Psychological and physiological aspects of the olfactory and trigeminal systems in humans

A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Medical Sciences (Dr. rer. medic)

by

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October / November 2017
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This thesis is approved for recommendation to the TU Dresden Graduate Council

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List of Abbreviations

ERP	Event-related potential
cERP	Chemosensory event-related potential
fMRI	Functional Magnetic Resonance Imaging
CN	Cranial nerve
ORN	Olfactory receptor neuron
OR	Olfactory receptor
OB	Olfactory bulb
POC	Primary olfactory cortex
OFC	Orbital frontal cortex
IC	Insular cortex
URTI	Upper respiratory tract infection
CN I	Olfactory cranial nerve
CN V	Trigeminal cranial nerve
V1	Ophthalmic nerve
V2	Maxillary nerve
V3	Mandibular nerve
TDI	Summed score of Threshold, Discrimination, and Identification
CO_2	Carbon Dioxide
PEA	Phenyl ethyl alcohol
BOLD	Blood-oxygenation level detection
MRI	Magnetic resonance imaging
^1H	Hydrogen atom
EEG	Electroencephalogram
ATCS	Adaption time to the cessation of smell
EOG	Electro-olfactogram
oERP	Olfactory event-related potential
H_2S	Hydrogen sulfide
MCS	Multiple chemical sensitivity
ENT	Ear, nose and throat
ISI	Interstimulus interval
EPI	Echo planar imaging
ROI	Regions of interest
PET	Positron emission tomography
PHC	Parahippocampal gyrus
MNI	Montreal neurological institute
Anteior cingulate cortex	ACC
Medial cingulate cortex	MCC
Posterior cingulate cortex	PCC
AAL	Automated anatomical labeling

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Pellegrino, R., Hähner, A., Bojanowski, V., Hummel, C., Gerber, J., & Hummel, T. (2016). Olfactory function in patients with hyposmia compared to healthy subjects-An fMRI study. *Rhinology*, 54(4), 374.

Pellegrino, R., Sinding, C., de Wijk, R.A. and Hummel, T. (2017). Habituation and adaptation to odors in humans. *Physiology and Behavior*, In press.

Pellegrino, R. Drechsler, E., Hummel, C. and Hummel, T. (2017). Bimodal odor processing before and after perception of trigeminal component. *Neuroscience*, In press.

1. Introduction

1.1. Forward

The external environment is experienced internally through the five senses: sight, sound, taste, touch and smell. Losing or impairing either one of these senses impacts our perception of the world, giving us an altered reality that may affect our quality of life compared to those around us. Similarly, many objects externally perceived are built off the coprocessing of several senses through a process called multisensory integration. One such object is an odor object which is built from odorants. Odorants are chemical compounds that activate sensory cells (chemoreceptors) within the olfactory system, or additionally activate the trigeminal system (CN V) which are both located within the nose. The acknowledgement of an odor can tell an individual to approach or avoid an item or situation such as a new encounter with a person or food. Indeed, odors are crucially involved in behaviors essential for the survival of individuals, including identification of predators, recognition of individuals for procreation or social hierarchy, location of food, as well as attachment between mating and nurturing pairs. Similarly, odors are closely tied with memories and emotion, and the past experience of an odor can shape the perception of it. Anatomically, this is due to the unique route an odorant travels along the olfactory nerve to the brain where information is relayed directly to the limbic system (an area associated with memory and emotional processes) rather than through the thalamus like other sensory systems. Impairment of the olfactory system is not rare, occurring in almost a quarter of the population and an even higher rate in elderly. Olfactory impairment has varying degrees of severity, where partial loss is called hyposmia and the total loss of smell is called anosmia. In

this thesis, we explore several processes of odor perception in healthy and impaired individuals including habituation and the integration of two chemical senses.

1.2. The olfactory system (CN I)

1.2.1. Anatomy and physiology

An odorant may enter the nasal passage through direct orthonasal airflow through the nostril or retronasal flow from within the mouth through the nasopharynx. The nasal septum medially divides the nasal cavity into two nostrils (left and right) while the superior, middle and inferior turbinates laterally compartmentalize the interior (Figure 1.1). As an odorant enters a nostril, it travels to the olfactory cleft located at the insertion of the middle turbinate and olfactory receptors (OR) on the surface of mucus-surrounded cilia of olfactory receptors neurons (ORN) receive the odorant. ORNs are bipolar cells located in the neuroepithelium that contain only one type of odorant receptor with most receptors broadly tuned to a range of odorants and typically working in groups to detect molecular features of the odorant (Buck and Axel 1991; Lapid et al. 2011; Mori et al. 2006). In other words, an odorant is able to bind to a set of ORs, and humans have approximately 340-400 different functional olfactory receptor genes that code for ORs (Malnic, Godfrey, and Buck 2004; Tamura et al. 2008; Teixeira, Cerqueira, and Ferreira 2015). ORNs then synapse to spherical structures made of second order neurons (mitral and tufted cells) within the olfactory bulb (OB) (Mombaerts et al. 1996). The OBs are ovoid in shape and located in the anterior crandial fossa, above the cribriform plate of the ethmoid bone, under the frontal lobe. Once the OBs receive and organize ORNs signals, they project olfactory information down the olfactory tract to a wide number of brain regions within the frontal lobe and the dorsomedial surface of the temporal lobe (e.g. piriform cortex, rostral entorhinal cortex, periamygdaloid

cortex, anterior olfactory nucleus, olfactory tubercle), often referred to as primary olfactory cortex (POC). The POC then projects to higher processing areas such as the orbitofrontal cortex (OFC), the insular cortex (IC), thalamus, hippocampus and hypothalamus. Additionally, centrifugal input is provided to the OB from the olfactory cortex and higher brain structures to modulate the activity.

Figure 1.1. Anatomical depiction of important olfactory peripheral areas, including olfactory bulb (From Vokshoor 2013, http://img.medscapestatic.com/pi/meds/ckb/95/24495.jpg)

1.2.2. Olfactory dysfunction

Olfactory dysfunction is not uncommon due to the easy access of toxic chemicals to be carried by air across the epithelium and the fact that olfactory information relies on a single cranial nerve (CN I) whose first relay is the OB. Olfactory dysfunction may be classified as either quantitative, with impairment leading to reduced strength of an odor, or qualitative, relating to its identification or valence [see recent olfactory position paper for all dysfunctions (Hummel et al. 2017)]. In this thesis we will concentrate on the former, in which the severity of quantitative dysfunction can be broadly defined (but not limited) to two categories: 1) Hyposmia (partial loss), and 2) Anosmia (functional or total loss). Several population based studies have shown hyposmia to affect 15 to 24.5 % of individuals while anosmia affects 3.6 – 5.8% (Brämerson et al. 2004; Landis, Konnerth, and Hummel 2004; Vennemann, Hummel, and Berger 2008).

Olfactory dysfunction can further be defined according to the anatomical location of the lesion; however, this type of classification can be restrictive in which overlapping causes exist . For this reason, the underlying etiology has become common practice in describing the cause of

impairment (Hummel et al. 2017; Mullol et al. 2012). The most common cases of smell loss are post infectious [post-viral upper respiratory tract infection (URTI) (18 to 45% of the clinical population) and rhinosinusitis (7 to 56%)], followed by head trauma (8 to 20%), exposure to toxins or drugs (2 to 6%) and congenital loss (up to 4%) (Damm et al. 2004; Steven Nordin and Brämerson 2008). Additionally, olfactory function has been shown to deteriorate significantly with advancing age (Murphy et al. 2002; Nordin 2009; Seubert et al. 2017). For instance, data from the Honolulu-Asia Aging Study (HAAS) and Memory and Aging Project (MAP) reveal impairment to identify odors in 75% of men over 71 and 55.3 % in older individuals (mean age 80.6) (Ross et al. 2008; Wilson et al. 2006). The underlying factors involved in olfactory loss with age vary and may include para- and sympathetic deregulation, reduced mucosal blood flow, fibrosis of cribriform plate, inefficient ORN regeneration, and accumulation of damage from other etiologies over a lifespan (Loo et al. 1996). Additionally, age-related changes to the OB and central nervous system may be to blame (Attems, Walker, and Jellinger 2015). Lastly, a link exists between olfactory dysfunction and neurological diseases. Indeed, reports have shown a dampened olfactory functionality within individuals suffering from epilepsy (Hummel et al. 2013), myasthenia gravis (Leon-Sarmiento, Leon-Ariza, and Doty 2013), or those who have gone through a stroke (Aliani et al. 2013), and even reduction for patients with chronic neurological diseases such as Alzheimer's and Parkinson's disease (Barresi et al. 2012; Djordjevic et al. 2008; Doty 2012; Ward et al. 2016). Olfactory degradation in Parkinson's patients has been shown to predate motor dysfunction (de Lau and Breteler 2006).

1.3. The intranasal trigeminal system (CN V)

1.3.1. Anatomy and physiology

It is important to remember that an odorant generally interacts with the somatosensory system within the nasal cavity, for instance, the sensation of cooling from menthol or prickleback of CO_2 from carbonated drinks. These sensations are mediated by the trigeminal nerve (CN V) (Hummel and Livermore 2002). The trigeminal nerve is the largest of the cranial nerves and has three main branches: ophthalmic nerve (V1), maxillary nerve (V2), and mandibular nerve (V3). The upper nerve branches (V1 and V2) innervate the nasal mucosa, conveying chemosensory and somatosensory information during odor perception (Figure 1.2) while the lower nerve branch (V3) mostly concerns sensory and motor functions around the mouth. As these branches are stimulated information from the sensory-nerve fibers converge on the trigeminal ganglion (Gasserian ganglion, located in Meckel's cave) – an analogous process to incoming sensory fibers from the rest of the body that converge on the dorsal root ganglia of the spinal cord. From the trigeminal ganglion, sensory neurons project to the ipsilateral side of the rostral pons (located in the brainstem) in the trigeminal nucleus. From here, neurons project to lateral and medial thalamic nuclei and then to the somatosensory cortex depending on the branch. Intranasal trigeminal sensations (V1 and V2) are represented in the inferior portion of the postcentral gyrus (Borsook et al. 2003), and chemosensory stimulation to these nerve branches can activate olfactory and gustatory brain regions such as the piriform cortex, insula, and orbitofrontal cortex (Albrecht et al. 2010b).

Figure 1.2. Anatomical depiction of important trigeminal nerve branches (V1 and V2) for intranasal somatosensory perception (Henry Vandyke Carter - Henry Gray (1918) Anatomy of the Human; Gray's Anatomy, Plate 784)

1.4. Measuring system functionality

1.4.1. Psychophysical

Early epidemiological estimates of olfactory dysfunction used subjective "self-reporting" which showed a conservative prevalence, 4 to 10% of the population (Bhattacharyya and Kepnes 2015; Lee et al. 2013). Thus a more objective assessment was required to get an precise estimate of olfactory impairment among the general population (15 - 20 %) while also accurately diagnosing those with only mild impairment (e.g. hyposmic) that may go unnoticed.

Several tests are available to accomplish this goal and give an accurate measure of orthonasal olfactory functionality. Two popular tests in North America include the UPSIT [University of Pennsylvania Smell Identification Test; (Doty, Shaman, and Dann 1984)] and the Chemosensory Clinical Research Center Test [CCCRC, (W. S. Cain and Rabin 1989)] while this discussion will focus on an European test the Sniffin' Sticks which was used in the studies of this thesis (Hummel et al. 1997; Hummel et al. 2007). The Sniffin' Sticks test is based on felt-tip pens that dispense a particular odor, at a specific concentration, depending on the subtest (threshold, discrimination, and identification; see Figure 1.3). The threshold test (T) is surveyed with one scent, phenyl ethyl alcohol (PEA), in a triple-forced choice paradigm where participants must discriminate the odor from two blanks (filled with solvent propylene glycol). Using a two-way staircase paradigm, starting with the lowest concentration, the detection threshold is determined on correct answers. Odor discrimination (D) uses a triangle test in which two pens have the same odor while the other has a different scent. Participants are asked to choose the pen that smells different. Lastly, in the identification test (I), an individual's task is to choose an object that describes the odor from a multiple-choice of four options presented on flash cards that have both the picture and name of the object. The scores of the olfactory subtests are summed

up resulting in the overall TDI score which is then used to classify individuals on olfactory function depending on age (see Table 1.1).

Figure 1.3. Sniffin' Sticks test battery. (From back to front) Set of 16 pens for Threshold (T) test , Discrimination (D) test, and Identification (I) alongside a descriptive cue card and blindfold (used during T and D tests).

Table 1.1. Age-adjusted diagnose of TDI values according to (G. Kobal et al. 2000).

Age in Years	<16	16-35	36-53	>53
Healthy	>25	>32	>29	>28
Hyposmic	16-25	16-32	16-29	16-28
Anosmic	<16	<16	<16	<16

It is hard to exclude possible contamination of olfactory stimulation when testing trigeminal functionality; however, selective trigeminal stimulants do exist (CO2 and capsaicin). Carbon dioxide being the most popular stimulant, since it has reduced carryover effects, is a gas and must be administered in small bursts [due to at high concentrations (> 100,000 ppm needed for effective testing) thus making its application limited to olfactometers or a gauged apparatus (Shusterman and Balmes 1997). Therefore, a lateralization method has been developed for quick

testing of the degree of trigeminal activation through odors in which a mixed chemical stimulus (activating olfactory and trigeminal systems) is applied monorhinally and the patients must identify the stimulated nostril (i.e., right or left) . This test is based on the fact that humans are unable to localize pure odorants, but can localize mixed odorant relatively successfully (Hummel et al. 2003; Kobal, Van Toller, and Hummel 1989). The test can be done at a single concentration for a strong mixed odorant (e.g. menthol) over the course of twenty trials, concluding impairment for an individual that chooses the correct nostril below chance. Secondly, the test can be administered with increasing concentrations to determine a threshold (Cometto-Muñiz and Cain 1998; Frasnelli et al. 2011a). Alternatively a threshold can be obtained by measuring trigeminal stimulation to the cornea or conjunctiva of the eye which are innervated by the trigeminal nerve. These epithelia are sensitive to pain sensations (such as burning or stinging), not responsive to odorants and are highly correlated to intranasal trigeminal thresholds (Cometto-Muñiz, Cain, and Hudnell 1997). However, it is import to mask the nose to avoid co-activation during testing.

1.4.1. Physiological

1.4.2.1. Functional magnetic resonance imaging (fMRI)

A popular non-invasive tool for in vivo imaging of biological activity among human brains has been functional magnetic resonance imaging (fMRI) (Friston et al. 1998; Toro, Fox, and Paus 2008). For this approach, the blood-oxygenation level detection (BOLD) response is measured in response to a stimulus or task and then overlaid on the anatomical structure of the human brain. The BOLD signal is used as an indirect measurement of neural activation. We will first briefly discuss the imaging aspect of fMRI and then the BOLD signal that describes activations within

the image space. To successfully capture a MRI signal several things must be in place: 1) a static magnetic field, 2) a transmitter coil to direct the magnetic field to the subject, and 3) a receiver coil to read the electromagnetic emission from the subject. A larger magnetic field increases signal-to-noise (although may increase artifacts) thus a 1.5-Tesla and higher is preferable. For an MRI signal, machines are typically tuned to the frequency of hydrogen nuclei which has a positive spin (due to its odd number of protons, e.g.^{1}H) and under the influence of a magnetic field the spin axes of the millions of atomic nuclei become aligned instead of randomly oriented. These aligned, positive spinning nuclei create an electrical current that rotates around the main magnetic field. Once this system is setup, a pulse of radiofrequency (set at Larmor frequency, 42.58 MHz/Tesla, or the frequency at which a proton will absorb energy) is delivered from the transmission coil to perturb the system. In other words, the spin of the hydrogen atoms tip over from a low-energy state (longitudinal axis) to a high-energy state (transverse plane). As the system restores to its low-energy state, the atoms emit energy (at Larmor frequency) and the receiver coil detects changes in electrical current between the two states (low and high). Recovery along the low-energy state (longitudinal plane) follows the time-constant, T_1, while recovery along the high-energy state (transverse plane) follows the time-constant, T_2. Manipulating these time-constants towards one side during scanning, produces T_1-weighted and T_2-weighted brain scans. Additionally, varying the strength of external magnetic field allows each system protrusion to be spatially encoded since each would slightly differ in frequency (Huettel, Song, and McCarthy 2014).

While structural images (typically in the form of T1-weighted scans) are constructed via the method described above, functional scans construct the BOLD signal which measure the oxygen needed to drive aerobic respiration (conversion of glucose to ATP for energy) during

neuronal activity. Specifically, as the spent deoxygenated hemoglobin (which is paramagnetic) is replaced by fresh oxygenated hemoglobin, a T2*-weighted fMRI scan shows a brighter MR signal (Huettel, Song, and McCarthy 2014). Since the mid-1990s, studies in several scientific disciplines have used this technology to better understand the human brain. In the late 90s, several major olfactory studies were performed to demonstrate and record major underlying cortical networks (Lucien M. Levy et al. 1997; Sobel et al. 1997; Yang et al. 1997; D M Yousem et al. 1997), and more recent work focusing on cognitive domains of smell like valence (Anderson et al. 2003; Gottfried, O'Doherty, and Dolan 2002), intensity (Bensafi et al. 2008), memory (Levy et al. 1999) and integration with other systems (Bensafi et al. 2012; J A Boyle et al. 2007). Similarly, several fMRI studies have demonstrated activations in brain areas associated with intra-nasal trigeminal perception: the brainstem, ventrolateral posterior thalamic nucleus, anterior cingulate cortex, precentral gyrus, as well as in primary and secondary somatosensory cortices (Albrecht et al. 2010b). Interestingly, many of these studies reveal olfactory regions (piriform, orbitofrontal and insular cortex) are stimulated by trigeminal stimuli (Boyle et al. 2007; Hummel et al. 2009). Most studies to date have examined odors using a block design for a more pronounce BOLD response while event-related designs are becoming more popular (see Figure 1.4 for visual of a typical testing environment).

Although it has now been shown that the OB serves as the primary olfactory cortex, encoding the chemical features of odorants and organizing them into spatial patterns, there has only been limited imaging studies of this area with humans. This is due to the size and position of the human OB which, until now, has been a constant frustration of artifacts, producing more noise than signal. However, recent advances in head coils and magnetic power have proven

promising for future studies to examine the OB neural activities with imaging techniques such as fMRI (Fournel et al. 2017, in press).

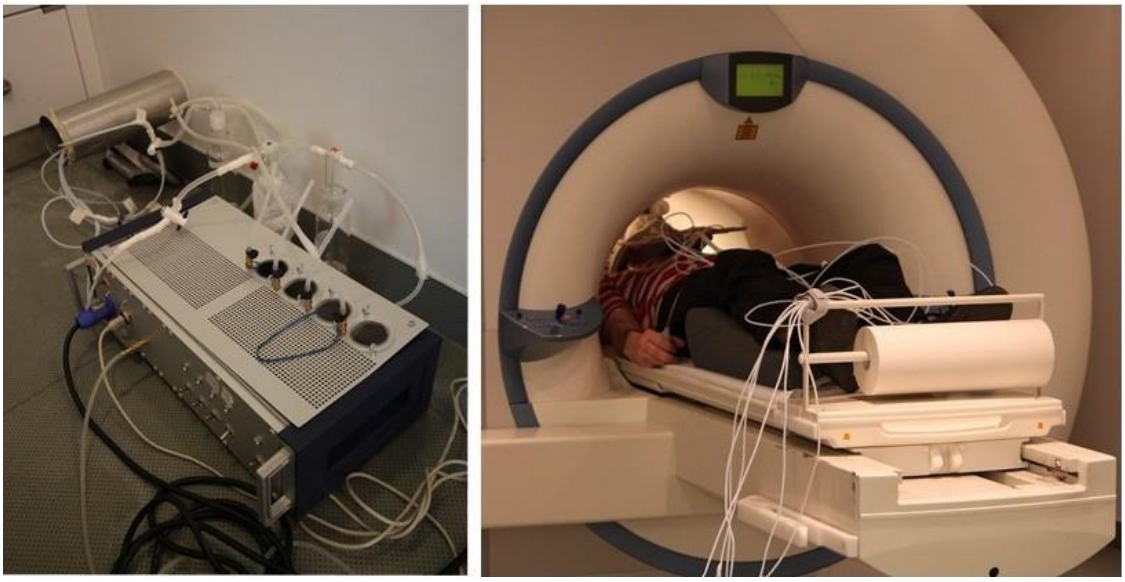

Figure 1.4. A portable olfactometer (pictured on the left) directs airs through a Teflon hose (typically at a rate of 1.5 to 2 L/min) which is connected to bottles holding either water or an odorant. From the bottle, the hose is fed through a pipe in the wall and into the scanner room to be presented in the nostril of the subject (pictured on the right).

1.4.2.2. Electroencephalogram (EEG)

Electroencephalogram (EEG) allows the examination of sequential processing of information. EEG, along with its event-related aspects, provides a direct and noninvasive measurement technique that reflects the immediate mass action of neural networks from a wide range of brain systems (Michel et al. 2009). For chemosensory research, stimuli must be presented clearly and timely while minimizing other distractive processes that could add noise to the signal. Responses elicited by a trigeminal stimuli tend to be more clear and easier to determine than olfactory; however, the measurement procedure for both stimuli should strive to reduce

background noise. To this point, an olfactometer is typically employed to deliver the stimulus of interest which does not alter mechanical or thermal sensations by mixing pulses of the stimulant in a constantly flowing air stream with constant temperature (36.5°C) and humidity (80% relative humidity) (Kobal and Hummel 1988). Signal-to-noise is further increased by the olfactometer delivering stimuli with a sharp onset and an exactly defined duration. During delivery, static noise and a visual task are used to mask olfactometer switching noises and reduce distractions for the subject, respectively. Multiple presentations of the same stimulus (> 8) are required to obtain a meaningful signal once averaged, and these stimuli are separated by 20 – 30 second intervals to reduce habituation (see Chapter 2). Under this design, EEG has become a reliable source of temporal information during chemosensory processing in research (Emilia Iannilli et al. 2013; Lascano et al. 2010; Lorig 2000) and clinical settings (Ph Rombaux et al. 2009).

Chemosensory event-related potentials (cERPs) are recorded in response to an odor or trigeminal stimulus embedded in a constant air-flow (Hummel et al. 1992; Kobal and Hummel 1988). It is an extracted signal (typically at electrode Cz and Pz) containing activity from thousands of cortical neurons. Chemosensory ERPs consist of early and late components. The early components (P1 and N1) are known to represent physical response to a stimulus while late components to a higher degree reflect internal response such as subjective evaluations (Kobal, Hummel, and Van Toller 1992).

1.5. Unimodal and bimodal odorants

1.5.2. Interactions between systems (CN I & V)

As mentioned earlier, most odors stimulate the trigeminal system, in addition to the olfactory system, especially at higher concentrations (Doty et al. 1978; Wysocki, Cowart, and Radil 2003). Additionally, psychophysical and neurological evidence shows that these two systems interact, by suppressing and enhancing each other (Brand 2006; Hummel et al. 1992; Hummel and Livermore 2002; Jacquot, Monnin, and Brand 2004a). This interdependence of each system can be demonstrated in patients with impairment to one of the systems. For instance, anosmics have lower sensitivity to trigeminal stimuli (Frasnelli et al. 2006; Gudziol, Schubert, and Hummel 2001; Hummel et al. 1996) while individuals that perceive lower strengths of trigeminal stimuli also demonstrate lower sensitivity to olfactory stimuli (Frasnelli, Schuster, and Hummel 2010). Furthermore, pure trigeminal stimuli activate olfactory-related areas in the brain (Chevy and Klingler 2014).

It is hypothesized that the interaction between these two sensory systems happens from the stimulus itself and/or an interaction at the peripheral and central level. Here, the chemical stimuli may activate both olfactory and trigeminal nerves simultaneously or each system may impact one another independent of the chemical stimulus. For example, although anosmics have a lower sensitivity to trigeminal stimuli, they show a higher peripheral response (Frasnelli, Schuster, and Hummel 2007; Porter et al. 2005). This may be the result of trigeminal nerve endings terminating in the glomerular layer (Schaefer et al. 2002) which modulate an excitatory network within the OB (Christie and Westbrook 2006). On the central level, congenital anosmics and control show no cERP differences to a trigeminal stimulus (Frasnelli, Schuster, and Hummel 2006) while those acquiring the impairment later in life (acquired anosmics) exhibit smaller cERP response amplitudes (Frasnelli, Schuster, and Hummel 2007). Lower activations for orbital frontal cortex, insula and primary somatosensory cortex during trigeminal stimulation may

explain the central contributions for this lower trigeminal sensitivity among anosmics (Iannilli et al. 2007). Additionally, a positive correlation exists between cERP to trigeminal stimuli and duration of olfactory impairment – showing the adaptive compensation between these two systems (Hummel et al. 1996).

2. Chapter 1: Habituation and adaptation to odors in humans

2.1. Hypothesis and objective

To date, there have been several reviews of sensory adaptation with most of them exclusively covering vision (Clifford et al. 2007; Kohn 2007; Rieke and Rudd 2009; Shapley and Enroth-Cugell 1984; Solomon and Kohn 2014; Wark, Lundstrom, and Fairhall 2007) and hearing (Eggermont 1985; Solomon and Kohn 2014; Wark, Lundstrom, and Fairhall 2007), leaving the senses of touch, taste and smell with limited reviews that look at sensory-specific adaptations (Dalton, 2000; McLaughlin, 1993; O'Mahony, 1979; Wilson, 2009). This review intends to partially fill this gap, providing an overview of the past and current research dealing with habituation and adaptation in humans. This non-systematic review of the field discusses underlying processes of adaptation at the peripheral and central nervous system and modalities of measurement for each, and then describes olfactory habituation principles.

We hypothesize several principles that constitute olfactory habituation which have not been studied in humans. Additionally, no standard experimental design to test olfactory habituation and adaptation has been developed, leaving large variance of effects across studies. Lastly, deficiency in habituation and several areas of adaptation, using new imaging techniques, may provide more avenues of research.

2.2. Habituation and adaptation

Thompson and Spencer determined in the late 60s the nine behavioral principles of habituation in a landmark paper (Thompson and Spencer, 1966), and these principles were repeated and expanded upon by Groves and Thompson in 1970 (Groves and Thompson, 1970). In 2009, Rankin and colleagues revisited and refined the characteristics of habituation based on results from a wide variety of animal species, resulting in the final definition of habituation with an

additional principle that is used today (Rankin et al. 2010). According to Rankin, "habituation is defined as a behavioral response decrement that results from repeated stimulation and that does not involve sensory adaptation/sensory fatigue or motor fatigue." This definition comes from traditional animal studies where observed behaviors were reduced, and does not encompass underlying processes that create such behavioral changes, as a decrease of a perception or of a sensation. Therefore, the term adaptation has been used to describe neural processes (peripheral and cerebral) that constitute this decrease in behavioral response. Working with humans, the observation of reduced intensity is a typical habituation measure [following the 10 rules of Rankin et al. (2010)], while direct reductions of peripheral and central processes constitute adaptation. Therefore, in this review, the term habituation was used to describe changes in perceptual intensity. Furthermore, decreases of neuronal responses in pre and post-glomerular neurons are termed peripheral adaptation and central adaptation respectively. Finally the term "odor" defines the sensation evoked by chemosensory stimulation, while the term "odorant" represents the molecule evoking the odor.

All sensory functions, alone or in combination with others, are subject to adaptation and thus to modification of the perception and possible consequent behaviors to create habituation. The ability to discern changes in our environment with all senses is crucial for survival and explains why forms of habituation can be seen in single cell organisms, e.g. amoeba and paramecium (Harris 1943). For instance, rapid visual adaptation is required to efficiently encode the several inputs encountered in a single visual scene to promote visually guided behavior. Here, adaptation affects the neurons accepting the visual stimuli (i.e. the retina), adjusts brain processing to the current environment, and thus improves performance in the visual task at hand. Similarly, the olfactory system continually encounters a wide variety of odorants [possibly more

than a trillion (Bushdid et al. 2014); but see also response to (Dunkel et al. 2014; Meister 2015)] and a mechanism must exist to segment them, otherwise the system would be overwhelmed with stimulation. Here, adaptation acts as a short-term filter, thus reducing perception to ambient odorants, possibly through inhibiting central processes, to reduce odor perception (i.e. habituate) and respond to more novel odorants. For example, without habituation to natural smells in the environment the detection of more immediate threats, such as odors relating to fires or enemies, or the presence of nearby rewards, such as food, would be severely impaired (Christensen, Heinbockel, and Hildebrand 1996). In the short term, adaptation may also contribute to background segmentation, where the nose unlike the eyes cannot determine new and already present odorants that are inhaled simultaneously, and must instead rely on rapid adaptation to separate changing odors from constant and non-informative ones (J. A. Gottfried 2010; Kadohisa and Wilson 2006; Linster et al. 2007; Uchida, Kepecs, and Mainen 2006).

2.3. Olfactory adaptation

Investigations into the phenomenon of human olfactory adaptation began with behavioral and psychophysical measurements. For example, studies evaluating absolute threshold or intensity often used reaction times or asked participants to scale or rate their experience. Although these measurements are reliable for testing broad concepts they cannot account for measurements beyond behavioral responsiveness such as the cessation of smell (ATCS) nor can they pinpoint the adaptation of neural features that are causing perceptual changes. Today still a debate exists on how each site (peripheral and cerebral) is involved during the adaptation processes to create habituation. To focus on this issue and get a cleaner picture of perception, behavioral research has shifted to cellular and molecular techniques (e.g. single-cell recordings) in animals (e.g.,

Zufall & Leinders-Zufall, 2000). However, studying olfaction in humans does not typically allow such precise, intrusive recordings and other, less invasive techniques have to be used. Next, we will explore some of the more modern techniques and their contribution to understanding olfactory adaptation at the peripheral and cerebral level.

2.3.1. Peripheral adaptation

Odorants may come into contact with olfactory receptor neurons (ORNs) through two pathways: retronasally and orthonasally. Retronasal olfaction occurs when odorants enter the mouth and propagates to the nasal cavity through the back of the nose (the nasopharynx) while odorants that are inhaled through the nose passively by smelling or actively by sniffing represent orthonasal olfaction (Rozin 1982; Small et al. 2005). Additionally, active smelling (i.e. "sniffing") through orthonasal olfaction influences adaptation in ORNs by changing the amount of odorant that reaches the olfactory epithelium (Beauchamp et al. 2014); however, this effect has been shown mostly in rat models and more human studies are needed (Mainland and Sobel 2006; Verhagen et al. 2007).

Early threshold studies implicated the periphery as the site of adaptation. These studies measured adaptation effects across sites where one nostril was adapted and then the same (ipsilateral) and opposite (contralateral) sites were tested for threshold sensitivity and recovery (e.g., Köster, 1971; de Wijk, 1989). The olfactory epithelium is separated by the septum to form a left and right epithelium. Therefore, olfactory stimulation of one side produces little or no activation in the other side [for example, in patients with no olfactory function on one side this can be shown very nicely: (Welge-Luessen et al. 2001)]. Following complete habituation to an odorant presented to one nostril, if subjects report a decrease of intensity when sniffing again the

odorant with the other nostril, then adaption is cerebral but does not exclude peripheral adaptation; if subjects do not report a decrease of intensity when smelling with the non-adapted nostril, then adaptation is only peripheral and the central nervous system is not involved at all. The results of three studies using this method showed that subjects habituated after mono-rhinal exposure to an odorant; although the contralateral nostril was less adapted and recovered more quickly than the ipsilateral side, revealing the influence of cerebral adaptation but not excluding the peripheral one (Cain, 1977; Köster, 1971; Stuiver, 1958).

Measurements in humans are necessarily less invasive than measurements in animals, which limits the options to gain exact insight into neural processes. However, the electro-olfactogram (EOG) is a validated technique in humans that represents the summated generator potentials of olfactory receptor neurons in response to an olfactory stimulus (Getchell & Shepherd, 1978; Kobal, 1981; Lapid & Hummel, 2013). EOG measurements provide an opportunity of recording neuronal input from the peripheral olfactory system during adaptation while simultaneously obtaining psychophysical responses in awake humans. For example, EOG experiments have shown that rapid adaptation (2 repetitions) does not occur in the periphery and EOG can still be obtained from stimuli that the subjects could not even perceive (Hummel et al. 1996; Hummel et al. 2006). Studies also show that intensities decrease more quickly than electrical peripheral recordings [see also (Lorig 2000)] Lastly, EOG recorded in response to orthonasal stimulation show larger amplitudes than recordings in response to retronasal stimulation, yet no studies have looked at adaptation effects from retronasally presented odors using EOG (Hummel, Seo, Pellegrino, & Heilmann, 2016).

2.3.2. Central adaptation

Human studies have shown that the central nervous system plays a pivotal role in olfactory adaptation, quickly filtering out external stimuli to notice and process new ones (Hummel et al., 1996;Hummel, Mojet, & Kobal, 2006). Nervous system components involved in adaptation include the piriform cortex, orbitofrontal cortex, amygdala, temporal lobe and anterior hippocampus as shown in humans (Li, Luxenberg, Parrish, & Gottfried, 2006; Poellinger et al., 2001) and animals (Kadohisa & Wilson, 2006; Wilson, 1998). Although in animal studies, the olfactory bulb (OB) shows little adaptation, (Zhao et al. 2015), the piriform cortex showed adaptation, in rats, after 30s of continuous exposure (Wilson, 1998). In humans the piriform cortex showed habituation within 60s of stimulation while orbitofrontal cortex was significantly activated during the whole exposure. Thus, orbitofrontal cortex may control olfactory inputs from piriform cortex, likely through inhibitory connections. Additionally, subcortical components have been shown responsible for particular processes of olfactory adaptation while the role of others is more elusive. For example, core components of the primary olfactory cortex (POC) like the piriform cortex have been associated with odor-background segmentation in animal and human models while habituating roles of the hippocampus and anterior insula are not known (Kadohisa and Wilson 2006; Sobel et al. 2000). However, similar to peripheral adaptation, research for central adaptation processing has focused mostly on animal models with only a handful of human studies.

A popular non-invasive tool for *in vivo* imaging of biological activity among human brains has been functional magnetic resonance imaging (fMRI) (Friston et al. 1998; Toro, Fox, and Paus 2008). For this approach, the blood-oxygenation level detection (BOLD) response is used as an indirect measurement of neural activation. Early fMRI recordings yielded small or no activation in areas of the POC in response to odorants. Sobel et al. (2000) stated this was due to

two issues: 1) odorant-induced neural activity in POC does not induce an overall local increase in blood flow and 2) odorant-induced neural activity in POC does induce an increase in blood flow, but the time course of the increase differs from the time course of odorant stimulation. To test the later, Sobel and colleagues consequently created a design to measure adaptation. Their results showed a consistent early increased activation in the POC followed by adaptation, or decrease of signal, of the same area after 30 – 40 seconds. Here, they demonstrated that rapid adaptation takes place in the POC, especially the piriform cortex, and must be accounted for in designs and analysis (Sobel et al. 2000). These results were later validated by other studies showing similar areas that initially increased and then decreased in BOLD response during prolonged odorous stimulation, and pointed out a similar trend for the hippocampus and anterior insula while the OFC exhibited a sustained increase in activation (Li et al. 2006; Poellinger et al. 2001).

Studies have recently utilized EEG which allows examination of sequential processing of information with a high temporal resolution. EEG, along with its event-related aspects, provides a considerable direct and noninvasive technique that reflects the immediate mass action of neural networks from a wide range of brain systems (Michel et al. 2009). Olfactory event-related potential (OERP) measurements are recorded in response to odors embedded in a constant air-flow (Kobal & Hummel, 1988). OERP consist of early and late components. The early components (P1 and N1) have been reported to represent more the physical response to a stimulus (e.g. odorant concentration) while late components (P2 and P3) to a higher degree reflect internal response such as novelty, familiarity or pleasantness (Duncan-Johnson & Donchin, 1977; Kobal, Hummel, & Van Toller, 1992; Lorig, 2000; Rombaux, Huart, & Mouraux, 2012).

Wang showed that olfactory adaptation is more rapid at the perceptual level (~2.5 s) than the electrophysiological (4 -10 s) with increasing stimulus frequency. Additionally, this study showed that perceived intensities completely adapted to zero, independent of pulse duration, while OERP remained at about 50 percent with increasing pulse duration (Wang 2002). However, habituation begins after an initial decrease in OERP responses at the central level (Boesveldt et al. 2007). These and other olfactory studies have shown that adaptation occurs with decreased ERP amplitudes while latencies show little effect of adaptation (Croy, Maboshe, and Hummel 2013; Scheibe, Opatz, and Hummel 2009), even for adaptation over a prolonged period (80 mins.) (Flohr et al. 2015). Scheibe et al. (2008) additionally showed that adaptation to suprathreshold chemosensory stimuli (PEA and CO_2) seems to be independent of sex in young participants. Andersson et al. (2011), while not using a setup to test adaptation, also reported this independency (Andersson et al. 2011). Lastly, Croy et al. (2013) reported P2 amplitudes decrease over time more strongly for unpleasant (H2S) compared to pleasant odors (PEA and peach). However, the P2 latency of unpleasant odors was shorter than to pleasant odors (Croy, Maboshe, and Hummel 2013).

To date, all studies on olfactory adaptation have used simple EEG protocols while several recent studies have suggested that OERPs may be localized back to their originating deep brain structures (Emilia Iannilli et al. 2013; Michel et al. 2009). Although this technique is still maturing, it may offer solutions to unresolved questions of olfactory adaptation. First, what are the temporal changes to olfactory pathways during increased respiration and its effects on adaptation? Secondly how does this rapid cerebral adaptation affect short-term feedback loops to the olfactory bulb thus enhancing discrimination of odor mixtures encountered in natural environments?

2.4. Olfactory habituation in humans

Although the 10 fundamental principles of habituation, as revised by Rankin et al. (2010), were defined for behavioral response decrements in unspecified sense modalities, most of these principles have been demonstrated in olfactory habituation (see Table 2.1). Many of these studies have concentrated on animal models (cf. review Wilson, 2009), and thus on the decrease of a specific behaviors (e.g. sniffing, go-no go) indicating a decrease of perception. However, human studies mostly measure perceptual changes rather than behavioral. We will first discuss the principles of habituation that have been studied (and neglect other principles that have not been studied for the olfactory system in humans), and then discuss other qualities and study caveats that affect olfactory perception in humans.

2.4.1. Principle 1: Repeated applications of a stimulus result in decreased responses

Early models of human olfactory habituation depicted linear trends where habituation was directly proportional to odorant exposure time and reported (the possible) total disappearance of odor at certain concentration levels (Köster, 1971; Stuiver, 1958; Woodrow & Karpman, 1917). Previously Elsberg (1935) had reported a similar linear habituation trend towards a perceptual disappearance of the odor, but could not substantiate the claims that it vanished (Elsberg and Levy 1935). However, these early studies lacked the modern instruments and knowledge of human perception. Consequently, well-controlled experiments (see *study caveats*) looking at habituation showed an exponential decline of odor intensity in respect to increased exposure to odorants, and this decreasing response did not reach zero (Ekman et al. 1967). This was further supported by Cain (Cain 1974) who had subjects freely adjust odorant concentrations to keep the

odor intensity constant. However, other research from the Köster's laboratory has once again reported that the total disappearance of an odor can occur, calling the phenomenon "adaptation time required for the cessation of smell" (ATCS) (de Wijk 1989). This difference can be explained using other measurement techniques (e.g., electro-encephalography EEG) indicating that as the detection of an odor becomes almost null, some neurons are still responsive (Wang 2002). This may be described by the sixth characteristic of habituation which states that "repeated stimulation may continue to accumulate even after the response has reached an asymptotic level."

2.4.2. Principle 2: Withholding the stimulus produces recovery

After odorant exposure, the effects of olfactory habituation wear off during a recovery period, restoring the ability to notice the same odorant when encountered again. However, recovery rate from habituation is duration and concentration-dependent as shown in some studies (Cain, 1974; Ekman et al., 1967; Köster, 1971; Pryor, Steinmetz, & Stone, 1970), while recovery appeared independent of odor concentration (and odor quality) used in another study (Stuck et al. 2014). For short-term exposure (under a minute), partial recovery is almost simultaneous, called spontaneous recovery, to the removal of the odorant while maximum habituation to an odorant may take several minutes or even days to weeks for long-term exposure (e.g. present in daily environment / workplace) (Dalton and Wysocki 1996; Gagnon, Mergler, and Lapare 1994; Philpott et al. 2008; Smith, Gamble, and Heil 2010; Stuck et al. 2014). Stuck et al. (2014) looked at recovery time after habituation to two odors, phenyl ethyl alcohol (PEA) and hydrogen sulfide (H_2S), at several concentrations at prolonged exposure. They reported that, for both odorants, subjects recovered at the same rate, with odors being rated as more intense over time periods of

recovery independent of the odorant. Additionally, Philpott et al. (2008) showed that the average total recovery time for PEA was 170 seconds after full habituation at prolonged exposure, and this was dependent on the subjects' age and mood. Odorous molecules do not immediately disappear after exposure like other sensory stimuli, but must be cleared from the peri-receptor environment (Dalton 2000). Here, odor clearance may vary due to physico-chemical properties of various odorants or variation in nasal clearance mechanisms such as nasal submucosal blood flow, nasal mucociliary clearance and expiratory desorption. Similarly, variations in anatomical structure of the nasal cavity in humans, leading to differences of airflow rates, may influence recovery times (Philpott et al. 2008).

2.4.3. Principle 4: Increased frequency of stimulation increases habituation

To induce habituation, odorants are typically presented as a continuous stream (Dalton and Wysocki 1996; Stone, Pryor, and Steinmetz 1972; Stuck et al. 2014) or repeated pulses at short inter-stimulus intervals (ISI) (Cain & Polak, 1992; Hummel, Knecht, & Kobal, 1996; Jacob, Fraser, Wang, Walker, & O'Connor, 2003; Wang, 2002). In general, increased pulse length and shorter inter-stimulus intervals produce faster rates of habituation; however, Smith et al. (2010) argue that habituation through discontinuous odorant presentation may be confounded by aspects of recovery. Therefore, his lab introduced a new psychophysical technique for estimating the onset of odor habituation in humans through intervals of the target odorant presented over a continuous flow of the same odorant at a lower intensity (Smith, Gamble, and Heil 2010; Yoder et al. 2014).

2.4.4. Principle 5: Weaker stimuli lead to more rapid habituation

The degree of habituation is influenced by the concentration of the odorant. Generally, a weak concentration will be habituated to more quickly than a stronger one relative to time and may perceptually disappear completely (Cain and Polak 1992; Jacob et al. 2003; Stone, Pryor, and Steinmetz 1972; Stuck et al. 2014). However, in terms of absolute decrease, the opposite may be true with larger concentrations leading to more rapid decrease in intensity, though not to complete disappearance. For instance, Stuck et al. (2014) showed that the time to complete habituation increased with increasing odorant concentrations for PEA and H_2S, and that the odor concentration has a significant influence on the time to complete habituation. These mechanisms may be the result of receptor recruitment; increasing concentration of an odorant results in the recruitment of new olfactory receptors (Laing et al. 2003). However, recovery rates from complete habituation have been shown to be independent of the odorant concentration (Stuck et al. 2014).

2.4.5. Principle 7: Habituation to one stimulus may generalize to other similar stimuli

Habituation has been further studied in the fields of olfactory learning and structure-activity relationships, concentrating on cross-adaptation, or the adaptive relationship between two odorants. This characteristic of adaptation is important when considering that very rarely odorants are encountered individually. Generally, odorants that are structurally similar provoke more cross-adaptation than distinct odorants, even if these odorants are discriminable (Cain and Polak 1992; Pierce et al. 1995, 1996). Additionally, unfamiliar odors show more cross-adaptation (Pierce et al. 1996; Pierce, Wysocki, and Aronov 1993), as they are less discriminable. Cross-adaptation between two odorants is not reciprocal, meaning adaptation in odorant A may induce adaptation in odorant B, but an adaptation in B may not influence adaptation in odorant A

(Wilson, 2010). Furthermore, the effect of cross-adaptation is always weaker than the effect of adaptation to one odorant (Köster, 1971; de Wijk, 1989). However, most natural odors are mixtures of multiple separate odors and it is thus difficult to actually assess cross-adaptation within a natural odor.

2.4.6. Principle 10: Long-term habituation

In the revised view of habitation (Rankin et al. 2010), Rankin and colleagues acknowledged the need to define two forms of habitation, short-term and long-term habituation. Long-term habituation is demonstrated when "some stimulus repetition protocols may result in properties of the response decrement that last hours, days or weeks." In a combined field and laboratory study, Dalton and Wysocki (1996) exposed 8 individuals for two weeks at a minimum of 6 hours a day with a pleasant odor (either citralva or bornyl acetate, randomized among individuals) in their home, then tested their odor threshold and supra-threshold intensity prior to exposure, weekly during exposure and weekly (for two weeks) after exposure in the laboratory. Within a week of exposure ¾ of the individuals showed habituation to the odorant while all individuals had habituated after two weeks. Recovery rates were extended past short-term exposure with only half of the individuals showing complete recovery after two weeks, whereas one other individual showing no recovery at all. These results demonstrate the large variation in the rates of recovery among individuals after long-term exposure. Furthermore, the effect of habituation was more pronounced at threshold levels than at supra-threshold levels.

2.4.7. Other odorant sensory and physicochemical characteristics that effect habituation

Among the 10 principles of habituation (Rankin et al. 2010), only one principle concerned the odorant itself: a high concentration of odorant molecules delays or decreases habituation compared to a lower concentration of the same odorant. In a recent study, the question of whether habituation differs between odorants was investigated (Sinding et al. 2017). Habituation was evaluated for 32 odorants varying in sensory (intensity, hedonicity, trigeminal activity and familiarity) and physicochemical characteristics (e.g. number of carbon atoms in the chain, number of double bonds, hydrophobicity, molecular weight, vapour pressure). Trigeminal activity appeared as a factor strongly reducing habituation as well as several physicochemical characteristics (high vapour pressure, small molecular weight, low number of double bonds). The trigeminal nerve is commonly activated by odorants and its branches are composed of different somatosensory and pain fibers that can react to texture, temperature, or chemicals. Their description can be as variable as burning, fizzy, soft, warm, cold, tingling, prickling, pungent, creamy, irritating, etc. Additionally, the trigeminal system may be seen as a sentinel of the respiratory systems, increasing arousal and decreasing habituation. For instance, repeated stimulation with high concentration of CO_2, which specifically activates trigeminal system, has been shown to activate pain fibers of the trigeminal nerve and even produce an increase in perceived intensity (Hummel, Gruber, Pauli, & Kobal, 1994). However, for CO_2 at lower concentrations the effect is different. Flohr et al. (2015) found a steeper decrease of brain activity in response to a pure "trigeminal molecule" (CO_2), compared with a relatively selective "olfactory molecule" (Phenyl Ethyl Alcohol or H_2S) (Flohr et al. 2015). Therefore, it seems that the association between the olfactory and trigeminal systems is necessary in order to see a delay of habituation. It also appears that the activation of the trigeminal system and potentially the

affinities of odorants for receptors, mucus and odorant binding protein significantly modulate habituation.

Another important feature of odorants that may impact on habituation is their hedonicity. Odorants perceived as pleasant habituate at a slower rate, with larger differences between concentrations, than unpleasant odors (Croy, Maboshe, and Hummel 2013; Jacob et al. 2003; Stuck et al. 2014). Results from these studies appear counterintuitive because unpleasant odors are associated with danger and would benefit from more initial attention, but could be explained by the decrease in that attention (Andersson, Lundberg, Åström, & Nordin, 2011) and loss of emotional salience (Schettino and Vuilleumier 2013) over repeated exposure. Indeed, unpleasant odors may produce a relatively strong first response, involving a startle response for warning purposes, which then, because it is very strong, decreases at a faster pace than pleasant stimuli (Croy, Maboshe, and Hummel 2013). Sinding et al. (2017) found contrary results, that unpleasant odorants would produce weaker habituation. However the odorants that were unpleasant were also more trigeminal. Therefore, pleasantness alone may not be a relevant factor for modulating the rate of habituation, and only a combination of factors may be enough informative to modulate habituation. For this reason, odorants should be carefully chosen when considered for a habituation study, especially when comparing these results across other studies.

2.4.8. Study caveats

Several experimental biases are entangled with the study of habituation and modulate the responses to odorous stimuli. For example, asking subjects to report "when the odor disappears" falsely facilitates total disappearance of odor to prolonged exposure because it is expected by the subject (Cain 1974). Additionally, priming effects such as explanations given to the subject on

the biological importance of the odor (e.g. hazardous, relaxing, etc.) may considerably modify adaptation. For instance, a novel odor that is perceived as hazardous reduces or delays perceived adaptation to that odor in comparison to perceiving the same odor under the context that it is beneficial or neutral (Dalton 2000; Kobayashi et al. 2007).

Lastly, perceptual responses to olfactory stimuli require a precise production and delivery of odorants to obtain consistent results. Sight and hearing adaptation experiments can rely simply on light and tones, while chemical substances cannot as easily be directed to the olfactory epithelium. Ideally, olfactometry systems should be used controlling for stimulus steepness and timing, flow, humidity, and temperature (Kobal & Hummel, 1988).

Table 2.1. Rankin et al (2010) principles of habituation and adaptation as related to human olfactory research.

Characteristic	Description	Olfactory Evidence
1	Repeated application of a stimulus results in a progressive decrease in some parameter of a response to an asymptotic level. This change may include decreases in frequency and/or magnitude of the response. In many cases, the decrement is exponential, but it may also be linear; in addition, a response may show facilitation prior to decrementing because of (or presumably derived from) a simultaneous process of sensitization.	Aronsohn, 1886; Eisberg, 1935; Mulline, 1955; Ekman et al. 1967; Cain, 1974; Wijk, 1989
2	If the stimulus is withheld after response decrement, the response recovers at least partially over the observation time ("spontaneous recovery").	Pryor et al. 1970; Gagnon et al. 1994; Philpott et al. 2008; Stuck et al. 2014
3	After multiple series of stimulus repetitions and spontaneous recoveries, the response decrement becomes successively more rapid and/or more pronounced (this phenomenon can be called potentiation of habituation).	No studies

4	Other things being equal, more frequent stimulation results in more rapid and/or more pronounced response decrement, and more rapid spontaneous recovery (if the decrement has reached asymptotic levels).	Cain and Polak, 1992; Wang et al. 2002; Hummel et al. 1996; Jacob et al. 2003
5	Within a stimulus modality, the less intense the stimulus, the more rapid and/or more pronounced the behavioral response decrement. Very intense stimuli may yield no significant observable response decrement.	Stone et al. 1972; Stuck et al. 2014
6	The effects of repeated stimulation may continue to accumulate even after the response has reached an asymptotic level (which may or may not be zero, or no response). This effect of stimulation beyond asymptotic levels can alter subsequent behavior, for example, by delaying the onset of spontaneous recovery.	Wijk, 1989; Wang et al. 2002
7	Within the same stimulus modality, the response decrement shows some stimulus specificity. To test for stimulus specificity/stimulus generalization, a second, novel stimulus is presented and a comparison is made between the changes in the responses to the habituated stimulus and the novel stimulus. In many paradigms (e.g. developmental studies of language acquisition) this test has been improperly termed a dishabituation test rather than a stimulus generalization test, its proper name.	Cain and Polak, 1992; Pierce et al. 1993; Pierce et al. 1995; Pierce et al. 1996
8	Presentation of a different stimulus results in an increase of the decremented response to the original stimulus. This phenomenon is termed "dishabituation." It is important to note that the proper test for dishabituation is an increase in response to the original stimulus and not an increase in response to the dishabituating stimulus (see point #7 above). Indeed, the dishabituating stimulus by itself need not even trigger the response on its own.	No Studies
9	Upon repeated application of the dishabituating stimulus, the amount of dishabituation produced decreases (this phenomenon can be called habituation of dishabituation).	No studies
10	Some stimulus repetition protocols may result in properties of the response decrement (e.g. more rapid rehabituation than baseline, smaller initial responses than baseline, smaller mean responses than baseline, less frequent responses than baseline) that last hours, days or weeks. This persistence of aspects of habituation is termed long-term habituation.	Gagnon et al. 1994; Dalton and Wysocki, 1996; Schiffman and Williams, 2005; Dalton and Hummel, 2011

2.5. Deficiency in habituation and adaptation

In a clinical setting, habituation may aid in diagnosis of some pathologies and impaired olfactory functionality. For instance, a large percentage (9 to 33%) of the adult population, and even higher percentage of occupational laborers, may report a chemical intolerance (CI) to odors; aspects of this are referred to as multiple chemical sensitivity (MCS) (Caress and Steinemann 2003; Johansson et al. 2005; Kreutzer, Neutra, and Lashuay 1999). Those considered to have MCS are not characterized by acute chemical sensitivity [e.g. increased odor intensity or decreased odor absolute detection thresholds; (Andersson et al. 2009)], but may have decreased olfactory habituation (Andersson et al. 2009, 2015). For example, one study exposed 18 participants with MCS and 18 healthy controls to low concentrations of the odorant n-butanol (11.5 mg/m3) for 42 minutes in an odor chamber. MCS participants reported greater perceived odor intensity, more unpleasantness and increased symptoms over time compared to controls. Similarly, throughout an OERP experiment Andersson and colleagues (2009) showed this effect at the central processing level with N1 amplitudes of chemical sensitive individuals remaining constant (Andersson et al. 2009).

Additionally Autism Spectrum Conditions (ASC), which are characterized by social communication difficulties alongside repetitive behaviors and special interest (APA, 2003), has been associated with sensory decline through anecdotal reports, questionnaires, and psychophysical tests (Chamak et al. 2008; Leekam et al. 2007; Suzuki et al. 2003). For olfactory habituation, one study using "Sniffin' Sticks" showed that adults with ACS did not differ in threshold nor habituation (Tavassoli and Baron-Cohen 2012). However, this study focused on adults (ages 28 – 30 years) while most studies showing olfactory dissimilarities in ASC, such as decreased olfactory identification and increased olfactory impairments, were on children and

adolescents (age 10 -18 years) (Bennetto, Kuschner, and Hyman 2007; Lane et al. 2010; Leekam et al. 2007).

Age-related olfactory loss has also long been reported extensively with a decline in odor identification, detection, and discrimination (Hummel, Kobal, Gudziol, & Mackay-Sim, 2007), and similarly, research has shown that older people are more prone to olfactory habituation and are slower at recovery than younger people (Stevens, Cain, & Oatley, 1989; Stevens, Cain, Schiet, & Oatley, 1989). Temporal studies have shown that older participants produce smaller N1 and P2 amplitudes with longer latencies than younger participants (Hummel, Barz, Pauli, & Kobal, 1998). For olfactory adaptation, a similar trend with age can be seen with decreased amplitudes for shorter ISIs in older males (Morgan et al. 1997).

2.6. Future areas of research

Several questions regarding olfactory habituation remain open. For instance, according to our literature search, some principles of habituation [set by (Thompson and Spencer 1966)] have not been explored properly for the human olfactory system such as potentiation of habituation or habituation of dishabituation. Similarly, it is evident that odor perception involves short-term application for approach and avoidance of odorous and other environmental stimuli; however, much research is still needed to determine long-term effects of habituation specifically in odor to fully understand the added, tenth principle presented by Rankin et al (2009). Most long-term studies to date have concentrated on trigeminally active volatile organic compounds which may pose health risks, leaving many open questions pertaining to other odorants (Dalton, Dilks, and Hummel 2006; Dalton and Wysocki 1996; Gagnon, Mergler, and Lapare 1994; Schiffman and Williams 2005). For instance, how does concentration and frequency of presentation of mixed

odorants, which represent more realistic settings, change perception over long periods of time? More specifically to odor, which mental processes constitute the bulk of these changes (e.g. sensory adaptation, shifts in attention, odor memory)? These questions have practical importance, for example, in industry fields where workers are continually exposed to different odorants, and may help explain behavioral changes over time (Post 1980).

Olfactory adaptation is a distributed process, operating at peripheral and central levels. For instance, research shows that ORN adapt slower and recover more quickly than central nervous system structures involved in the processing of chemosensory information (Hummel et al., 1996, 2006; Sobel et al., 2000; Wang, 2002). Here, the peripheral receptors stay responsive to all odorants while the central processing units (especially piriform cortex) rapidly adapt to the stable, less intense background focusing on identification of the new odorants presented in the foreground. However, we feel that more research is needed on the interaction of peripheral and central processes involved in adaptation and mechanisms that modulate this interaction. For instance, human sniffing, which increases with alertness, modulates adaptation at the peripheral and central level, but the degree to which each are impacted is not well understood. Similarly, feedback loops from peripheral to cerebral structures are not clearly defined and their role in adaptation processes are relatively unknown. Furthermore, adaptation in a realistic setting is a multisensory experience, yet little research has evaluated peripheral or the cerebral cross-adaption of olfactory activations with other senses involved in perception.

The combination of non-invasive tools, such as EOG, EEG and fMRI, with creative experimental designs offer an opportunity to answer some of these questions in humans not under anesthesia. Similarly, the increasing maturity of source localization through multi-channel EEG may help define peripheral-cerebral feedback loops involved in adaptation that happen

early on in processing of chemosensory stimuli (Lascano et al. 2010). However, advancements in techniques and tools are still needed for an accurate portrayal of adaptation in human.

Lastly, in combination with modern measurement techniques, human studies should try to minimize variance by implementing appropriate designs to study olfaction. Whenever possible, specific olfactory or trigeminal stimuli should be chosen, and, if possible, delivered with high-precision olfactometers. Similarly, study designs focusing on characteristics of habituation should control for similar caveats specific to odors (e.g. hedonics). For instance, prolonged exposure, as stated by the fourth characteristic laid out by Rankin (Rankin et al. 2010), results in a different degree of habitation than odorants presented at varying intervals.

3. Chapter 2: Olfactory processing in normosmic patients and patients with olfactory loss

3.1. Introduction and objective

Anosmia is the inability to perceive odors or lack of olfactory function. A less studied olfactory disorder is hyposmia which is the partial loss of smell. In total, about 5 % of the population exhibit anosmia and approximately 15% are considered hyposmic while this number increases when considering specific impairment in detection, recognition and identification (Brämerson et al. 2004; Landis, Konnerth, and Hummel 2004; Mullol et al. 2012; Murphy 2002). Furthering the understanding of olfaction, prevalence of loss of smell and risk factors: a population-based survey). This diminished sense of smell can be attributed to several factors including demographics, brain morphology and physiological responses. For instance, several studies have shown that olfactory loss increases as age increases with 50% of individuals over 65 years of age showing olfactory impairment (Doty et al. 1984; Murphy 2002). Diseases associated with olfactory functionality may also contribute to the age-related impairment; for instance, the majority of hyposmic cases can be classified by inflammation of the nose and paranasal sinuses (Damm et al. 2004) while other, less frequent hyposmic cases may be psychiatric (Moberg et al. 1999), or neurodegenerative (Doty, Deems, and Stellar 1988; Müller et al. 2002; Ponsen et al. 2004).

Common techniques to examine the morphology and cerebral processing of olfactory information include EEG-derived event-related potentials (Kobal et al. 2000; Welge-Lüssen et al. 2009), positron emission tomography, PET (Bohnen et al. 2008), computed tomography / magnetic resonance imaging, CT / MRI (Bitter et al. 2010; Levy, Bartsch, Rajan, Schellinger 1995; Mueller et al. 2005; Rombaux, Duprez, and Hummel 2009; Rombaux et al. 2010) and

functional MRI (Welge-Lüssen et al. 2009; Yousem et al. 1996). Using CT and MRI, studies have been able to determine differences in structural components such as the olfactory bulb and the olfactory sulcus that correlate with olfactory impairment (Bitter et al. 2010; Levy Bartsch, Rajan, Schellinger 1995; Mueller et al. 2005; Rombaux, Duprez, and Hummel 2009; Rombaux et al. 2010; Yousem et al. 1993, 1996). Several fMRI studies have been able to further identify these olfactory process differences in individuals with neurodegenerative diseases (Barresi et al. 2012; Hummel et al. 2010), while only a few studies have concentrated on differences between individuals with olfactory deficiencies due to other causes (Levy et al. 1998; Welge-Lüssen et al. 2009). Therefore, more research to determine differences in central olfactory processing among typical hyposmic patients and healthy individuals is needed.

In this study, we use psychophysical tests (e.g. "Sniffin' Sticks") to create two balanced groups, individuals with healthy (normosmic) and decreased (hyposmic) olfactory functionality. Participants were additionally screened for potential other causes of olfactory function loss, excluding patients with neurological disease and patents with olfactory loss due to acute or chronic inflammation of the nose and paranasal sinuses. Olfactory processing was measured using fMRI while two pleasant, food-related odors were sampled with odor perception being evaluated in-between stimuli.

3.2.Material and methods

3.2.1. Subjects and stimuli

A total of 23 subjects participated in the study. Eleven women with an age range 42 to 71 years (mean age ± SD = 59.6 ± 8.9 years) had hyposmia (determined from the TDI scores, see psychophysical measures). The remaining normosmic control group consisted of five women and seven men with an age range of 47 to 69 years (55.5 ± 6.0 years). None of the women were

pregnant, and none of the participants had significant health problems (e.g. kidney failure) currently or in medical history that may be associated with disorders of olfactory function. Furthermore, each underwent a standard ENT examination with endoscopy and individuals with polyps, acute or chronic inflammation of the nose, paranasal sinuses, or major septum deviations were excluded from the study. All subjects were right-handed as established by means of the Edinburgh Inventory (Oldfield 1971). Additionally, subjects reported no claustrophobia and were able to undergo MRI examinations. The study design met the requirements of the Declaration of Helsinki and had been approved by the Ethics Committee of the Medical Faculty Carl Gustav Carus at the Technical University of Dresden (ethics protocol number EK 286112007).

After examining the medical history and assessment of olfactory functionality, each subject was informed of the testing procedures, specifically MRI procedures, and gave written informed consent. In the MRI scanner, the endings of odor dispensing cannulas (4-mm inner diameter) were placed in the subjects' nostril. The odor delivery was carried out by an olfactometer positioned in a neighboring room. For stimulation, the two odors chosen were peach and coffee (Pfirsich-Aroma, Kaffee-Aroma; Frey und Lau, Henstedt-Ulzburg, Germany) while water was used as a control. Odors were chosen since they are familiar to at least 75% of the German population. Clean air (from hospital resources) was passed at 2 L / min via a pulse generator for odor presentation to the subject. The pulse generator was set at a pulse length of 1 second at interstimulus intervals (ISIs) of two seconds; odors were presented for a period of 20 s (ON period), with intervals of 20 s (OFF period) where only odorless air was presented (see. Figure 1). Both stimulus qualities (coffee and peach) were presented in undiluted concentrations clearly perceivable and without causing any trigeminal sensation.

The fMRI study began with a "shim" sequence to counter the effect of magnetic field inhomogeneity (Jezzard and Clare 1999). This was followed by six odor (ON) and no-odor (OFF) blocks of scanning with each block consisting of 8 scans. In each run, only one scent (coffee or peach) was used and the stimulus was directed to only one nostril (left or right), again, in order to make the sessions more interesting to the participants and also to minimize adaptation to the odors. Thus, 96 scans were performed per odor on each nostril, and the order of runs was randomized for each subject. After each run subjects were asked to identify the presented odor. Odor identification answers within the same category as the odor presented (e.g. fruit for peach or cappuccino for coffee) were counted as correct. In addition, subjects were asked to rate the intensity (0 to 10; "Not perceived" to "Very strongly perceived") and valence (-5 to 5; "Extremely unpleasant" to "Extremely pleasant"). As mentioned above, none of the subjects reported a stinging or burning sensation in response to odorous stimulation. After all fMRI runs had been completed, brain anatomy scans were taken for anatomical correlation.

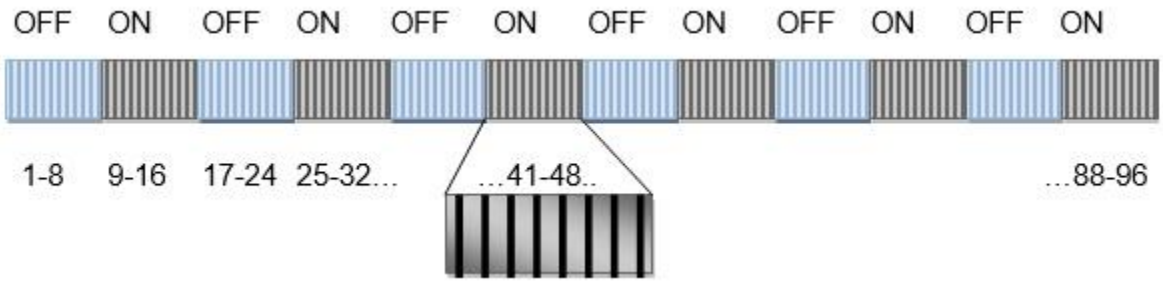

Figure 3.1. Represent the schematically structured passage of MRI scan. This consisted of 6 ON- (with odor delivery) and 6 OFF-blocks (without odor delivery). In each block, 8 scans were held. Therefore, 96 scans were performed in a single pass.

3.2.2. Psychophysical measures

A test of orthonasal olfactory function was carried out using pen-like odor dispensers called "Sniffin' Sticks". "Sniffin' Sticks" were used to test three different olfactory functions: olfactory threshold (phenyl ethyl alcohol), odor discrimination and odor identification. Results of the 3

subtests were presented as a composite score for threshold, discrimination, and identification (TDI score) which was then used to classify olfactory function groups for the study, hyposmia or normosmia (control) according to the age-matched normative data (Hummel et al. 1997; Kobal et al. 2000).

3.2.3. fMRI scanning parameters

A 1.5 T MRI scanner (Siemens Sonata, Erlangen, Germany) and a full-head eight-channel receiver coil were used for image acquisition. A gradient echo T2*-sensitive echo planar imaging (GE-EPI) sequence was employed (TR 2500 ms, TE 40 ms, image matrix 64x64, in-plane resolution 3 mm, through-plane resolution 3.75 mm). The time of echo was selected because it had been established for 1.5 Tesla scanners for the imaging of limbic structures (Stöcker and Shah 2006). Images were acquired in the axial plane oriented parallel to the planum sphenoidale to minimize artifacts. A total of 96 functional volumes per run in twenty-six slice locations (covering the entire head) were acquired per session. A full brain T1-weighted turbo FLASH 3D-sequence was acquired to overlay functional data (TR 2200, TE 3.93, slice thickness: 1 mm).

3.3.4 fMRI data processing

Data was analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm) in the Matlab framework (Matlab 6.5 R3, The MathsWorks Inc., Natick, MA, USA). Functional data was motion corrected and coregistered with the anatomical images. Segmentation of the latter into white and grey matter compartments yielded parameters for normalization with respect to the MNI space. Finally, functional normalized data was smoothed with an 8 x 8 x 8 mm^3 FWHM Gaussian kernel.

First level analysis was carried out with the standard canonical hemodynamic response function used in SPM 8. Contrast images for "odor ON > odor OFF (modeled baseline)" were generated for each subject. In second level analysis, these images were subjected to a random effect analysis using (1) independent sample t-test for within *olfactory group* comparisons of On and Off conditions and (2) a 3 X 2 factorial design with *olfactory group* as a between subject and *odoran*t and *site specific activation* as within subject factors. To evaluate bi-directional main effects between groups, results of the one-sample t-tests are reported with a threshold of $p < 0.001$, uncorrected. Furthermore, main effects between olfactory groups underwent ROI analysis for areas relevant to olfactory processing (piriform cortex, amygdala, thalamus, hippocampus, insula, orbito-frontal cortex). All masks were created using the "automated anatomical labeling (aal)" atlas (Tzourio-Mazoyer et al. 2002), embedded in WFU PickAtlas 2.4 software (Maldjian et al. 2003), except for the piriform cortex (defined according to the criteria described in (Berglund, Lindström, and Savic 2006) and the hypothalamus (6-mm sphere around (–6 | 0 | –14) (Zelano et al. 2005). For ROI analysis, thresholds were set at $p < 0.05$, corrected with a cluster criterion of five voxels for whole brain analysis and Bonferroni-corrected for multiple comparisons of the eight ROIs ($p < 0.05 / 8 = 0.006$) with a cluster criterion of five voxels.

3.3.Results

3.3.1. Psychophysical measures

As shown in Table 3.1, normosmic and hyposmic groups differed significantly in the composite TDI score, and its constituent tests – threshold, discrimination and identification. For instance, the mean (SD) TDI score for the control group was 33.81 (3.72) compared to hyposmic subjects who scored 19.50 (4.77) while the threshold and identification showed the largest

difference between the olfactory groups. For hyposmic subjects, the most frequent cause of olfactory dysfunction was viral (n = 6) followed by idiopathic (n = 4) and traumatic (n = 1).

Table 3.1. Characteristics of hyposmia and normosmia groups (mean ± SD).

Olfactory Group	Age (years)	Olfactory Impairment (N)	Impairment duration (years)	TDI	Threshold (T)	Discrimination (D)	Identification (I)
Hyposmia	59.64 ± 8.86	Post-viral (6) Idiopathic (4) Post-traumatic (1)	2.14 ± 2.12	19.50 ± 4.77	3.23 ± 1.77	9.45 ± 2.34	6.82 ± 1.72
Normosmia	55.50 ± 5.95	-	-	33.81 ± 3.72	8.81 ± 2.25	12.00 ± 2.04	13.0 1.21

3.3.2. Evaluation of odors during the fMRI sessions

Between odors, peach was identified significantly more often than coffee among normosmic subjects ($p < 0.001$). Additionally, peach and coffee were identified correctly significantly more by normosmic subjects (58 % and 38 %, respectively) than hyposmic subjects (9% for both odors) ($p < 0.001$). The peach odor was also more intense among normosmic than hyposmic subjects ($p < 0.001$). Additionally, normosmic subjects rated both peach and coffee significantly more pleasant than the hyposmic group ($p = 0.01$ and $p = 0.02$, respectively).

3.3.3. Neuroimaging results

Comparing the odor (ON) and non-odor (OFF) blocks during runs (Figure 3.2), hyposmic subjects showed significantly less and weaker brain activations than for the normosmic subjects. Normosmic subjects showed significant differences between odor and non-odor blocks in the left insula, left amygdala, and left orbital frontal cortex (OFC), with the largest activations in the OFC (39 Vox / Cl). In contrast, hyposmic subjects showed significant differences between block conditions in the left OFC and left insula, with the largest activation in the insula (18 Vox / Cl).

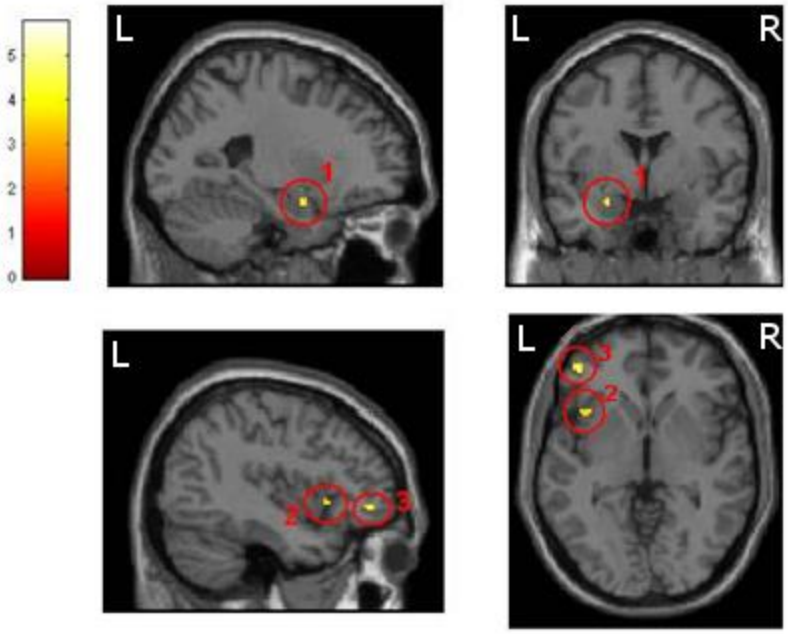

Figure 3.2(a). Odor vs. non-odor for normosmic subjects: The Figure shows an activation of the left amygdala, the left insula and left OFC under the stimulus condition. The red ring 1 marks the voxel clusters in the left amygdala (coordinates: x: -24mm, y: 0 mm, z: -20mm), ring 2 in the left insula (coordinates: x: -16mm, y: 16mm, eg: - 2mm) and ring 3 in the left OFC (coordinates: x: -44mm, y: 46mm, z: -4mm). The scale represents the t-value of the voxel clusters and defines the color of the cluster (with mask, p <0.001, Vox / Cl> 5).

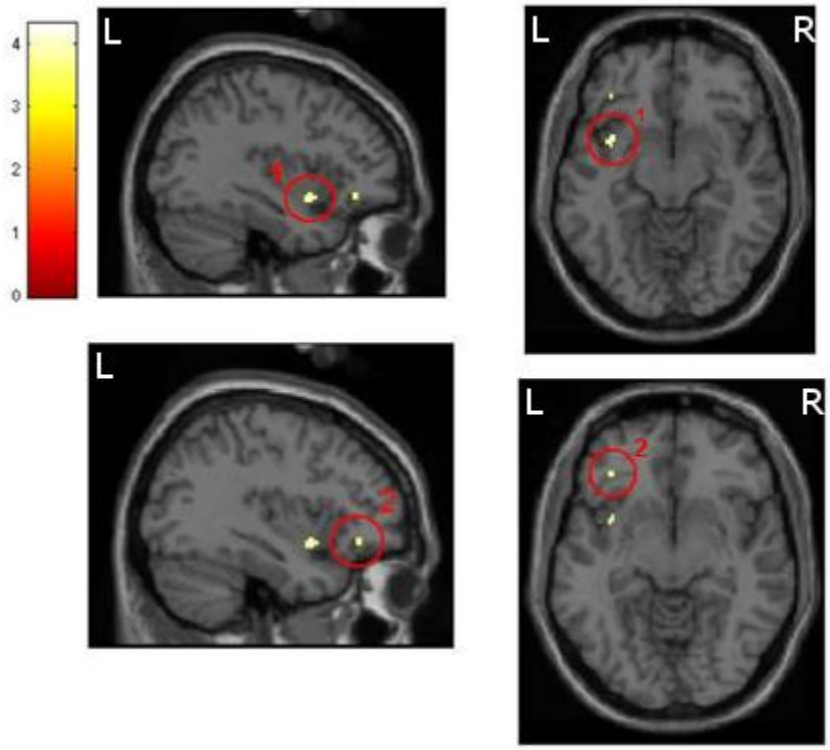

Figure 3.2(b). Odor vs. non-odor for hyposmic subjects: The figure shows an activation of the left insula and left OFC. Ring 1 marks the voxel clusters in the left Insulation (coordinates: x: -36mm, y: 8 mm z: 10 mm) and ring 2 in the left OFC (coordinates: x: -36mm, y: 34 mm, for example: - 8 mm). The scale represents the t-value of the voxel clusters and also defines the color of the cluster. (with mask 1; $p < 0.001$, Vox / Cl ≥ 5).

In a direct comparison (Figure 3.3), normosmic participants showed higher activations than hyposmic subjects in olfactory regions such as the left anterior cingulate and right OFC. However, hyposmic subjects showed larger activation in three areas of the limbic system; the right posterior cingulate gyrus, left posterior cingulate gyrus and the right parahippocampal gyrus.

For more details on activation differences within and between patient comparisons see Table 3.2.

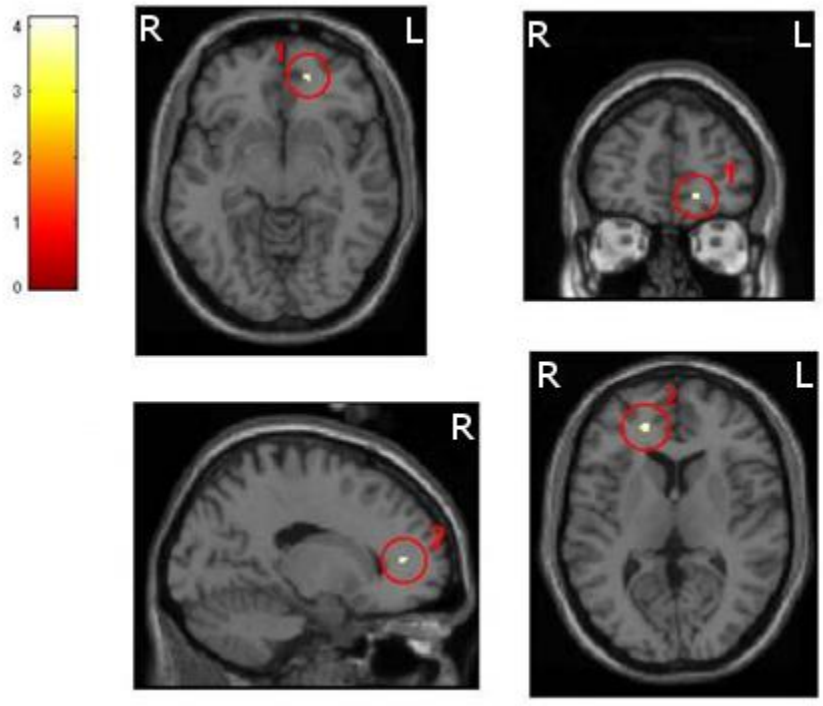

Figure 3(a). Normosmic against hyposmic subjects: The Figure shows larger activations in the left anterior cingulate and right OFC for normosmic subjects. The red ring 1 marks the voxel

clusters in the left limbic sheet (coordinates: x: -18 mm, y: 44 mm, for example: 8 mm) and the ring 2 in the right OFC (coordinates: x: 16 mm y: 48 mm, e.g. : -8 mm). The scale represents the t-value of the voxel clusters and also defines the color of the cluster (with mask, p <0.001, Vox / Cl ≥ 5).

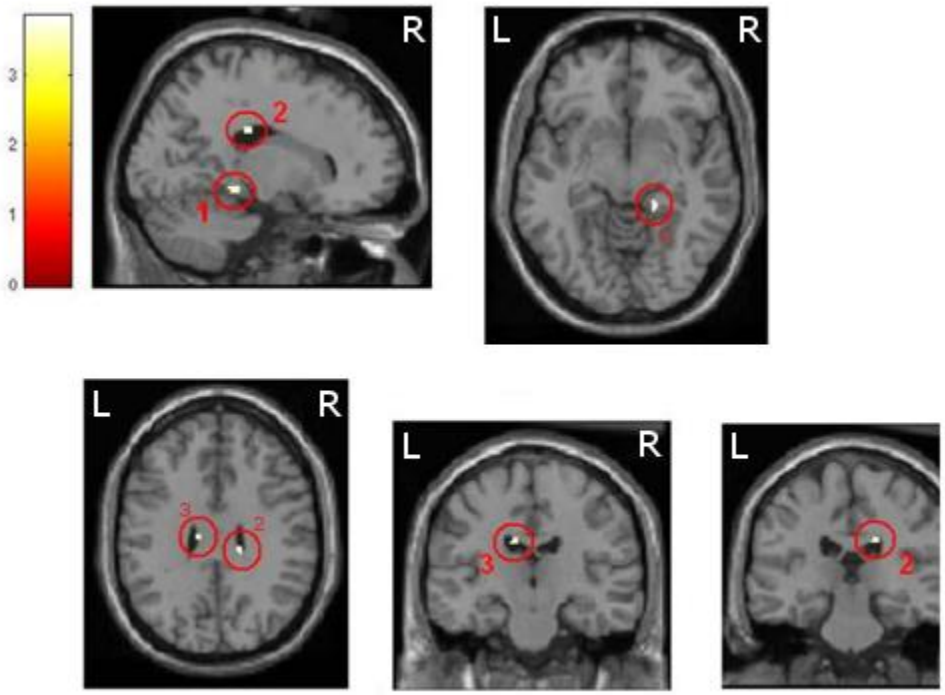

Figure 3(b). Hyposmic against normosmic subjects: The Figure shows larger activations in three areas of the cingulate cortex for hyposmic subjects. The red ring 1 marks the voxel clusters in the right parahippocampal gyrus (coordinates: x: 18 mm, y: -36 mm, eg: -8 mm), ring 2 in the right posterior cingulate gyrus (coordinates: x: 18 mm, y: -26 mm, eg: 30 mm) and ring 3 in the left posterior cingulate gyrus (coordinates: x: 12 mm, y: -18 mm, eg 28 mm). The scale represents the t-value of the voxel clusters and also defines the color of the cluster. (with mask, p <0.001, Vox / Cl ≥ 5).

Table 2. Comparison between blocks and patient groups for healthy and hyposmic subjects.

	Between Blocks (Odor - No Odor)									
	Normosmia					**Hyposmia**				
Brain Areas (Hemisphere)	**x**	**y**	**z**	**Voxel**	**t-score**	**x**	**y**	**z**	**Voxel**	**t-score**
Orbital frontal cortex (L)	-44	46	-4	39	5.75	-36	34	-8	6	3.50
Amygdala (L)	-24	0	-20	7	3.87	-	-	-	-	-
Insula (L)	-40	16	-2	9	3.68	-36	8	-10	18	4.31
Parahipppocampal gyrus (L)	-26	-52	4	8	3.66	-16	-12	40	5	3.67
Inferior frontal gyrus (L)	-40	24	-16	6	3.67	-	-	-	-	-

	Between Groups									
Anterior cingulate (L)	-18	44	8	14	3.98	-	-	-	-	-
Orbital frontal cortex (R)	16	48	-8	6	3.72	-	-	-	-	-
Parahipppocampal gyrus (R)	-	-	-	-	-	18	-36	-8	10	3.83
Parietal cingulate (L)	-	-	-	-	-	-12	-18	28	8	3.63
Parietal cingulate (R)	-	-	-	-	-	18	-26	30	15	3.60
Precuneus (R)	-	-	-	-	-	6	-52	10	5	3.54

3.4.Discussion

As expected, healthy subjects showed brain activity in regions that are associated with olfactory processing such as the amygdala, OFC, insula and limbic system. This observation confirms several PET and fMRI studies that show similar regions activated during odor stimulation (Sobel et al. 1998; Zald and Pardo 1997; Zald and Pardo 2000; Zatorre et al. 1992). Hyposmic subjects showed activations for similar brain regions such as the left insular and OFC; however, these activations were substantially weaker. Decreased activations may be due to decreased olfactory perception, where hyposmic subjects were only able to identify both odors 10% of the time and intensity ratings were much lower than in healthy subjects. Similarly, Levy et al. (Levy et al. 1998) presented three odors (pyridine, menthone, and amyl acetate) to eight patients with hyposmia during an fMRI paradigm. In comparison to 17 healthy subjects undergoing similar studies, they showed that brain activation was lower in each section of the olfactory cortex in hyposmic patients, varying one-third to one-half that of normal subjects, and significant mean activation differences were gathered for six of the nine individual brain sections studied. Additionally, their study showed forward processing activation centers of the CNS such as the frontal and temporal cortex were much less activated or even with no activation in patients compared to normal subjects. Our study supports these observations with a direct comparison of healthy and hyposmic patients. An explanation for differences could be structurally related in

which various volumetric changes in the brain may explain some of the reduction of stimulus response in higher processing functions. For instance, several studies have shown that reduced olfactory function may be associated with a reduction of olfactory bulb volume and that this structural reduction is more pronounced the longer an olfactory disorder persists (Goektas et al. 2009; Haehner et al. 2008; Mueller et al. 2005; Rombaux, Duprez, and Hummel 2009; Rombaux et al. 2010). Reduced olfactory perception, and thus reduced odor pleasantness and intensity, may also explain the absence of amygdala activations in hyposmic patients (Winston et al. 2005).

Direct comparison of the two subject groups provides more detail into odor processing similarities and differences. Overall, all subjects showed similar areas of activation since both groups still had a sense of smell although functioning at different levels. However, healthy subjects showed larger activation in the central olfactory processing areas right OFC and left cingulate. Similarly, other studies have shown reduced response within the frontal areas and cingulate regions of the limbic system when comparing hyposmic and healthy subjects (. Furthermore, in our study hyposmic subjects showed significantly more activation across the posterior cingulate and the surrounding regions. This brain region is highly involved in memory-odor associations which are formed in adolescence and remembered over a long time (Arshamian et al. 2013; Chu and Downes 2000; Herz 2004). In this study, the average duration of olfactory dysfunction was around 2 years, raising the point that subjects had ample time to associate odors with memory and these memory-odor associations may be used more frequently to compensate for olfactory loss. For instance, Levy et al. (Levy et al. 1999) asked 21 normal subjects to imagine odors of banana and peppermint and then actually smell the corresponding odors while using multislice FLASH MRI to measure their responses. Anterior to posterior temporal brain regions were activated for both imagined and actual odors were present; however,

imagined odors showed less activation than the response to the actual odor. Additionally, this study performed the same test with two subjects with hyposmia that showed an opposite trend where imagined odors had higher activations than the actual odors. Thus, this anecdotal report indicates that the retrieval of odor memories in the expectation of an odor could constitute higher memory processing while underperforming in olfactory processing. More specifically, the right parahippocampal gyrus (PHC) is involved in working memory and may be used as a temporary storage system for the entrance and retrieval of information from episodic memory, termed episodic buffer (Axmacher et al. 2008; Luck et al. 2010). Arshamian et al. (Arshamian et al. 2013) support this juncture that odor evoked autobiographical memories (OEAMs) result in more activity in the parahippocampus. Their study also showed increased activation from OEAMs in the precuneus which relates to visual vividness. Furthermore, hyposmics showed lateralized activation of the posterior cingulate gyrus and this brain region has consistently been activated during standard and autobiographical memory retrieval (Maddock, Garrett, and Buonocore 2001).

Similarly, the posterior cingulate has been associated with semantic memory processes and the strength of its BOLD response increases with continual rehearsal of episodic details to help create more vivid memories (Binder et al. 2009; Bird et al. 2015). In our study, hyposmic patients were aware that an odor was being presented, and having partial loss, may have increased their engagement to explicitly recall the odor identity with past information. Therefore, motivational differences may exist between healthy and hyposmic patients with the later showing increase activation as a result of higher motivation to actively smell and identify an odor. For instance, a common psychophysical method to assess olfactory function is the University of Pennsylvania Smell Identification Test (UPSIT) which asks subject to scratch paper strips

containing a microencapsulated odor and rate its intensity. Doty and colleagues (Doty, Genow, and Hummel 1998) analyzed the density of marking on 1680 such strips from tests administered to 42 anosmic, hyposmic and normosmic subjects and reported that hyposmic participants attempted to increase perceived intensity of odor by scratching the scent strips more vigorously than the other two groups.

Findings from the present study add to the limited information concerning differences among individuals having partial loss of olfactory sense and their healthy counterpart; however, it is important to note limitations of this study. For instance, the hyposmic group under examination consisted of only women. In many psychophysical tests women have shown better olfactory function than men, regardless of age and ethnic background (Doty et al. 1984; Hummel et al. 2007; Landis, Konnerth, and Hummel 2004) while several PET and MRI studies report no gender differences in activation areas of central olfactory processing (Bengtsson et al. 2001b; Levy et al. 1997; Savic 2005; Yousem et al. 1999). Additionally, participants in both groups had an average age above 55 years. Here, despite the equal age distribution on both groups, a certain age effect is possible since olfactory performance declines as age increases (Doty et al. 1984; Hummel et al. 2007; Murphy 2002) including anatomical and physiological changes (e.g. volume of olfactory bulb or number of olfactory receptors) (Conley et al. n.d.; Cowan and Roskams 2002). Lastly, a key limitation to this study is the hyposmics patients sampled were not homogenous in diagnosis (consisting of patients with olfactory loss due to trauma, viral infections and idiopathic causes). Due to these study caveats, results should be interpreted with some caution and additional studies should be performed to examine olfactory function of normal and hyposmic patients.

4. Chapter 3: Processing of unimodal and bimodal odors

4.1. Introduction and objective

The perception of objects may be represented by a single sense, but it typically incorporates other senses to provide more information. For instance, an object's shape can be determined through our senses of touch or vision; however, using both senses gives us more information about the object. Despite the multiple brain routes taken by these senses, we perceive a single representation of the object through the process of multisensory integration. Similarly, natural odors represented to the olfactory system typically interact with more than one sense to relay additional information about the encountered stimuli. Here, an odorant interacts with both the olfactory and the trigeminal systems (Doty et al. 1978).

Olfactory and trigeminal systems interact during chemosensory perception which can be shown on perceptual and neural levels. For instance, the intensity of trigeminal stimuli (CO_2) increases when perceived together with an olfactory stimulus (H_2S or vanillin) (Kobal and Hummel 1988; Livermore, Hummel, and Kobal 1992), and individuals with an impaired or absent sense of smell perceive trigeminal stimuli to a lesser degree than those with a healthy olfactory system (Hummel et al., 1996).

A pure odorant (vanillin) elicits activity in typical primary and secondary olfactory cortex areas such as the insula, amygdala and piriform cortex, whereas bimodal odors (e.g., acetone which stimulates both olfactory and trigeminal systems) induce widespread activation of brain regions including the insula, claustrum, anterior cingulate cortex, somatosensory cortex, cerebellum, thalamus, hypothalamus and pons/medulla (Savic, Gulyás, and Berglund 2002). Furthermore, weaker activations are found for trigeminal stimuli (e.g. CO_2) in anosmic people compared to healthy individuals in typical nociceptive areas (Albrecht et al. 2010a) including the

somatosensory cortex, prefontal cortex and insula (Boyle, Frasnelli, Gerber, Heinke, & Hummel, 2007; Boyle, Heinke, Gerber, Frasnelli, & Hummel, 2007; Iannilli, Gerber, Frasnelli, & Hummel, 2007).

The influence of trigeminal stimuli on the perception of odors has been less studied. Here, olfactory thresholds (for the rose-like odor phenyl ethyl alcohol) decrease with prior exposure to trigeminal stimuli (allyl isothiocyanate) (Jacquot, Monnin, and Brand 2004b); conditioning with a trigeminal stimulus can increase olfactory event-related potentials (ERP) (Bensafi et al. 2007).

Furthermore, neural activations in response to trigeminal or olfactory stimuli of different intensities has only been studied for unimodal stimuli (Bensafi, Iannilli, Gerber, & Hummel, 2008). Therefore, the current study was designed to explore the perceptual and central-nervous activations in response to pleasant bimodal odors using functional magnetic resonance imaging (fMRI).

4.2. Material and methods

4.2.1. Participants and stimuli

Sixteen healthy individuals, ten females and six males (mean age 25.9 years, sd 4.5), volunteered to participate in the study. All participants were non-smokers and right-handed as established by means of the Edinburgh Inventory (Oldfield 1971). None of the women were pregnant, and none of the participants had significant health problems (e.g. kidney failure) that may be associated with disorders of olfactory function, nor any acute or chronic inflammation of the nose and paranasal sinuses. Each individual was assessed for olfactory and trigeminal function with the "Sniffin' Sticks" test battery and the menthol lateralization test, respectively (Frasnelli, Hummel, Berg, Huang, & Doty, 2011; Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). All

participants scored in the healthy range for both olfactory and trigeminal tests. Additionally, subjects reported no claustrophobia and were able to undergo MRI examinations. The study design met the requirements of the Declaration of Helsinki and had been approved by the Ethics Committee of the Medical Faculty Carl Gustav Carus at the Technical University of Dresden (EK394102014).

Two bidmodal odors were chosen, strawberry and orange odor (at 10% concentration) with a "cooling" trigeminal component (Coolact, Takasago International Corp, Tokyo, Japan) at sub- and suprathreshold concentrations based on individual thresholds to coolact. Coolact was used since it produces a pleasant trigeminal sensation with minimal odor perception. Stimuli were presented to the right nostril using a computer-controlled air-dilution olfactometer with multiple channels for each odorant (Sommer et al. 2012). Right-nostril stimulation was chosen because of evidence indicating that the right hemisphere seems to be more strongly involved in aspects of the processing of olfactory and trigeminal chemosensory information than the left hemisphere (Iannilli et al. 2007; Lübke et al. 2012; Zatorre et al. 1992).

The experiment, which lasted approximately 60 min, comprised six conditions presenting each odor alone and with subliminal and supra-threshold concentrations of coolact. For fMRI acquisition, a block design was applied, with six alternating periods of a condition and odorless air (stimulus duration 1 s, interstimulus interval 2 s; duration of each period of stimulation 20 s) within each session. One condition was set for each session, and the session odor was randomized per individual. After each of the 6 sessions, subjects verbally reported intensity and pleasantness of the stimuli. Intensity was rated along a scale between 0 (not perceived) and 10 (extremely strong), while the hedonics scale ran from -5 (very unpleasant) through 5 (very pleasant).

4.2.2. fMRI acquisition

A 3 T MRI scanner (Siemens Verio, Erlangen, Germany) and an eight-channel receiver head coil were used for image acquisition. A gradient echo T2*-sensitive echo planar imaging (GE-EPI) sequence was employed (TR 2500 ms, TE 40 ms, image matrix 64x64, in-plane resolution 3 mm, through-plane resolution 3.75 mm). Images were acquired in the axial plane oriented parallel to the planum sphenoidale to minimize artifacts. A total of 96 functional volumes per session in thirty-three slice locations (covering the entire head) were acquired per session. A full brain T1-weighted turbo FLASH 3D-sequence was acquired to overlay functional data (TR 2180 ms, TE 3.93 ms, slice thickness: 1 mm).

4.2.3. fMRI data processing

Pre- and post-processing of the data was performed using SPM8 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, University College London, London, UK). Functional images were motion corrected and coregistered with the respective anatomical images, normalized (to MNI template) and smoothed (7*7*7 mm^3 FWHM Gaussian kernel). Alternating periods of condition and odorless air were contrasted sessionwise for each subject, and the resulting data fed into group analyses.

A factorial design was created with *odor* (orange and strawberry) and *coolact level* (no coolact, subliminal, supra-threshold) as within subject factors. Comparisons were calculated for orange and strawberry stimuli separately and pooled, contrasting zero (no coolact) vs. 1 (subliminal coolact), 1 vs 2 (supra-threshold coolact), and zero vs. 2, and vice versa. Areas of significant activation underwent ROI analysis for areas known to be relevant to olfactory and trigeminal processing [orbitofrontal cortex (OFC), thalamus, postcentral gyrus, insula, cerebellum, and amygdala] and multisensory processing [superior temperal gyrus and cingulate

cortex]. The cingulate cortex was further partitioned to its anterior (ACC), medial (MCC) and posterior (PCC) parts and a mask for the medioldorsal part of the thalamus was also created. All masks were created using the "automated anatomical labeling (aal)" atlas (Tzourio-Mazoyer et al. 2002), embedded in WFU PickAtlas 2.4 software (Maldjian et al. 2003), except for the orbitofrontal cortex [defined according to the criteria described in (Kahnt et al. 2012)] and the mediodorsal thalamus [defined by (Mavridis 2014)]. For ROI analysis, thresholds were set at $p < 0.005$.

Additionally, psychophysical data were analyzed with the SPSS software (vs. 23; SPSS Inc., Chicago, Ill., USA) using a mixed ANOVA with either hedonic or intensity ratings for each odor as the response to coolact level while the participant was set to a random predictor.

4.3. Results

4.3.1. Psychophysics

According to the ANOVA (see Figure 4.1), the intensity of the strawberry odor significantly increased linearly with more coolact ($F[2,28]=4.52$, $p=0.02$). A similar, but non-significant trend was seen with the orange odor ($F[2,28]=2.79$, $p=0.078$). No significant difference to hedonic ratings by coolact level were shown for either strawberry or orange odor ($p=0.27$ and $p=0.82$, respectively); however, both were on average perceived as pleasant.

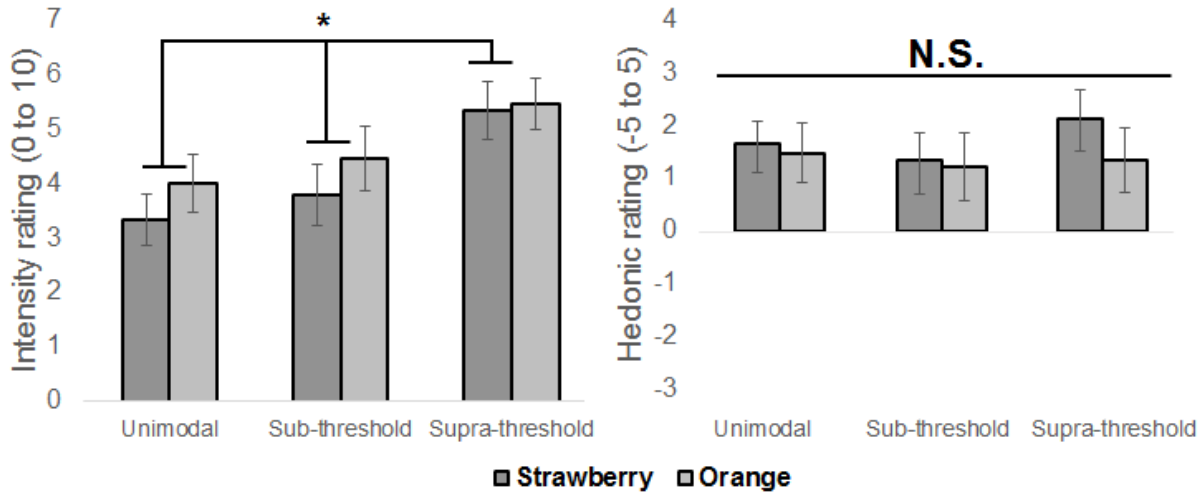

Figure 4.1. Intensity and hedonic ratings for each odor at unimodal (0) and bimodal conditions [sub-threshold (1) and supra-threshold (2) trigeminal concentrations] (±standard error; * - $p<.05$; N.S. – not significant).

4.3.2. Neural activations among unimodal and bimodal odors

To identify the neural substrates across conditions, odorants (strawberry and orange) were pooled. MNI coordinates (x, y, z) of activated brain areas and statistical t values are presented in parentheses. Looking at all activations from the factorial design, most voxels were activated during sub-threshold bimodal odor processing (951 voxels) followed by the supra-threshold bimodal odor condition (679 voxels). The largest significant activations for the subliminal bimodal odor were located bilaterally in the OFC (, left: -32, 50, 0, t = 4.23; right: 28, 38, 6, t = 5.02; see Figure 4.2).

Reviewing the results from ROI analysis (Table 1), for the unimodal condition there were significant activations within the right thalamus when contrasted with the subliminal bimodal (10, -24, 16, t = 2.93) and the left cerebellum (-38, -58, -32, t = 3.6), right thalamus (14, -6, 4, t = 3.0) and left MCC (-12, 16, 34, t = 2.82) when contrasted with the suprathreshold bimodal

condition. No other ROIs exhibited differences. The sub-threshold bimodal condition contrasted by unimodal condition showed activations in most ROIs except amygdala and superior temporal gyrus. Bilateral activations were found for the insula (left: -42, 6, 8, t = 3.34; right: 46, 6, 6, t = 4.13), cerebellum (left: -4, -48, -16, t = 3.65; right: 22, -56, -24, t = 3.73), and MCC (left: -8, 4, 34, t = 3.64; right: 4, -12, 32, t = 3.58). Furthermore, significant activations were shown in the left OFC (-34, 52, -2, t = 3.59), ACC (0, 4, 28, t = 3.75), right thalamus (9, -26, 0, t = 3.1) and right postcentral areas (54, -28, 52, t = 3.18). Supra-threshold stimuli contrasted by unimodal stimuli showed bilateral activations within the cerebellum (left: -14, -40, -24, t = 3.45; right: 12, -56, -16, t = 4.33) and MCC (left: -4, -6, 40, t = 3.42; right: 12, -18, 44, t = 3.31) while other significant activations were shown in the right insula (38, 20, -6, t = 4.13), right postcentral gyrus (18, -36, 72, t = 3.85), left thalamus (-22, -32, 4, t = 3.45), right superior temporal gyrus (52, 0, -10, t = 3.26) and left ACC (-4, 46, 16, t = 3.06).

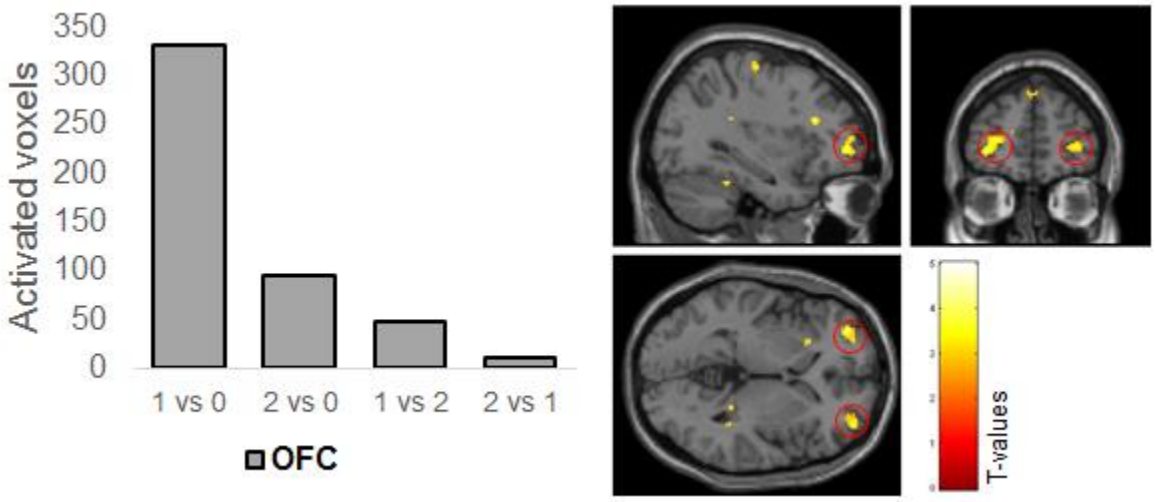

Figure 2. OFC activations during bimodal odor stimulation (condition 1 vs 0). Left: Voxel count from significantly activated OFC clusters for sub-threshold (condition 1 vs 0), supra-threshold (2 vs 0), integration (condition 1 vs 2) and intensity modulation (condition 2 vs 1) conditions;

largest activations were located bilaterally for sub-threshold bimodal stimulation. Right: fMRI results for sub-threshold bilateral OFC activations.

Table 4.1. Significant brain activations based on ROI analysis for contrasts between unimodal and bimodal conditions.

	MNI Coordinates (mm)				
Brain Regions (Hemisphere)	**x**	**y**	**Z**	**Voxel Count**	**Peak T**
Unimodal - sub-threshold					
Thalamus (R)	10	-24	16	7	2.93
Unimodal - supra-threshold					
Cerebellum (L)	-38	-58	-32	14	3.6
Thalamus (R)	14	-6	4	11	3
MCC (L)	-12	16	34	7	2.82
Sub-threshold - unimodal					
Insula (R)	46	6	6	25	4.13
ACC	0	4	28	18	3.75
Cerebellum (R)	22	-56	-24	23	3.73
Cerebellum (L)	-4	-48	-16	11	3.65
MCC (L)	-8	4	34	28	3.64
OFC (L)	-34	52	-2	19	3.591
MCC (R)	4	-12	32	11	3.58
Insula (L)	-42	6	8	9	3.34
Postcentral Gyrus (R)	54	-28	52	7	3.18
Thalamus (R)	9	-26	0	9	3.1
Supra-threshold - unimodal					
Cerebellum (R)	12	-56	-16	87	4.33
Insula (R)	38	20	-6	35	4.13
Postcentral Gyrus (R)	18	-36	72	29	3.85
Cerebellum (L)	-14	-40	-24	15	3.45
Thalamus (L)	-22	-32	4	14	3.45
MCC (L)	-4	-6	40	9	3.42
MCC (R)	12	-18	44	18	3.31
Superior Temporal Gyrus (R)	52	0	-10	10	3.26
ACC (L)	-4	46	16	11	3.06

4.3.3. Encoding of Trigeminal Component in Bimodal Odors

To look at activations related to integration of trigeminal and odor components, sub-threshold stimuli were contrasted by supra-threshold stimuli (condition 1 vs. 2; Table 2). The largest activated clusters appeared in the left OFC (-34, 50, -2, t = 3.73) and the right cerebellum (26, -76, -24, t = 3.45) while other significant ROIs were the left thalamus (-8, -34, 6, t = 3.36), right ACC (2, 10, 24, t = 3.28), and left MCC (-12, 0, 40, t = 3.28).

To identify neural mechanisms during bimodal intensity encoding a contrast between supra-threshold and sub-threshold (condition 2 vs 1) was created (Table 4.2). The largest activations were found in the left MCC (-4, 14, 40, t = 3.89) and right cerebellum (14, -38, -18, t = 3.68) while bilateral activations were seen in the insula (left: -36, 12, -14, t = 3.32; right: 44, 6, -10, t = 3.28) and superior temporal gyrus (left: -48, 2, -4, t = 2.86; right: 50, 0, -12, t = 3.23).

Table 4.2. Significant brain activations based on ROI analysis for contrast between bimodal conditions with trigeminal stimulus at sub or supra-threshold concentrations.

	MNI Coordinates (mm)				
Brain Regions (Hemisphere)	**x**	**y**	**z**	**Voxel Count**	**Peak T**
Sub-threshold - supra-threshold					
OFC (L)	-34	50	-2	19	3.73
Cerebellum (R)	26	-76	-24	15	3.45
Thalamus (L)	-8	-34	6	10	3.36
ACC (R)	2	10	24	5	3.28
MCC (L)	-12	0	40	9	3.28
Supra-threshold - sub-threshold					
MCC (L)	-4	-14	50	26	3.89
Cerebellum (R)	14	-38	-18	30	3.68
Insula (L)	-36	12	-14	11	3.32
Insula (R)	44	6	-10	12	3.28
Superior Temporal Gyrus (R)	50	0	-12	5	3.23
OFC (L)	-4	40	-10	6	3.2
Postcentral Gyrus (R)	6	-38	74	6	3.05
Superior Temporal Gyrus (L)	-48	2	-4	5	2.86

4.4. Discussion

In natural settings, we are continuously bombarded with smells, most of which activate the trigeminal nerve in addition to the olfactory. In our study, we measured the neural response to a pleasant bimodal odors, combining an odorant with a cooling stimulus.

4.4.1. Neural activations among unimodal and bimodal odors

Research to date has revealed that additional circuitry is activated during odor processing when a trigeminal stimulus is present. For example, Boyle et al. (2007) presented individuals with a relatively selective olfactory stimulus (phenyl ethanol), a trigeminal stimulus (CO_2), and a mixture of the two. The olfactory stimulus activated areas common to olfactory processing [piriform cortex, insula, and orbitofrontal cortex (OFC)] while the trigeminal stimulus activated somatosensory brain areas (cerebellum, thalamus, and postcentral gyrus) in addition to olfactory areas. However, the mixture of both stimuli activated more brain areas than the sum of its individual components (Boyle et al., 2007). The current results support these findings while showing additional brain areas to be activated before the trigeminal component is perceived (e.g. present at a sub-threshold level). For instance, bimodal processing at this level of concentration showed the largest activations, varying across most regions of interest (OFC, insula, thalamus, cerebellum, postcentral gyrus and cingulate cortex). Bilateral activations of the OFC were the largest with other large activations bilaterally in the insula, cerebellum and parts of the cingulate cortex. Furthermore, functional overlap between the olfactory and trigeminal systems has been seen in many of these brain regions (Albrecht et al., 2010; Hummel et al., 2009; Hummel, Iannilli, Frasnelli, Boyle, & Gerber, 2009). Trigeminal brain activations are often more pronounced than their olfactory counterparts (Bensafi et al., 2008; Boyle et al., 2007) and both systems encode qualities differently (Bensafi et al., 2008).

The cingulate cortex and insula have been proposed as multi-integrative structures during concurrent processing of chemosensory stimuli (Boyle et al., 2007; Österbauer et al., 2005; Veldhuizen & Small, 2011), and additionally evaluate the congruency and pleasantness of chemosensory mixtures within posterior ACC and the right insula (Bensafi et al., 2012, 2013; Small et al., 2004; Vogt, 2005). For instance, one study exposed 23 individuals to two different bimodal odors (CO_2 combined with either the smell of orange or the smell of rose) while their brain activations were evaluated using fMRI. Individuals who experienced the mixtures as pleasant showed significant activations in the posterior ACC and insula lateralization, with the right and left insula activating for the pleasant and unpleasant mixture, respectively (Bensafi et al., 2012). Interestingly, this study also points to several studies showing hemispheric asymmetry, in which the right hemisphere seems to specialize for pleasant stimuli (Anderson et al. 2003; Kollndorfer et al. 2015; Sela et al. 2009). In our study, both bimodal conditions were rated as pleasant and similar areas of activation were observed. Undetected levels of trigeminal sensation within a mixture showed bilateral insula activations with the right insula showing the largest activation. Also, it was only the right insula that showed neural activity when the trigeminal component in the mixture was at a perceptual concentration. Furthermore, the ACC showed activations for bimodal odors at both trigeminal concentrations.

Another interesting finding is the role of the thalamus during bimodal odor processing. The thalamus, which is part of the trigeminal pathway, is largely bypassed by early olfactory processing; however, several studies have shown that the thalamus plays a significant role in human olfaction, especially in higher-order thalamic relays (Courtiol and Wilson 2015; Plailly et al. 2008a, 2008b; Sela et al. 2009). For instance, the thalamus directly receives input from the primary olfactory cortex and has reciprocal connections with the OFC, leading to its involvement

in odor perception, discrimination, learning, and attention [for a review see (Courtiol and Wilson 2015)]. We add evidence to this notion, showing significant activations within the thalamus during unimodal and bimodal odor processing with additional activation of the OFC processing the later. Furthermore, the contrast between sub- and suprathreshold bimodal conditions reveals that most of the activations happens before the trigeminal agent is perceived which might point to subliminal attentional processing to the added chemosensory stimulus to consciously analyze it. In other words, although perceptually unware, the thalamus may be mediating attention towards the presence of two stimuli to help guide processing of discrimination and identification. Similarly, in a cross-modal study, individuals were presented with (or without) an odor and with (or without) a tone, and asked to selectively attend to one modality. Attention to odor significantly modulated neural coupling within the indirect olfactory pathway, strengthening thalamus–OFC connectivity (Plailly et al. 2008a). Similarly, thalamic lesions contribute to an impairment in olfactory perception, significantly affecting odor identification (Sela et al. 2009).

4.4.2. Encoding of Trigeminal Component in Bimodal Odors

Although olfactory and trigeminal systems have distinct peripheral pathways, they share central processing areas such as the orbitofrontal cortex, insula and secondary somatosensory cortex (Albrecht et al., 2010; Boyle et al., 2007). Similarly, many of these areas and other areas involved in multisensory integration have been suggested as integration points for these two systems during bimodal odor processing (Bengtsson, Berglund, Gulyas, Cohen, & Savic, 2001; Bensafi et al., 2012; Boyle et al., 2007; Savic et al., 2002). If integration does happen at the subliminal stages of bimodal processing, our results agree with previous findings that the OFC is involved with integration, but in contrast to many studies, other overlapping brain areas are not –

or at least not at this stage of processing. Instead, our data suggests early integration may happen within the cingulate, yet as mentioned earlier this activation may be related to valence. Alternatively, integration may happen at the OFC and thalamus independently or interdependently. It is known that the thalamus projects massively to the prefrontal cortex (Courtiol and Wilson 2015) while receiving input from the primary olfactory cortex (Illig 2005) and the trigeminal nerve (Hummel, Iannilli, Frasnelli, Boyle, & Gerber, 2009), and therefore may be involved in integrating the two systems with the OFC.

Intensity encoding of pure olfactory and trigeminal stimuli has been studied while less attention has been given to intensity encoding for bimodal odors. For example, it is well known that structures like the amygdala, cerebellum, entorhinal cortex, visual and frontal regions play an integrative role in modulating the intensity of an olfactory stimulus, with the former doing so independently of valence (Anderson et al., 2003; Bensafi et al., 2008; Rolls, Kringelbach, & de Araujo, 2003; Winston, Gottfried, Kilner, & Dolan, 2005). Meanwhile, only one fMRI study has measured the intensity encoding for a trigeminal stimulus and reveals a less complex network than olfactory encoding (Bensafi et al., 2008). Participants were presented with an olfactory (H2S) and trigeminal stimulus (CO_2) at low (9% and 37%, respectively) and high (27% and 49%, respectively) concentrations. Trigeminal intensity modulation from low to high revealed specific activations in sub-regions of the cingulate cortex (anterior, ventral, and posterior). In our study, we modulated the intensity of the trigeminal component from sub to supra-threshold levels in a bimodal odor, which in turn increased the overall intensity of the odor. Our data show intensity encoding during bimodal processing also engages the medial area of the cingulate cortex, but not the anterior and posterior. Similarly, other areas specific to the somatosensory system (e.g. postcentral gyrus) activate during trigeminal concentration changes. Additionally,

since the intensity of the overall substance changes, thus involving olfactory perception, the complexity of encoding increases with olfactory-related brain areas being activated, e.g., the cerebellum and areas typically associated with integration such as the insula and the superior temporal gyrus; however, no activation from the amygdala was seen. It is important to note that unlike odor intensity, trigeminal intensity encoding has not been shown to be independent of valence; therefore, current results may differ due the pleasant nature of our trigeminal stimulus compared to CO_2 which produces a “stinging” rather than a “cooling” sensation.

5. Overall conclusion

All objects materialize in the mind by a series of events that are presented to the senses. This thesis has dealt with odor events that allow us to identify objects. Similar to the visual event of seeing a char mark on sliced bread, our nose encounters a burnt scent that travels from the nose to the brain to determine the object of interest (e.g. burnt toast). Most of the smell events encountered in the environment are complex mixtures of several odorants, many of which activate two systems in the nose. These two systems are the olfactory and trigeminal systems, and they follow many of the same principles that govern all sensory systems (e.g. habituation/adaptation) and when damaged change the way an individual perceives the world.

In our first study (Chapter 2), we defined habituation to odors as a decreased behavioral response from repeated exposure, whereas adaptation relates to the neural processes that constitute this decrease in behavioral response. As with all senses, the olfactory and intranasal trigeminal system (branches V1 and V2) continually encounters an enormous variety of odorants which is why mechanisms must exist to segment them and respond to changes. Thus far, psychophysics in combination with modern techniques of neural measurement indicate that habituation to odors, or decrease of intensity, is relatively fast with adaptation occurring more quickly at higher cerebral processes than peripheral adaptation. Similarly, it has been demonstrated that many of the characteristics of habitation apply to human olfaction; yet, evidence for some characteristics such as potentiation of habituation or habituation of dishabituation need more support. Additionally, standard experimental designs should be used to minimize variance across studies, and more research is needed to define peripheral-cerebral feedback loops involved in decreased responsiveness to environmental stimuli.

In our second study (Chapter 3), we demonstrate how individuals with impaired olfactory functionality smell the world. Individuals with partial loss of smell, called hyposmics, represent a large sector (15 %) of the population that is likely to grow with the current aging population; however, our understanding to how hyposmics centrally process odors is still not clear. Thus, we used a popular non-invasive tool, fMRI, to understand differences in olfaction processing between patients with hyposmia and healthy controls. The activations of the healthy group were localized in typical olfactory areas (insula, orbitofrontal cortex [OFC], limbic system and amygdala). The hyposmic group showed similar regions of activation (insula, OFC, limbic system), however, less activation was found in the amygdala, left anterior cingulate and right OFC, but higher activation was shown in the right parahippocampal and both the left and right posterior cingulate gyrus which are assumed to play an important role in the processing and remembrance of memories. These results indicate similar central olfactory processing among groups, yet subjects with partial loss may attempt to compensate smell impairment with odor memory or higher motivation to smell.

In our last study (Chapter 4), we designed a study to explore the perceptual and central-nervous activations in response to pleasant bimodal odors using fMRI. This was accomplished by exposing healthy subjects to odorants alone (unimodal) or with a "cooling" trigeminal component (bimodal) at sub- and suprathreshold concentrations with a portable olfactometer in a fMRI scanner. Many of the regions of interest [orbital frontal cortex (OFC), insula, thalamus, cerebellum, postcentral gyrus and cingulate cortex] were activated during bimodal odor conditions when contrasted with unimodal, and interestingly, most of these activations were seen prior to trigeminal perception (e.g. at a sub-threshold level). This includes large bilateral activations within the OFC, insula, cerebellum and parts of the cingulate cortex. Additionally,

activation of the thalamus was seen early in the stages of bimodal odor encoding suggesting its role of mediating attention towards the presence of two stimuli. Lastly, intensity encoding during bimodal processing shows overlap of previously demonstrated simple trigeminal encoding areas (MCC) and the more complex olfactory encoding areas (bilateral insula, superior temporal gyrus, OFC, and cerebellum), but not the amygdala.

These studies add to our understanding of orthonasal odor perception, and provide many new avenues of research for future studies. For instance, our first study demonstrates several principles of habituation (which was set in the 60s) that have not been tested with odors. It also discusses adaptation mechanisms, especially at the central level, that can now be explored due to emerging technologies and techniques in the field. Our second study brings attention to a growing sector of the population, those affected by partial olfactory impairment. To date, no studies have given much attention to this large segment of the population and we show neural differences that need to be explained in detail with future studies. Lastly, our third study adds more understanding on the central mechanisms taking place for the most common form of odorants in our environment – those which activates both intranasal nerves (CNI and CNV). Here, we spotlight the need to further uncover the role of the thalamus (and its indirect pathway with the OFC) in bimodal processing and multisensory integration.

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