.8	-24	47	31
	Superior frontal gyrus	L	58	6.7	-18	23	55
	Supramarginal gyrus	R	91	6.6	57	-46	34
	Middle frontal gyrus	L	137	6.6	-36	20	40
	Middle frontal gyrus	L	71	6.0	-27	56	10
	Middle orbital gyrus	L	12	6.0	-24	44	-17
	Middle cingulate cortex	L	12	5.5	-3	-19	37
	Inferior frontal gyrus	L	13	5.4	-51	20	1

5.2.1 Modality-Independent Integration Sites for Bimodal Stimulation

To reveal brain regions that consistently responded in a super-additive fashion across all bimodal conditions, we assessed the overlap of all three above mentioned bimodal integration effects. The left IPC/IPS, MFG, IFG, as well as right smPFC exhibited super-additive activation during any type of bimodal stimulation (Figure 9A, Table 5).

5.2.2 Modality-Independent Integration Sites for Trimodal Stimulation

To identify brain regions exhibiting a modality-independent super-additive response profile for trimodal stimulation, we first computed modality-specific trimodal integration effects and subsequently computed the overlap of these integration effects. Modality-specific trimodal integration was defined as a super-additive response for trimodal stimulation relative to the sum of activations separately evoked by one of the bimodal conditions and the respective unimodal complement.

The right SFG, the left MFG, and left middle orbital gyrus, as well as bilateral IPC/IPS, IFG, and MTG exhibited an increased response for trimodal stimulation compared to the sum of activation evoked by odor-sound and video stimulation (Table 4).

Trimodal stimulation evoked a super-additive response relative to the sum of responses evoked by mere sound and combined odor-video stimulation in the right precentral gyrus, the left

MFG, IFG, ACC, MCC, precuneus, and posterior-medial frontal gyrus, as well as bilateral IPC/IPS, MTG, and SFG (Table 4).

The left IFG and IPC/IPS were activated in a super-additive fashion for trimodal stimulation relative to the sum of activations elicited by odor-sound and video stimulation (Table 4).

Overlapping super-additive effects for trimodal stimulation were found in the left IFG and bilateral IPC/IPS (Figure 9B, Table 5).

Table 4. Significant super-additive activation evoked by trimodal stimulation in Study II. Contrasts resulted from a random-effects GLM ($t_s > 4.79$, $p_s < .05$, whole-brain-corrected for multiple comparisons (FWE), $k > 10$ voxels). Stereotaxic coordinates of local maxima of activation are expressed as x;y;z values in MNI space. Numbers within parenthesis indicate Brodmann areas (BA).

Contrast	Brain region	Hemisphere	Size	<i>t</i>	x	y	z
odor-sound-video + control > odor-sound + video	Superior frontal gyrus (BA 44)	R	39	6.9	18	53	31
	Inferior parietal cortex/Intraparietal sulcus	L	456	8.2	-45	-58	46
	Inferior parietal cortex/Intraparietal sulcus	R	338	7.3	51	-37	43
	Middle frontal gyrus	L	18	6.2	-33	38	19
	Middle temporal gyrus	R	155	6.7	60	-40	-5
	Inferior frontal gyrus	R	16	5.7	48	41	-14
	Middle temporal gyrus	L	53	6.5	-60	-34	-11
	Middle orbital gyrus	L	99	6.2	-33	50	-5
	Superior frontal gyrus	R	11	5.6	18	23	55
	Inferior frontal gyrus	L	16	6.0	-51	17	1
odor-sound-video + control > odor-video + sound	Superior frontal gyrus	R	216	7.5	21	53	31
	Inferior parietal cortex/Intraparietal sulcus	R	155	7.2	57	-43	31
	Inferior parietal cortex/Intraparietal sulcus	L	201	5.9	-48	-52	43
	Middle temporal gyrus	R	175	6.7	54	-34	-8
	Inferior frontal gyrus	L	18	5.7	-51	17	-2
	Precuneus	L	11	5.6	-6	-73	37
	Superior frontal gyrus	R	128	6.4	18	23	55
	Anterior cingulate cortex	L	87	6.4	-6	47	7
	Middle temporal gyrus	L	41	6.3	-57	-34	-14
	Middle cingulate cortex	L	57	6.2	-3	-28	37
	Superior frontal gyrus	L	16	5.9	-21	50	31
	Precentral gyrus	R	29	5.8	45	5	46
	Middle frontal gyrus	L	10	5.5	-33	41	22
	Posterior-medial frontal gyrus	L	19	5.3	-3	2	49
Middle frontal gyrus	L	21	5.3	-30	56	10	
odor-sound-video + control > sound-video + odor	<i>Inferior parietal cortex/Intraparietal sulcus</i>	<i>L</i>	<i>1*</i>	<i>4.8</i>	<i>-54</i>	<i>-37</i>	<i>46</i>
	<i>Inferior frontal gyrus (BA 44, 45)</i>	<i>L</i>	<i>4*</i>	<i>5.3</i>	<i>-48</i>	<i>17</i>	<i>1</i>

* Note that these activations represent statistical trends with clusters smaller than $k=10$.

5.2.3 Core Multisensory Integration Sites—Invariance to Changes in the Number and Type of Sensory Input Streams

To identify brain regions that responded in a super-additive fashion independent of how many and which senses were stimulated, we computed the overlap between modality-independent integration effects for bimodal and trimodal stimulation. Overlapping super-additive activation was found in the left IFG and left IPC/IPS (Figure 9C, Table 5).

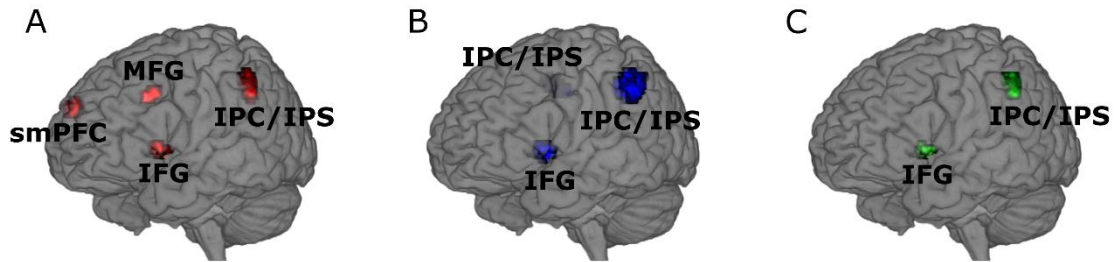


Figure 9. Bimodal and trimodal sensory processing in Study II. **A)** Significant super-additive activation for modality-independent bimodal processing. **B)** Significant super-additive activation for modality-independent trimodal processing. **C)** Significant overlapping super-additive activation for modality-independent bimodal and trimodal processing is situated in the left IFG and IPC/IPS. IFG = Inferior frontal gyrus, IPC/IPS = inferior parietal cortex/intraparietal sulcus, smPFC = superior medial frontal gyrus, MFG = middle frontal gyrus.

Table 5. Significant super-additive activation for modality-independent bimodal and trimodal processing in Study II. Contrasts resulted from a random-effects GLM ($t_s > 3.16$, uncorrected, $p_s < .001$, $k > 10$). Stereotaxic coordinates of local maxima of activation are expressed as x;y;z values in MNI space. Numbers in parenthesis indicate Brodmann areas (BA).

Brain region	Hemisphere	Size	<i>t</i>	x	y	z
<i>Super-additive bimodal processing</i> (odor-sound + control > odor + sound) \cap (odor-video + control > odor + video) \cap (sound-video + control > sound + video)						
Inferior parietal cortex/Intraparietal sulcus (BA 40)	L	28	3.75	-54	-40	46
Superior medial frontal gyrus (BA 9)	R	22	4.2	12	56	28
Middle frontal gyrus	L	16	3.98	-33	17	37
Inferior frontal gyrus (BA 44, 45)	L	16	4.3	-48	20	1
<i>Super-additive trimodal processing</i> (odor-sound-video + control > odor-sound + video) \cap (odor-sound-video + control > odor-video + sound) \cap (odor-sound-video + control > sound-video + odor)						
Inferior parietal cortex/Intraparietal sulcus (BA 40)	L	88	4.79	-54	-37	46
Inferior parietal cortex/Intraparietal sulcus (BA 40)	R	43	3.88	60	-31	49
Inferior frontal gyrus (BA 44,45)	L	31	4.92	-48	17	-2
<i>Super-additive processing independent of the number and type of stimulated channels</i> (odor-sound + control > odor + sound) \cap (odor-video + control > odor + video) \cap (sound-video + control > sound + video) \cap (odor-sound-video + control > odor-sound + video) \cap (odor-sound-video + control > odor-video + sound) \cap (odor-sound-video + control > sound-video + odor)						
Inferior parietal cortex/Intraparietal sulcus (BA 40)	L	24	3.75	-54	-40	46
Inferior frontal gyrus (BA 44, 45)	L	11	4.3	-48	20	1

5.3 STUDY III: DECODING AN OBJECT'S SMELL FROM ACTIVITY IN VISUAL REGIONS

In Study I and II we could show that the perception of an olfactory object in a multisensory setting appears to involve a network of early sensory as well higher-order cortical regions. Other previous studies have further shown that even in a unisensory setting, olfactory object processing is not exclusively accomplished by regions within the olfactory system but instead engages a more widespread network of brain regions. Regions belonging to the visual system, for example, have been repeatedly shown to be involved in higher-order olfactory tasks such as olfactory object identification or judging whether an odor represents an eatable or uneatable object (Qureshy et al., 2000; Royet et al., 1999). It could further be demonstrated that visual areas are functionally involved in the processing of an object's odor (Jadavji et al., 2012). We therefore aimed in **Study III** to assess what the engagement of visual areas in olfactory object perception represents. That is, whether areas of the brain that are principally concerned with processing visual object information also hold neural representations of olfactory object information, and if so, whether these representations are similar for odors and pictures of the same underlying object.

5.3.1 Visual and Olfactory Object Perception Activates Areas Within the Ventral Visual Object Pathway

We first assessed whether we could replicate previous findings showing activation of visual regions during olfactory object perception. To determine which brain regions were generally recruited during recognition of olfactory objects in **Study III**, we conducted a univariate analysis of the collected fMRI data. In line with previous studies, we found activation in areas of the ventral visual object pathway, such as superior, middle, and inferior occipital gyri, as well as various other brain regions (Figure 10). As a control, we also assessed which brain regions were activated during visual object recognition. As expected, this task engaged, among others, primary and higher-order visual areas (Figure 10). Overlapping activation for olfactory and visual object recognition was found in several brain regions, including calcarine, superior, middle, and inferior occipital gyri (Figure 10).

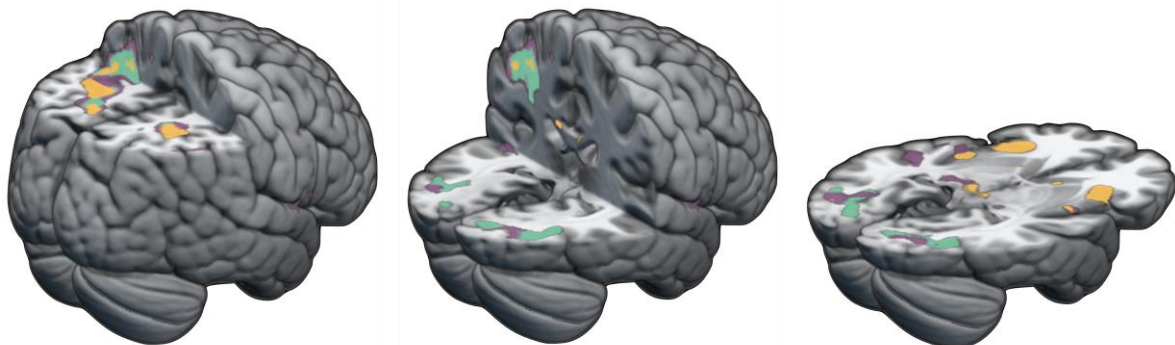


Figure 10. Results of the whole-brain univariate analysis in Study III. Group results for the main effects of odor (yellow) and picture (green) were voxel-level corrected for multiple comparison (FWE $p < .05$, $k > 10$). The results of the conjunction analysis (purple) were cluster-level corrected for multiple-comparisons at an FWE rate of $p < .05$.

5.3.2 Olfactory Objects Can Be Decoded From Multi-Voxel Activation Patterns in V1 and LOC

Having determined that olfactory object recognition activated regions within the visual system, we subsequently assessed whether this odor-induced activation represents a mere diffuse or actual object-specific pattern of activation. Object-specific activation patterns would allow us to successfully decode an object's identity from the odor-induced visual activation. Using an SVM based classification analyses, olfactory objects could be successfully classified in both V1 and LOC. As a control, we assessed whether the classifier could also discriminate the four pictures of objects. As expected, classification was successful in both V1 (group average decoding accuracy = 62.44 %, empirical chance level = 25.02%, $p_e = 10 \times 10^{-6}$, p -value [p_e] corrected for total number of possible permutations) and LOC (group average decoding accuracy = 54.36 %, empirical chance level = 25.07%, $p_e = 10 \times 10^{-6}$) (Figure 11).

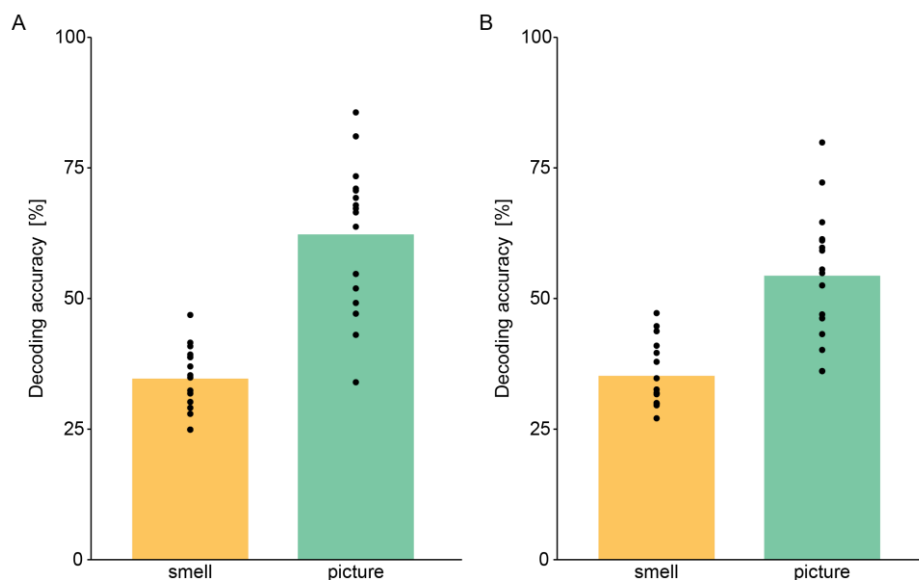


Figure 11. Decoding performance for classification of odors and pictures in Study III. Bars show the mean accuracy across participants with which smelled or viewed objects could be decoded from activation patterns in (A) V1 and (B) LOC. Points indicate individual decoding accuracy values. Empirical chance level at 25.02% for V1 and 25.07% for LOC.

5.3.3 Decoding of Olfactory Objects in the Whole Brain

To examine whether also other brain regions than our predefined ROIs hold neural representations of olfactory objects, we expanded the classification analyses to the whole brain. Olfactory objects could successfully be decoded from regions along the ventral visual object pathway such as V1, V2, V3, V4, lateral occipital cortex, and fusiform gyrus. Significant decoding performance was also found in bilateral inferior parietal lobe, angular gyrus, insula lobe, pre- and postcentral gyri, rolandic operculum, as well as middle, superior and posterior-medial frontal gyri (Figure 12, Table 6). Additionally, above-chance classification was observed in left thalamus and left cerebellum, as well as right supramarginal gyrus. Visual

objects could be successfully decoded from V1, V2, V3, and V4 in both hemispheres as well as right fusiform and right hippocampus.

Table 6. Results of the whole-brain searchlight analysis in Study III. MNI-coordinates depict local maxima of significant above-chance decoding performance. Group results were cluster-level corrected for multiple-comparisons at a FWE rate of $p < .05$.

	Brain Region	Hemisphere	Size	t-value	x	y	z
Smells	Middle Occipital Gyrus	L	42140	8,503	-36	-93	0
	Superior Occipital Gyrus	L	42140	7,315	-19	-74	42
	Inferior Occipital Gyrus	L	42140	7,260	-32	-89	-10
	Inferior Occipital Gyrus	R	42140	6,595	30	-83	-12
	Cuneus	R	42140	6,570	14	-83	23
	Calcarine Gyrus	L	42140	6,470	-8	-97	0
	Superior Frontal Gyrus	L	16522	8,476	-17	38	42
	Middle Frontal Gyrus	L	16522	7,950	-28	35	42
	Superior Frontal Gyrus	R	16522	6,789	29	12	56
	Posterior-Medial Frontal	L	16522	5,363	1	20	58
	Posterior-Medial Frontal	R	16522	5,300	6	24	51
	Insula Lobe	R	7275	6,666	36	23	7
	Middle Frontal Gyrus	R	7275	4,992	49	50	8
	IFG (p. Triangularis)	R	7275	3,843	49	23	25
	IFG (p. Triangularis)	L	7001	5,642	-37	30	19
	IFG (p. Orbitalis)	L	7001	5,494	-49	40	1
	IFG (p. Opercularis)	L	4754	7,989	-56	2	23
	Rolandic Operculum	L	4754	6,719	-44	-8	7
	Insula Lobe	L	4754	6,220	-40	-11	-3
	Temporal Pole	L	4754	5,205	-44	8	-11
	Middle Temporal Gyrus	R	2780	6,267	49	-59	13
	Posterior Temporal Insula	R	2311	5,743	43	-17	-10
	Insula Lobe	R	2311	5,136	48	3	3
	Angular Gyrus	R	2310	5,456	52	-59	40
	Inferior Parietal Lobule	R	2310	5,110	40	-52	42
	Precentral Gyrus	R	1918	6,816	51	-9	39
	Postcentral Gyrus	R	1918	4,980	54	-12	32
	Postcentral Gyrus	R	1816	5,492	38	-20	32
	Rolandic Operculum	R	1596	4,986	53	-31	25
	SupraMarginal Gyrus	R	1596	4,846	56	-33	48
	Precentral Gyrus	R	1558	6,423	-49	-7	57
	Inferior Parietal Lobule	L	1558	4,567	-55	-25	44
Postcentral Gyrus	L	1558	5,830	-46	-21	39	
Precentral Gyrus	L	1558	6,420	-54	-7	51	
Posterior-Medial Frontal	R	1555	4,302	16	-27	55	
Thalamus	L	1442	7,054	-21	-27	-1	
Cerebellum (IV-V)	L	1442	4,241	-18	-44	-18	
Fusiform Gyrus	L	1442	4,150	-19	-41	-14	
Inferior Parietal Lobule	L	1288	6,092	-52	-49	47	
Angular Gyrus	L	1288	5,750	-44	-52	38	
Pictures	Middle Occipital Gyrus	R	135696	17,424	39	-79	1
	Inferior Occipital Gyrus	L	135696	15,920	-31	-90	-9
	Calcarine Gyrus	R	135696	15,727	18	-97	-4
	Middle Occipital Gyrus	L	135696	15,670	-35	-91	-1
	Fusiform Gyrus	R	135696	15,600	26	-80	-12
	Lingual Gyrus	R	135696	14,840	16	-88	-9
	Calcarine Gyrus	L	135696	13,700	-8	-89	-11
	Superior Occipital Gyrus	R	135696	13,670	27	-77	28
	Hippocampus	R	1389	6,425	30	-19	-13

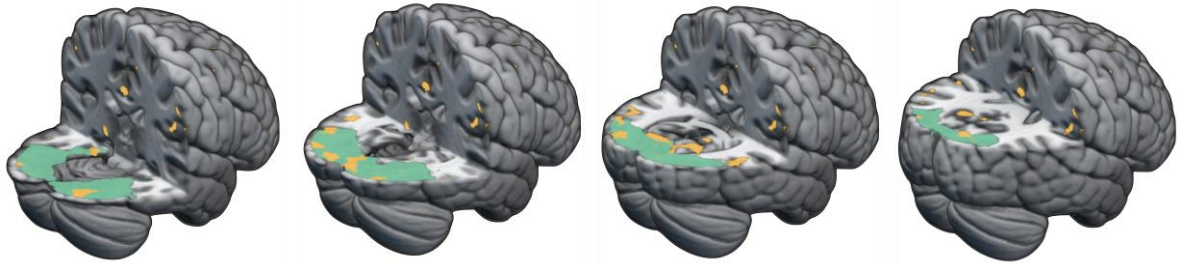


Figure 12. Results of the whole-brain searchlight analysis in Study III. Colored clusters indicate cortical regions where decoding of olfactory (yellow) and visual (green) objects was significantly above chance across participants. Group-level statistics are cluster-level corrected for multiple-comparisons at a FWE rate of $p < .05$.

5.3.4 Neural Representations for Olfactory and Visual Objects Differ in V1 and LOC

After having determined that ventral visual regions hold neural representations for not only pictures but also odors of objects, we examined the degree of similarity of these representations in V1 and LOC on the group level. For this purpose, we computed the correlation distance (1-similarity) between the neural response patterns for all odors and pictures of objects. The resulting distance measures are illustrated in a representational dissimilarity matrix for each ROI (RDM, Figure 13A). Visual inspection of the group RDMs and the spatial arrangement of the dissimilarities as revealed by multi-dimensional scaling (Figure 13B), suggests a high similarity between neural representations for odors of objects but no similarity between the odor and picture representations, in both V1 and LOC. If odors and pictures of objects would be represented in a similar manner, the neural representations of odors and pictures should be more similar to each other when they represent the same object (e.g., odor of banana and picture of banana) than when they represent different objects (e.g., odor of banana and picture of lemon). Using a non-parametric permutation approach, we tested statistically whether there would be a significant difference in similarity between activation patterns representing the same object and activation patterns representing different objects. We could not find any significant differences, neither in V1 ($p = .103$) nor in LOC ($p = .231$). We considered this result to confirm our previous observation that odors and pictures of objects are not represented in a similar way in visual regions.

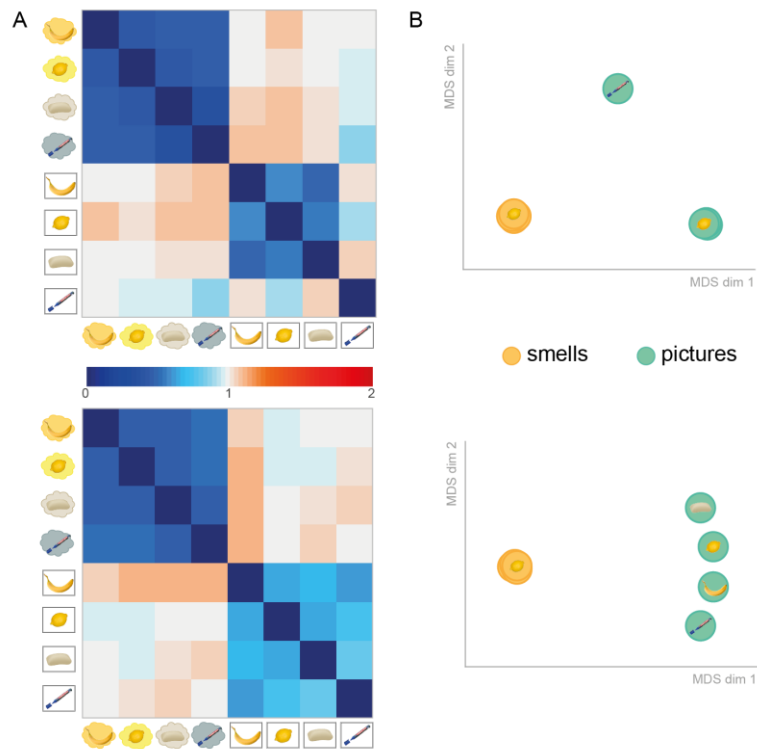


Figure 13. Representational dissimilarity structure obtained in Study III. **A)** Average RDM across participants in V1 (top row) and LOC (bottom row). Smaller values indicate lower dissimilarity (correlation distance: 0 = perfect correlation, 1 = no correlation, 2 = perfect anticorrelation). Entries on the diagonal reflect the dissimilarity of a given experimental condition with itself and are, therefore, equal to zero. **B)** Structure of the representational space in V1 (top row) and LOC (bottom row), revealed by non-metric multidimensional scaling. The distance between two points reflects the dissimilarity of the associated activation patterns.

6 DISCUSSION

The general aim of this thesis was to assess how our senses interact during olfactory object processing. More specifically, we sought to resolve three main questions. First, whether information about an object's odor and other sensory information related to that object converges and merges already at the level of primary olfactory cortex, and thereby enhances the processing of the olfactory object (**Study I**). Second, whether and which higher-order brain regions support the combination of object information from different senses (**Study II**). And third, whether the recruitment of the visual system during olfactory object perception reflects that olfactory object information is encoded in visual regions (**Study III**).

In **Study I**, we found evidence that assisting input from our senses of vision and hearing supports the processing of olfactory object information in the PPC, and that the more assisting input we receive the more the neural processing of the odor is boosted. In **Study II**, we found that multisensory object information also converges in the IPC, which likely serves the function of relating the different sensory information to each other. Finally, in **Study III**, we found that regions that are seemingly specialized at processing of visual object information also hold neural representations of olfactory object information, and that the representations of olfactory objects are distinct from the corresponding visual representations.

Overall, the studies included in this thesis add to recent findings demonstrating that the human brain is much more intertwined than it had been assumed in the past. Moreover, they demonstrate that the perception of an object's odor is not accomplished by the olfactory system alone, but in fact involves interaction of several sensory systems and processing in various brain regions.

6.1 FROM A SEGREGATED TO A MULTISENSORY BRAIN

For years it was assumed that the human brain is strictly segregated into different sensory systems, one system for each sense. Accordingly, olfactory information would be exclusively processed in areas belonging to the olfactory system while visual input would be only processed in visual regions. Moreover, it was believed that each sensory system in itself, but also the whole brain in general, would be hierarchically structured (Felleman & Van Essen, 1991). This means that primary sensory regions would process simple stimulus features while higher unisensory areas would process more complex features. At the same time, simple processes, such as processing of unisensory information, would occur before more complex processes, such as interaction and merging of the different unisensory streams. Convergence and integration of different sensory information was assumed to occur exclusively in higher-order brain regions that are not dedicated to one specific sense. Examples for such multisensory integration sites are STS, intra- and temporoparietal areas, as well as regions within prefrontal and premotor cortices (Barraclough et al., 2005; Driver & Noesselt, 2008; Ghazanfar & Schroeder, 2006; Macaluso & Driver, 2005; Molholm et al., 2006; Sugihara et al., 2006).

In the past two decades, a plethora of studies have contributed to turn this picture of a strictly segregated and strictly hierarchically organized brain upside down. It is now known that sensory signals are not processed in a strictly serial manner (Lamme & Roelfsema, 2000; Lamme et al., 1998; Sikkens et al., 2019; Sillito et al., 2006) and that interactions between senses can occur already at an early stage of perceptual processing, in originally assumed unisensory areas (Foxy & Schroeder, 2005; Giard & Peronnet, 1999; Schroeder & Foxy, 2005). The growing pool of evidence that also unisensory regions possess multisensory properties has led to the notion that multisensory interactions are an integral part of all stages of perceptual processing (primary as well as higher-order), and that in real life, our senses never operate in isolation (Ghazanfar & Schroeder, 2006). However, many studies on multisensory integration have primarily used simplified artificial bimodal stimulus combinations, such as beeps and flashes, that do not resemble stimulus combinations encountered in our natural environment. It is therefore debatable whether we can extrapolate from the processing and integration of simplified laboratory stimuli to multisensory integration of naturalistic stimuli. Moreover, the field of multisensory processing remains to this day heavily dominated by studies on visual-auditory integration, from which general principles of multisensory perception are extrapolated. As each of our senses possesses distinct characteristics and processing pathways, sensory processing in each modality constitutes a separate puzzle, and it is ill-advised to generalize principles of multisensory processing across senses without studying them specifically. To shed light on the multisensory characteristics of primary olfactory regions and investigate multisensory interactions in the whole brain during olfactory processing, we attempted to better emulate real-life object processing by using dynamic and meaningful visual, auditory, and olfactory stimuli either separately or in different combinations.

6.2 MULTISENSORY INTEGRATION IN THE PPC

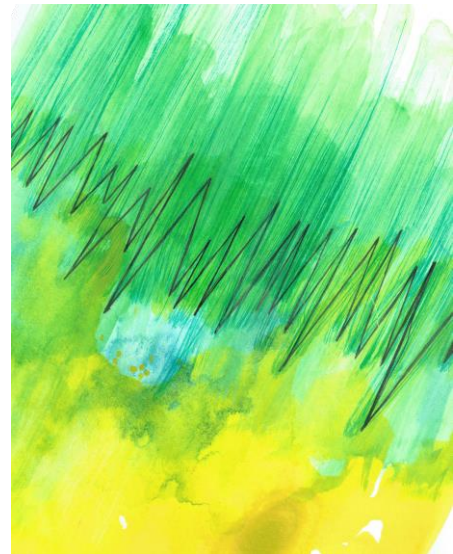
In **Study I**, we found evidence for multisensory responsiveness in terms of cross-modal activation and multisensory integration in terms of multisensory response enhancement in the PPC. This suggests that the PPC can be considered a primary olfactory region with multisensory properties.

In line with the notion that all brain regions receiving direct input from the olfactory bulb constitute the primary olfactory cortex (Gottfried, 2006, 2010; G. Zhou, Lane, Cooper, Kahnt, & Zelano, 2019), we have labeled the PPC as primary olfactory region. However, I am aware that it is still under debate whether it should be considered a primary or secondary processing area (D. M. Johnson, Illig, Behan, & Haberly, 2000; L. M. Kay, 2011). The definite classification of the PPC as a primary or secondary olfactory region does, however, not impact the following interpretation of the results and the conclusion I have drawn.

Despite previous findings showing cross-modal responsiveness of the PPC to images and sounds in absence of olfactory input (Gnaedinger et al., 2019; Gottfried & Dolan, 2003; Varga & Wesson, 2013; G. Zhou, Lane, Noto, et al., 2019), we only observed a significant PPC response to visual, but not auditory stimulation alone. A potential explanation for visually-induced activation of the PPC could be that even in absence of any olfactory stimulus, visual

object information is transmitted to the PPC to prepare it for potential incoming olfactory object information. The visual signal hereby serves as a prior of what might come (Klemen & Chambers, 2012; Talsma, 2015). The subsequent olfactory object information might then be processed more rapidly and easily (Talsma, 2015). The observed absence of activation in response to unisensory auditory stimulation could potentially be attributed to an inherently weaker association between sounds and odors of objects. That is, the PPC might only respond to visual and auditory object information if it is associated with an odor, and the strength of such an association might further modulate the amplitude of the response.

In addition to demonstrating that the PPC does not exclusively respond to olfactory but also to visual object information, we could also show that the PPC integrates object information from various senses. Multisensory integration manifested in a response enhancement for *multi-* compared to *unisensory* stimulation. More precisely, the PPC's response increased linearly with the number of senses that simultaneously received matching object information. If the PPC would process object information arising from different sensory modalities in parallel without actually integrating the information, it would not matter whether the information matches or not, activation would invariably increase with the number of input streams. Our results showed, however, that this increase was only present for input that carried information about the same object, but not for mismatching input. As such, the observed response enhancement cannot be attributed to a mere increase in sensory stimulation alone, but instead, very likely reflects actual integration of the multisensory object information.



6.3 IS THE NEURAL RESPONSE IN THE PPC DIRECTLY LINKED TO BEHAVIOR?

The observed multisensory enhancement effects in the PPC indicate that the neural response to a smelled object increases when more information about the object is available. In line with previous studies showing a link between increased activity in unisensory regions during multisensory stimulation and improved perception (Calvert et al., 1999), we speculate that the observed increased neural response leads to improved identification of the smelled object. However, the lack of a behavioral measure of object recognition performance in **Study I** does not allow us to *directly* link increased neural activity in the PPC to better object recognition. We refrained from employing an object identification task because it creates the risk that participants employ a strategy to exclusively focus on the sense that provides the most reliable object information. Such focused attention and exclusive reliance on one sense would lead to a skewed performance measure. As our visual stimuli consisted of videos of clearly recognizable objects, objects were easily identifiable based on the visual input alone and no additional sensory input was necessary. Therefore, no gain from multisensory integration was

expected, meaning that any multisensory condition including visual stimulation would result in the same identification proficiency as the video only condition. This means, identification performance would be biased by the visual input and a potential benefit of multisensory stimulation on olfactory object identification (which has repeatedly been shown to exist) would be masked. Not only the behavioral effects of multisensory integration would be concealed by an object identification task, but also neural integration effects could be masked by focused attention on the visual sense. Multisensory integration processes have been shown to be strongly modulated by attention (Talsma, Senkowski, Soto-Faraco, & Woldorff, 2010), with integration effects occurring only when all senses are attended (Talsma, Doty, & Woldorff, 2007). To ensure that we would be able to detect multisensory integration effects on the neural level, we decided to employ a task that required participants to spread their attention equally across the stimulated senses. Based on the profound evidence that multisensory stimulation improves the perception of an object's odor on the behavioral level, we assume that our findings represent the underlying neural mechanism. We, therefore, speculate that improved olfactory object perception is mediated by enhanced processing of the olfactory object information in the PPC.

6.4 DOES THE PPC POSSESS MULTISENSORY OBJECT REPRESENTATIONS?

While **Study I** provided important insights into the multisensory properties of the PPC by showing that the presence of congruent multisensory information enhances activation, it remains unknown what this enhancement reflects. Cross-modal activation and multisensory enhancement of neural responses in specific cortical areas have often been taken as evidence for a multisensory nature of representations in these regions (Amedi et al., 2001; Amir Amedi, Jacobson, Hendler, Malach, & Zohary, 2002; Naumer et al., 2010). However, this general inference is controversial. It does not necessarily need to be a multisensory representation mediating the multisensory enhancement effect. An alternative underlying mechanism could be that multisensory stimulation leads to activation of co-existing object representations—one for each modality—and that the sum of parallel activations causes the enhancement effect (Figure 14A). Such parallel activation of several representations can, however, not explain the multisensory enhancement effect that we observed in **Study I**. If the PPC possessed a separate object representation for each sensory modality, multisensory stimulation would always lead to co-activation of those separate representations, independent of the signals' congruency. That is, it would be immaterial if all sensory input streams carried information about the same object or whether each input stream carried information about a different object, the sensory-specific representations would always be activated in parallel. As the observed increase in activation was, however, dependent on the congruency of the signals, co-existing object representations are unlikely to constitute the underlying mechanism. The more parsimonious explanation is that olfactory cortex also possesses multisensory object representations, as previously demonstrated in the visual domain (Erdogan et al., 2016). Such a multisensory object representation could exist either in parallel to the unisensory olfactory object representation (Figure 14B) or overlap with the unisensory representation (Figure 14C).

In the former case, the increased activation during multisensory stimulation could be explained by activation of co-existing representations (unisensory olfactory plus multisensory). In the latter case, multisensory stimulation would fine-tune the object representation, thereby leading to an increased neural response as observed in **Study I**.

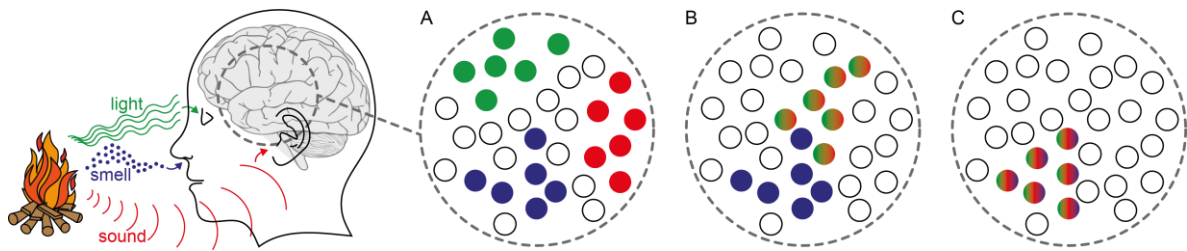


Figure 14. Various forms of object representations can explain the observed multisensory response enhancement in the PPC. A) Smelling, hearing and seeing the object fire leads to activation of A) co-existing sensory specific representations, **B)** a multisensory representation, existing in parallel to the unisensory olfactory representation, **C)** a multisensory representation that represents a fine-tuned version of the unisensory olfactory representation.

For now, we are unable to determine which of those mechanisms applies to the PPC. Previous studies investigating the neural representations underlying multisensory responses have often relied on measures of fMRI adaptation (Gottfried et al., 2006; Grill-Spector, Henson, & Martin, 2006; Grill-Spector & Malach, 2001; Hasson, Skipper, Nusbaum, & Small, 2007; Tal & Amedi, 2009) or MVPA (Haxby et al., 2001). The idea of fMRI adaptation is that activation decreases when the same neural population is repeatedly stimulated because the neuronal firing rate adapts, but no decrease in activation occurs if distinct neural populations are targeted. In our case, this would mean that if there are distinct modality-specific representations, the measured activation should not be reduced when an object is presented first as an odor and subsequently as a video or sound because separate representations are stimulated. In contrast, if there is only one shared representation, one should observe reduced activation since the same neural representation is targeted twice in a row. However, whether one can infer the type of neural representations from adaptation effects is a debated issue, because the effects could be confounded by differences in low-level stimulus properties or attentional differences (Epstein & Morgan, 2012; Mur, Ruff, Bodurka, Bandettini, & Kriegeskorte, 2010). For example, the PPC response to the repeated presentation of an object's odor could decrease because adaptation to the repeated exposure of the same chemical molecules has already occurred at earlier stages of the olfactory processing hierarchy, such as olfactory receptor neurons in the olfactory epithelium (Pellegrino, Sinding, de Wijk, & Hummel, 2017) or neurons in the APC (Wilson, 1998). A decrease in activation for the alternating presentation of an object's odor and the corresponding video or sound could also be explained by a general attenuated response to videos and sounds compared to odors, as observed in **Study I**. Moreover, a "release from adaptation" for the presentation of an object's odor followed by the corresponding video or sound could simply occur because a change in the modality of stimulation might capture increased attention and thereby lead to an enhanced response. A more appropriate measure for overlapping neural representations might therefore be representational similarity analysis

(Kriegeskorte et al., 2008), which assesses how representations differ from each other by examining the similarity between activation patterns. The logic of this approach is that measurements of high pattern similarity indicate overlapping representations, while low similarity values indicate dissimilar representations. Hence, if distinct object representations would exist for each modality (Figure 14A), the activation patterns would be dissimilar between senses. Separate representations for unisensory olfactory objects but overlapping representations for other sensory objects (Figure 14B) would result in low similarity values for unisensory olfactory versus other sensory stimulation, but high similarity values for visual and auditory stimulation. On the other hand, a shared multisensory object representation (Figure 14C) would be manifested by similar activation patterns across senses and number of stimulated sensory modalities. As we used representational similarity analyses in **Study III** to investigate how odors and pictures of objects are represented in the visual system, one might ask why we did not expand the analyses to the PPC and investigated whether it holds overlapping neural representations for odors and pictures of objects. Unfortunately, the data collected in **Study III** suffered from BOLD signal loss in olfactory and neighboring brain regions (a common problem in studies involving breathing (Weiskopf, Hutton, Josephs, Turner, & Deichmann, 2007) and did not allow us to disentangle the nature of neural object representation in the PPC. Further research is therefore needed to shed light on which of the above-described scenarios applies to object representations in the PPC.

6.5 EARLY MULTISENSORY OBJECT INTEGRATION—A UNIQUE FEATURE OF THE PPC?

While we were primarily interested in revealing the multisensory characteristics of the PPC, we also compared the PPC's response pattern to response patterns in the APC, a brain region that encodes the chemical identity of an odor and is assumed to directly precede the PPC in the olfactory processing hierarchy. We found evidence for multisensory integration even in the APC. That is, both the PPC and APC exhibited an increase in activation for an increasing number of stimulated senses. This multisensory enhancement effect was, however, much less pronounced in the APC. The observation that also the APC's response is modulated by multisensory stimulation could either indicate that even earlier olfactory regions possess multisensory properties or that the PPC's multisensory response is down-propagated to the APC. Future studies investigating temporal aspects of these multisensory effects could bring some clarity on this question.

To determine whether the observed multisensory response patterns are exclusive to olfactory regions or whether also primary and secondary regions of the visual and auditory systems respond to cross-modal input and integrate multisensory object information, we assessed activation in visual and auditory regions that are assumed to correspond to the functionalities of the PPC and the APC. While all visual and auditory regions exhibited some cross-modal responsiveness, none of them demonstrated signs of an enhanced response to multisensory stimulation. This could potentially be due to the effectiveness of the visual and auditory object signals, meaning that the unisensory signals themselves carry clear enough object information

so that multisensory stimulation does not provide any gain. However, it is possible that also visual and auditory regions exhibited weaker integration effects but that we missed to detect them with the employed analyses.

6.6 MULTISENSORY OBJECT PROCESSING FROM THE WHOLE-BRAIN PERSPECTIVE

Study II expanded our search for integration effects during multisensory object perception to the whole brain. We were especially interested in identifying brain areas that integrate multisensory information independently of the type and number of senses providing information. We found that neural activity in the left inferior frontal gyrus, left inferior parietal cortex, and adjacent intraparietal sulcus increased in a super-additive manner from unimodal to bimodal, and from bimodal to trimodal stimulation. That is, the response to a combination of an object's odor and sound, for example, was bigger than the sum of activations for the odor only and the sound only conditions. Further, the trimodal combination of an object's odor, sound and video evoked an even higher response amplitude than the bimodal combination of odor and sound. This increase in activation was independent of the specific combination of sensory modalities.

These findings are in line with the previous literature, which frequently reports engagement of inferior frontal and inferior parietal areas during multisensory integration. We expand on this work by demonstrating that their engagement appears to be modality-independent and that activation increases non-linearly (super-additively) with an increasing number of stimulated senses. Earlier studies have associated the left IFG with conflict detection and predictive processes, meaning that it accumulates evidence about the incoming multisensory input to guide decision making (d'Acremont, Fornari, & Bossaerts, 2013; Iglesias et al., 2013; Morís Fernández, Macaluso, & Soto-Faraco, 2017; Noppeney, Ostwald, & Werner, 2010; Paraskevopoulos, Chalas, Kartsidis, Wollbrink, & Bamidis, 2018). The IFG has further been linked to learning of multisensory associations as well as processes linking multisensory object representations to concepts in semantic memory (A Amedi, von Kriegstein, van Atteveldt, Beauchamp, & Naumer, 2005; Hein et al., 2007; Y. Li, Seger, Chen, & Mo, 2020). While also the IPC and IPS have repeatedly been shown to be involved in multisensory integration, their exact role has remained understudied (Bremmer et al., 2001; Calvert, Campbell, & Brammer, 2000; Driver & Noesselt, 2008; Grefkes & Fink, 2005; Hein et al., 2007; Macaluso & Driver, 2001; Molholm et al., 2006; Senkowski, Saint-Amour, Kelly, & Foxe, 2007). In general, the IPS is involved in guiding attention in a top-down manner (Corbetta, Patel, & Shulman, 2008; Szczepanski, Pinsk, Douglas, Kastner, & Saalmann, 2013; Tang, Wu, & Shen, 2016). It is, for example, functionally involved in grouping individual components, such as moving dots, into one holistic percept, such as a moving square, by directing attention to global instead of local aspects of a stimulus (Zaretskaya, Anstis, & Bartels, 2013). This function is crucial for our everyday life, as it enables us to relate and bind individual elements and thereby “allows us to perceive scenes and objects as a whole rather than as a meaningless collection of individual features” (Zaretskaya et al., 2013). As the process of relating and binding components is

fundamental to multisensory integration, and attention strongly modulates multisensory integration processes (Talsma et al., 2007, 2010), the IPS appears to play an important role in the integration of multisensory input. It has been suggested that its specific role is to allocate additional attentional resources when the integration task is more demanding (Regenbogen et al., 2018). A similar functional role has been proposed for the IPC (Kassuba et al., 2011; Senkowski et al., 2007). Thus, it appears that the proposed function of IPS and IPC are overlapping. This is likely due to their anatomical adjacency and sometimes even inseparability. The integration effects we observed in **Study II**, for example, could neither be exclusively attributed to the IPC nor the IPS but instead formed a cluster covering parts of both regions. I will, therefore, group the IPC and IPS for simplicity and subsequently refer to them as IPC.

6.7 WHAT IS THE IPC'S ROLE IN INTEGRATING MULTISENSORY OBJECT INFORMATION?

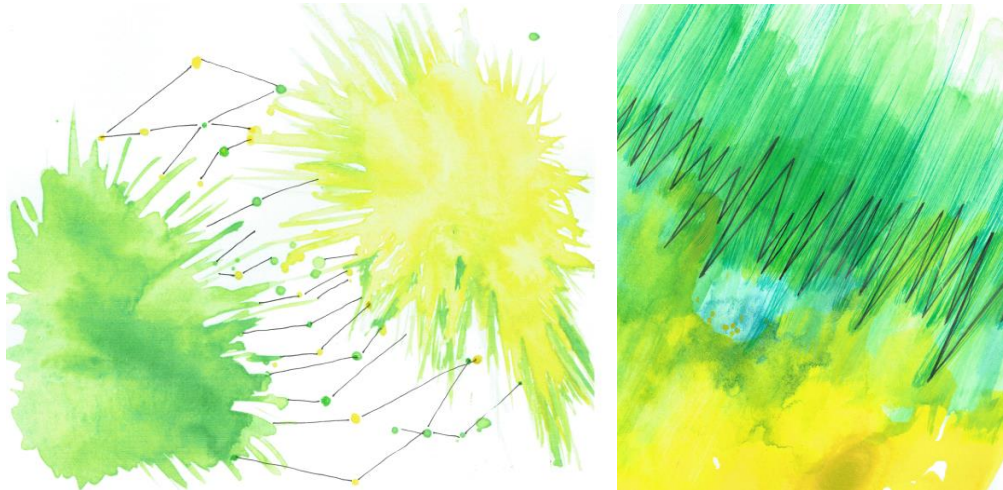


Our results that activation in the IPC increased when the number of to-be-integrated senses increased, is in line with the previously observed engagement of IPC in relating different inputs and its proposed function of allocating attentional resources. We assume that relating an increasing number of input streams constitutes a more demanding task for the IPC and therefore requires more attentional resources, which would be reflected in an increased neural

response. This assumption is consistent with findings of an increased IPC response for processing of trimodal compared to bimodal object stimuli (Kassuba et al., 2011), as well as higher IPC engagement during processing of artificial audiovisual stimuli than of naturalistic audiovisual stimuli (Hein et al., 2007; Senkowski et al., 2007). Differential IPC recruitment for artificial and naturalistic stimuli is thought to be due to differences in inherent relatedness of the auditory and visual signals. That is, while an intrinsic meaningful relation exists between the individual sensory components of a naturalistic multisensory stimulus, the sensory components of an artificial multisensory stimulus are not naturally related. Hence, processing an artificial multisensory stimulus might entail an extended search for relatedness, which manifests in increased IPC recruitment. This process of relating different sensory input streams should be independent of the congruency of the sensory components, but only determined by the number of input streams. That is, the IPC would match the incoming inputs against each other independently of whether they match in their meaning or not. The more signals it must match, the more demanding the task. As a consequence, activation would increase with the number of input streams, even if they are incongruent. This hypothesis is partly confirmed by an exploratory analysis where we tested whether the IPC exhibits super-additive activity also

for incongruent multisensory stimulation. We found that the IPC responds in a super-additive manner to trimodal stimulation and shows a tendency for super-additive activation for bimodal stimulation even if each sense carries information about a different object. Taken together, our results are in line with previous findings that activation in the IPC increases with attentional load and that the IPC plays an important role in relating and binding sensory components.

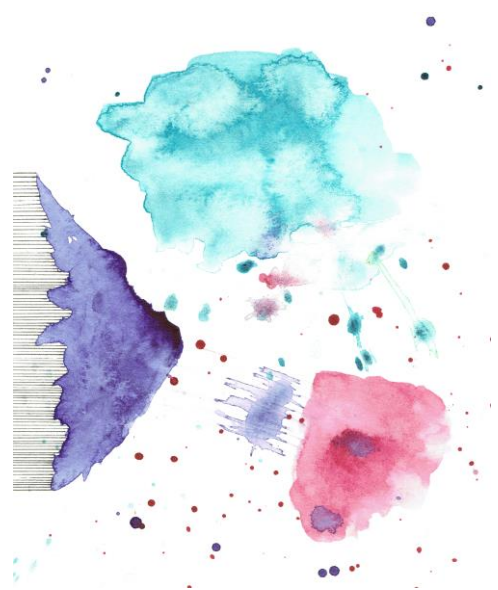
6.8 LINKING FINDINGS FROM STUDY I AND STUDY II



In **Study II**, I demonstrate that the IPC is involved in multisensory object processing and that its function of relating incoming signals is not sensitive to their congruency. In **Study I**, I demonstrate that the PPC integrates multisensory object signals only if they carry information about the same object. Based on these results, I speculate that the IPC propagates the result of the matching procedure down to the PPC where the signals are integrated only if they are congruent. Accordingly, the perception of an olfactory object in a multisensory setting appears to involve a network of early sensory as well higher-order cortical regions.

6.9 OLFACTORY OBJECT PROCESSING IN VISUAL CORTEX

A growing body of research indicates that olfactory object processing is not exclusively accomplished by regions within the olfactory system but rather engages a more widespread network of brain regions. For example, earlier studies showed that higher-order olfactory tasks such as object identification, odor quality discrimination, or edibility judgments activate prefrontal regions and parts of the cingulate gyrus as well as the insular cortex and the cerebellum (Qureshy et al., 2000; Royet et al., 1999; Savic, Gulyas, Larsson, & Roland, 2000). In addition, recruitment of primary as well as higher-order visual areas has been observed during naming and edibility judgement of odors (Qureshy et al., 2000; Royet et al., 1999). It has further been demonstrated that such



odor-induced activations in visual areas reflect a functional engagement of the visual system in the processing of an object's odor: olfactory object discrimination improves when the neural processing of the primary visual cortex is artificially increased (Jadaji et al., 2012).

Study III shows that visual regions are not merely active during perception of an olfactory object, but that they encode information about an object's odor. That is, when smelling an object and trying to identify it based on the odor alone, areas within the ventral visual object pathway process the olfactory object information and represent it in form of distinct neural activation patterns. While previous studies have shown that the LOC, a key region for visual object recognition, does not only hold representations of visual but also tactile and auditory objects (Erdogan et al., 2016; Man et al., 2015; Murray, Thelen, et al., 2016; Pietrini et al., 2004; Snow et al., 2014; Vetter et al., 2014), we are the first to show that this also applies to olfactory objects. Furthermore, we demonstrate that not only the LOC but all regions along the ventral visual object pathway, from V1 to LOC, encode olfactory object information.

6.10 WHY IS THE VISUAL SYSTEM RECRUITED DURING OLFACTORY OBJECT RECOGNITION?

We speculate that the reason for recruitment of the visual object pathway during non-visual object perception lies in the sophisticated object recognition properties of the visual system. Its advanced recognition properties allow us to instantaneously recognize an object in our environment when seeing it. Imagine seeing a lawn mower, for example. Just by looking at it you will be instantly able to correctly name the object you see. Now imagine hearing it instead. Will you be able to correctly identify it as a lawn mower when only hearing the sound of it? Probably not, because the sound can be easily confused with the sound of a scooter, a leaf blower, or a woodchipper. The same holds true for olfactory objects. Our ability to recognize an object based on its odor alone is rather poor: we are, on average, only able to correctly identify a mere third of presented, common odors and usually misidentify even such a familiar odor as banana (Desor & Beauchamp, 1974; Engen & Ross, 1973). Therefore, it appears beneficial to cross-modally recruit a system that is highly suited and specialized for object recognition if the sense through which we perceive the object is poorly suited. Moreover, sharing the task of recognizing the perceived object across sensory modalities, instead of overwhelming one sense with it, potentially reduces the computational demands and allows the brain to work more efficiently (Vasconcelos et al., 2011).

6.11 A POTENTIAL FEEDBACK PATHWAY FROM V1 TO PPC

The findings of **Study III** that smelling an object leads to object-characteristic activation of areas along the ventral visual object pathway suggest that olfactory object information is processed in a similar manner and along the same pathway as a visual object. Although we cannot resolve why this cross-modal processing occurs, we speculate that the engagement of visual areas during perception of an olfactory object has the purpose of facilitating processing and perception of the perceived odor. This is supported by the finding that upregulation of the primary visual cortex improves odor object discrimination (Jadaji et al., 2012). We speculate

that this improvement is established by transferring the olfactory object signal that has been processed along the ventral visual object pathway (Kravitz et al., 2013) back to the PPC. This hypothesis of a back projection to the PPC is based on the findings of **Study I** that visual input activates the PPC and can enhance processing of an olfactory object, as well as on other studies showing a direct information exchange between visual and olfactory regions during olfactory-visual object integration (Lundström, Regenbogen, Ohla, & Seubert, 2018; Porada, Regenbogen, Seubert, Freiherr, & Lundström, 2019).

Regions along the ventral visual pathway are specialized for processing visual objects (Kravitz et al., 2013). As one moves along the ventral stream from posterior to anterior regions, the representations of object features increase in complexity. Two key areas for visual object recognition within the ventral stream are the LOC and the perirhinal cortex (PRh). The LOC encompasses a region in the lateral occipital cortex extending into the posterior fusiform gyrus, and is thought to represent the shape of objects (Grill-Spector et al., 2001). The PRh constitutes the anterior tip of the ventral visual pathway, and carries the most complex representation that is necessary for fine-grained object discrimination (Barense et al., 2012; Buffalo et al., 1999; Buffalo, Ramus, Squire, & Zola, 2000; Bussey, Saksida, & Murray, 2002; Gaffan & Murray, 1992). The results of **Study III** indicate that olfactory object information is encoded in all regions along the stream from V1 to LOC.

Although we did not find any evidence for olfactory object representations in the PRh in our whole-brain searchlight analysis, I speculate that the odor-induced object signal is transferred from the LOC to the PRh and the absence of object-specific activation in the PRh is caused by signal loss in areas close to the olfactory cortex. I further speculate that as object information has reached the PRh—the anterior tip of the ventral stream—it is projected to the entorhinal cortex (Insausti, Amaral, & Cowan, 1987; Suzuki & Amaral, 1994), which can be considered a relay station between visual and olfactory areas. On the one hand, it receives major input from visual areas through the PRh (Garcia & Buffalo, 2020; Insausti et al., 1987; Suzuki & Amaral, 1994), and on the other hand, it modulates the piriform cortex in a top-down manner and thereby plays a key role in fine odor discrimination (Chapuis et al., 2013). This pathway remains, however, a speculation as it is impossible to infer any functional connectivity between olfactory and visual areas from our results.

6.12 OLFACTORY OBJECT PROCESSING ALONG THE VENTRAL VISUAL STREAM—IS IT JUST VISUAL IMAGERY?

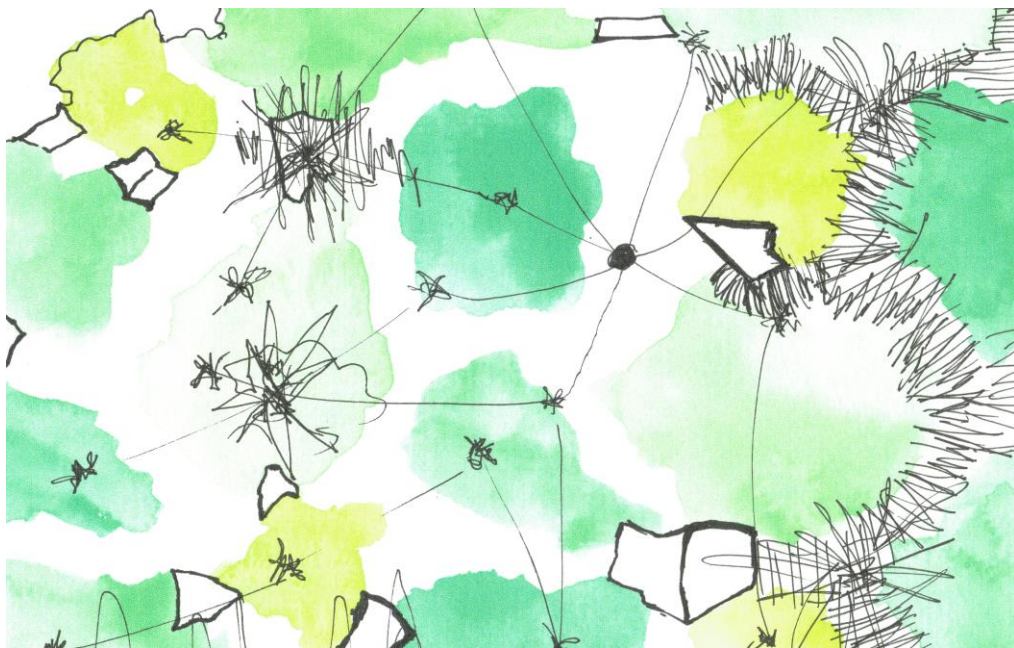
While activation in visual regions during olfactory object processing has often been attributed to visual imagery of the smelled object, direct evidence has not yet been provided (Jadavji et al., 2012; Qureshy et al., 2000; Royet et al., 1999). According to the visual imagery theory, it is not the olfactory object information itself, but a mental image of the perceived odor that is represented in visual areas. That is, perceiving the odor of lemon, for example, would trigger the formation of a visual mental image of a lemon. This mental image would be represented in the visual system in a similar activation pattern as a real image of the lemon, and thereby allow successful decoding of which object was smelled. Since participants in **Study III** were neither

instructed to mentally visualize the perceived odor, nor to explicitly refrain from mental visualization, we cannot disentangle whether it is the odor itself or a mental image that led to object-specific activation in visual areas. However, if participants in our study employed visual imagery to identify the perceived odor without being instructed to do so, it can be considered an automatically triggered mechanism. Such automatically induced visual imagery could either be directly triggered by olfactory stimulation or generated in a top-down manner (Spence & Deroy, 2013). The hypothesis of a top-down generated visual image appears to be supported by our finding that also frontal and parietal regions, which are usually recruited during visual imagery and multisensory integration (Amir Amedi, Malach, & Pascual-Leone, 2005; Ishai, Ungerleider, & Haxby, 2000; Lacey, Flueckiger, Stilla, Lava, & Sathian, 2010), were engaged during olfactory object recognition. The observed activation in frontal and parietal regions potentially indicates that the perception of an object's odor did not directly trigger a mental image of the smelled object, but that the identified higher-order regions mediated the generation of a mental visual image. Regardless of whether mental imagery would be induced in bottom-up or top-down manner, the mental image of an object would always be similar to seeing the same object in real life. Hence, the same neural representation should be evoked by visual imagery and actual visual perception. However, the results from the pattern similarity analysis in **Study III** indicate that the neural representations for odors and pictures of objects in V1 and LOC are not similar. This finding thus contradicts the hypothesis that perceiving an object's odor evokes visual imagery and thereby leads to activation of a visual representation of the smelled object. Instead, our results suggest that odors and pictures of objects are represented by distinct, modality-specific neural activation patterns, suggesting that it is indeed an object's odor that is represented in the visual system.

6.13 DOES OLFACTORY OBJECT INFORMATION TAKE A BOTTOM-UP OR TOP-DOWN ROUTE WHEN PROPAGATING TO THE VISUAL SYSTEM?

Based on the results from the representational similarity analysis that odors and pictures of objects are represented in terms of separate modality-specific neural response patterns, we speculate that olfactory object information is transferred to the visual cortex, where it evokes object-specific activation. This information transfer might either be established by an early interaction between the olfactory and visual sense or mediated by higher-order multisensory regions. Support for the hypothesis of an early and direct interaction is provided by previous studies showing that ipsilateral processing of odors and pictures facilitates their integration (W. Zhou, Zhang, Chen, Wang, & Chen, 2012) and that the presentation of an odor can modulate the perception of a visual stimulus, even in absence of awareness of the odor or the visual stimulus (Kuang & Zhang, 2014; Seigneureic, Durand, Jiang, Baudouin, & Schaal, 2010; W. Zhou, Jiang, He, & Chen, 2010). The alternative hypothesis of a top-down mediated information transfer, in contrast, is supported by previous findings that higher-order multisensory regions feed down information to unisensory cortices, possibly to provide them with a prediction of a potential incoming stimulus (Klemen & Chambers, 2012; Naumer et al., 2011; Talsma, 2015; Vetter et al., 2014). Moreover, our finding that smelling an object evoked object-specific activation in frontal and parietal regions appears to further support this

hypothesis. In line with our results that olfactory object perception evokes object-specific activation in visual and multisensory regions, also the perception of an auditory object leads to an object-specific response in early visual areas, such as V1, V2, V3, and in multisensory integration sites, such as superior temporal sulcus as well as medial and superior frontal regions (Vetter et al., 2014). Given these findings, it appears plausible to assume that olfactory object information is transferred from the PPC via multisensory regions to the visual cortex. However, whether it was indeed a pathway via multisensory regions or a direct route that established the information transfer cannot be determined based on the present data. To resolve this question, future studies are needed that investigate the functional connectivity and direction of information flow between the detected brain regions.



Taken the results of all three studies together, we show that olfactory object perception, whether in a uni- or multisensory setting, engages a widespread network of brain regions. This indicates that the human brain is much more intertwined than it had previously been assumed and that the perception of an object's odor is not accomplished by the olfactory system alone, but in fact involves interaction of several sensory systems and processing in various brain regions. We can thus conclude that olfactory object perception and the human brain are both multisensory in nature.

7 CONCLUSIONS

The general aim of this thesis was to explore how our senses interact during olfactory object processing. More specifically, the included studies aimed to answer the following questions:

1. Does assisting input from our sense of vision or hearing enhance processing of olfactory object information in brain regions that are attributed to the sense of smell? And if yes, does the enhancement depend on the number of senses that provide information about the to-be-processed object?
2. Are there brain regions that process multisensory object information independent of from which senses the information arises and independent of the number of senses that provide object information?
3. Do areas of the ventral visual stream that are specialized to process visual object information also hold neural representations of olfactory object information? If yes, are these representations distinct for odors and pictures of objects?

Our results indicate that all questions can be answered in the affirmative. We demonstrated that assisting visual and auditory inputs increase the processing of olfactory object information in the PPC, and that the more assisting input we receive the more the processing is enhanced. As this enhancement occurs only for matching inputs, it likely reflects integration of multisensory object information. Furthermore, we found evidence that multisensory object information converges also in the IPC, where the different sensory information is probably related to each other. Lastly, we showed that regions of the ventral visual object stream are also engaged in recognition of an object's odor and represent olfactory object information in the form of distinct neural activation patterns. Our results further suggest that odors and pictures of objects are represented differently. Taken together, the studies included in this thesis revealed that olfactory object perception is a multisensory process that engages a widespread network of brain regions, even if we do not encounter ourselves in a multisensory setting but only perceive an object's odor.

8 POINTS OF PERSPECTIVE

The studies included in this thesis have provided us with insight into how our senses work together and influence each other when it comes to the processing of familiar objects. This influence seems to be highly dependent on the semantic congruency between sensory information. For instance, we have shown that multisensory stimulation only facilitates olfactory object processing if the content is semantically congruent. The semantic congruency between sensory information is something that is not innate but that we have learned throughout the course of our lifetime (Parise, 2016; Spence & Deroy, 2012). We have, for example, repeatedly experienced that a banana has a certain visual appearance and that it has a specific odor. Thereby, we have learned that these two sensory impressions are congruent and belong together. Knowing that these visual and olfactory signals belong together allows our brain to integrate them into a coherent percept of a banana.

Although congruency is such a fundamental component of multisensory integration, we still do not know how exactly correspondences between sensory information are established on a behavioral and neural level. Through interaction with the world we are living in, we are able to extract statistical information about co-occurrence and learn which events naturally correlate and which do not. For example, already early in life, we learn the correspondences between speech sounds and lip movements through mere exposure to the co-occurring events (Kuhl & Meltzoff, 1982). However, once such associations are learned, they are not rigid. Instead, they are highly plastic and can be modified through new experiences (Flanagan et al., 2008). We are also able to learn new associations between signals that we have learned are unrelated (Ernst, 2007). This plasticity demonstrates that our perceptual systems can adapt to the statistics of sensory input by interactively engaging with the environment. However, only a few studies exist that have used perceptual learning paradigms to investigate correspondences across modalities and how associations change during development and learning. Although one might think that this constitutes an interesting research question for the “multisensory community” only, multisensory interactions and thus also correspondences between senses play an essential role in the tasks the brain accomplishes all day long. Even the tasks that might not seem to involve other senses. The studies included in this thesis revealed that, even presumptive unisensory processes such as olfactory object perception are of multisensory nature and engage a widespread network of brain regions. Also including regions that are attributed to another sensory modality. This means that to truly understand sensory and developmental processes, as well as mental and developmental disorders that are associated to altered multisensory integration processes, and the disturbances and deficits related to these disorders, we need to always keep the multisensory nature of the brain in mind.

Thank you!

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