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Olfaction in affective disorders:

an investigation of psychophysiological, behavioral and social responses

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TABLE OF CONTENT

Smell is a potent wizard
that transports you across thousands of miles
and all the years you have lived.

Helen Keller

Overview and aim of the thesis

The present research has been conducted in the framework of the POTION project (European Commission Horizon 2020 research and innovation program, grant number 824153) which has the general aim to understand the mechanism of action of chemosignal communication and exploiting the possibility to recreate synthetic human body chemosignals.

Contrary to common sense, where olfaction has been always disregarded compared to the other senses, experimental and observational evidence highlighted the prominent role the sense of smell plays in human lives. Indeed, a lack or dysfunction in its functions leads to negative consequences, reducing well-being and in general the quality of life. In **Chapter 1**, a review of the olfactory system and its functioning is provided. An attempt has been made in furnishing an overview of the mechanisms responsible for the creation of the olfactory experience, which is made not only by the perception of the molecules composing the odorants but is shaped also by metacognitive abilities (for example odor awareness), as well as the emotional state during the encoding. The evidence of a reciprocal relationship between olfactory dysfunction and depressive disorders further confirms this mechanism. However, if the olfactory disfunction is the cause or the consequence of the disorder is still far from being fully understood.

Among olfactory stimuli, recently particular attention has been directed at odors that convey social information, the so-called chemosignals, which are substantially odors produced by human (body odors). **Chapter 2** is devoted at examining the communicative functions of chemosignals, with a focus on the communication of emotions. In the field of social communication by means of body odor many steps forward have been taken, but the results are often inconsistent and sparse, and many questions are still unanswered.

Given the role of body odor in social communication, many attempts, to date, have been made to identify the brain areas involved in the processing of these signals. However, also considering the sparsity of the experimental methods used to collect and present body odors, there are no clear conclusions so far. Hence, in **Chapter 3**, I conducted a meta-analysis of neuroimaging studies with the aim to systematically review the available literature and find a common ground of brain areas involved in the processing of body odors (both neutral and emotional). In addition, a critical review of the experimental procedures and the methodologies used is provided.

During my Ph.D, I tried to better characterize olfaction in affective disorders using a comprehensive approach, starting from the simple perception of common odors and the role of metacognitive abilities in shaping the olfactory experience, to the use of emotional social odors (i.e., chemosignals) as a medium for transferring both negative (i.e., fear) and positive (i.e., happiness) emotions in order to investigate their psychophysiological and subjective effects and, finally, their use as a catalyst for treatment. In the experiments presented in the present thesis, I decided to focus on subclinical forms of affective disorders, i.e., on otherwise healthy individuals presenting symptoms of anxiety, social anxiety or depression. This choice has been made for several reasons. First of all, I believe that a deeper understanding of olfactory processing in these individuals may help to understand the initial mechanisms that caused the altered olfactory abilities and might be useful as a possible future marker of vulnerabilities. Identifying subjective, behavioral, psychophysical and psychophysiological mechanisms that may be involved in the onset and maintenance of depressive and anxiety symptoms, especially in a young population, is fundamental to prevent and treat these disorders. In addition, the study of subclinical conditions is advantageous because it allows the study of psychopathological measures related with depression and/or anxiety without any confounding factors due to the use of medications or chronicity of the disorder.

Chapter 4 and **Chapter 5** were dedicated at the investigation of the olfactory metacognitive and perceptual abilities in individuals with depressive, anxiety and social anxiety symptoms. Considering the complex connections between perception, emotion and cognition, studying olfactory abilities in individuals with affective disorders can be extremely important for the characterization of the disorders, for their prevention and treatment. Indeed, despite the strict relation widely observed between olfactory disorders and depression, the underlying factors are not yet understood. I believe that one candidate factor is the “odor awareness”: the degree of attention individuals pays to the odors. Few studies examined these meta-cognitive abilities in relation to depressive, anxiety, and social anxiety symptoms (Burón et al., 2013, 2015, 2018), and none of them considered the awareness of social odors (i.e., body odors). Similarly, the association between odor awareness and olfactory abilities in individuals with affective symptoms has not been clarified yet.

In the studies reported in Chapter 4, the focus was on the investigation of the olfactory metacognitive abilities in a healthy population with different degrees of anxiety, social anxiety and depressive symptoms. There were already questionnaires developed to explore the attention individuals pay to common odors in the environment, the importance they attribute to the sense of smell and their olfactory imagery abilities. However, no instruments were available for the study of social odor awareness. Hence, the first step was the development and validation of an instrument that enabled us to effectively study the attention individuals pay to body odors. After this first step, the second study was devoted to administering a set of questionnaires on metacognitive abilities to individuals presenting different degrees of anxiety, social anxiety and depressive symptoms. This study revealed that affective disorders predict different levels of both common odor awareness and social odor awareness, with general anxiety being linked to higher attention toward common odors, while social anxiety and depression with altered attention toward social odors.

Given these promising results, the next step, reported in **Chapter 5**, was to investigate if odor awareness can moderate olfactory abilities in healthy individuals with different degrees of anxiety, social anxiety and depressive symptoms. As expected, a reduced odor awareness proved to be a key factor in olfactory dysfunction, but only in the presence of depressive symptoms. These results provide new insight into the understanding of the underlying factors implicated in the development and maintenance of olfactory dysfunction, possibly using odor awareness as a specific treatment target in clinical settings.

Finally, since affective disorders, specifically social anxiety and depression, are characterized by impaired social functioning and, as seen in Chapter 4, by altered social odor awareness, **Chapter 6** and **Chapter 7** focused on the use of emotional body odors (both happiness and fear body odor) to investigate the processing of these odors using a psychophysiological approach (Chapter 6) as well as their potential role in a mindfulness treatment (Chapter 7). In Chapter 6, through the employment of psychophysiological measures (HD-EEG), individuals with depressive and social anxiety symptoms, as well as healthy controls, underwent a passive viewing of neutral facial expressions presented in the context of happiness body odor (i.e., body odor collected during the viewing of happiness movies), fearful body odor (i.e., body odor collected during the viewing of frightening movies), and a control condition (i.e., clean air). The results confirmed the role of body odors in modulating the processing of neutral facial expressions, however, no differences have been found between fearful and happiness body odors. Regarding the group with social anxiety symptoms, as expected, an increased affective disposition toward social stimuli presented in the context of negative body odor has been found. On the other side, the group with depressive symptoms presented both an altered subjective response toward social stimuli presented with negative odors, but also a decreased motivation and a reduced processing of social stimuli compared to healthy controls only when they are presented with the clean air. However, this effect disappeared when the faces are presented with the odors, possibly because the presence of the odors may have helped these individuals to extract the social meaning of the situation.

In Chapter 7, an attempt to use emotional body odors as a catalyst during a mindfulness treatment has been provided. Here I focused only on individuals with social anxiety symptoms, which proved to benefit from a mindfulness treatment. Results showed that a significant reduction of anxiety levels has been achieved by individuals who performed the mindfulness treatment with both happiness and fear body odors, but not with clean air. On the other side, in line with previous studies, a significant decrease in vagal tone was reported only with fear body odor.

The last chapter of this thesis, **Chapter 8**, constitutes a general discussion of the empirical studies that composed the present dissertation, providing a unique framework in the study of olfaction and affective disorders.

This brief overview sums up the content that will be discussed in more detail in each chapter of this dissertation. Each chapter of the experimental part of this thesis (except the final conclusion chapter) reports studies that has been published as scientific paper or meant to be published in scientific journals, hence they are organized as to be read independently. Therefore, the reader can find some overlap between chapters, even though they constitute a unique component in the understanding of the underlying mechanisms of olfaction and chemosensory communication, and their link to affective disorders.

PART I:

Theoretical background

CHAPTER 1

The sense of smell: from anatomy to emotions

"... a complete, comprehensive understanding of odor ... may not seem a profound enough problem to dominate all the life sciences, but it contains, piece by piece, all the mysteries." — Lewis Thomas

One of the oldest beliefs in human perception is that we, as humans, have a poor sense of smell compared to other mammalian species (McGann, 2017). The sense of smell is one of the five senses through which we perceive the world. It is considered to be the oldest sense, since it has been of essential importance for survival long before species with some form of the brain developed, allowing primitive species to find food, sexual partners but also warning against potential predators. During evolution, new senses, sight, and hearing, started to develop, along with the flourishing of the neocortex, which allowed the processing of these new and more complex signals. Even today, in humans, the perception of odors is still relayed directly in the limbic lobe, the central hub of emotion. It is this connection that makes a single sniff of a scent able to suddenly retrieve feelings, emotions, and long-forgotten memories.

1.1. Anatomy and physiology

1.1.1. Peripheral structures

The first precondition of olfactory perception is the act of sniffing, which is a reflex activity elicited by chemicals. A sniff is not a simple olfactomotor activity with the function of molecules transportation from the entrance of the nostrils to the epithelium but is the earliest stage of olfaction, as compared to eye movement in vision (Mainland & Sobel, 2006). Moreover, the airflow passing through the sniff is affected by the anatomical structure of the nose. The nasal passages of the nose are divided by the nasal septum, and each lateral nasal passage is composed of four bony outgrowths or turbinates (inferior, middle, superior, and in some cases supreme). The area of the nasal cavity responsible for olfactory perception comprises the roof of the nasal cavity, the area extending inferiorly along the septum and middle and superior turbinate (Patel & Pinto, 2014) (Fig. 1.1).

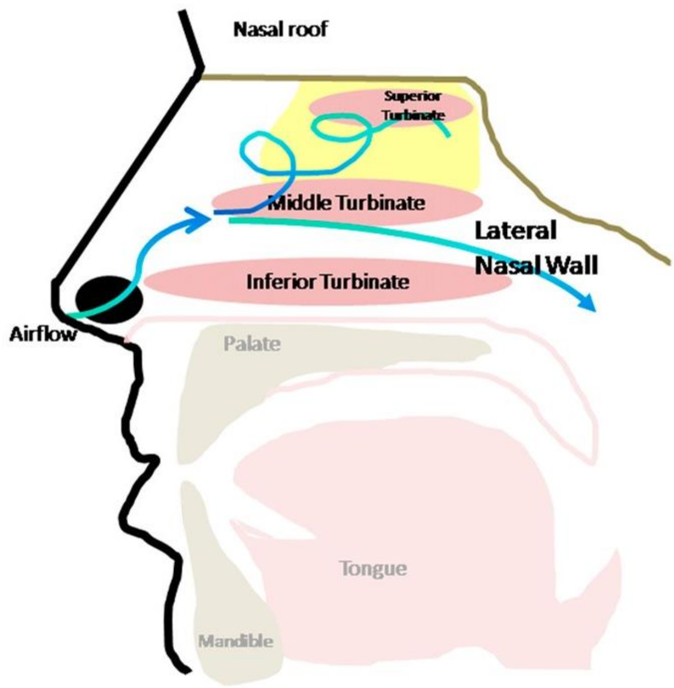

Fig. 1.1. Structure of the nasal cavity. In *yellow* is depicted the olfactory epithelium, extending from the medial surface of the middle and superior turbinates (depicted in *pink*) to the nasal roof/cribriform plate (depicted in *beige*). The airflow is transported upward toward the epithelium by turbulences. Normal airflow goes toward the nasopharynx. (Adapted from Pinto, 2011)

When an odor is sniffed, the alteration of the normal airflow results in turbulence that directs the air and, hence, the odorous molecules, up to the nasal cavity, reaching the olfactory epithelium, which is a receptor structure, where occurs the transduction of olfactory information (Fig. 1.2). In the olfactory epithelium are present different cell types, the major being: olfactory sensory neurons and their cilia, sustentacular cells, and basal cells (Pinto, 2011) (Fig. 1.3). In particular, the olfactory sensory neurons (OSNs) are single-dendrite bipolar neurons ending with a knob-like protrusion, each presenting several microvilli, called olfactory cilia. The cilia, then, spread inside a thick layer of mucus produced by secretory glands (i.e., Browman's glands) distributed throughout the epithelium (Fig. 1.3). The olfactory mucus contains odorant-binding proteins that create an ideal environment to facilitate odorant-receptor interaction. However, direct access to odorant molecules exposes OSNs to potential damage from airborne pollutants, allergens, microorganisms, etc. Several mechanisms take place to overcome this problem: the presence of the respiratory epithelium that moistens the inspired air, the secretion of the mucus that traps potential particles, and, more importantly, the replacement of the OSNs in a constant cycle of degeneration and regeneration from the basal cells (Choi & Goldstein, 2018).

In the nasal mucosa, where the odorants bind the receptors, the signal is then transmitted by an action potential that travels along the axon of the receptor cell through the cribriform plate directly into the brain, forming the olfactory nerve (cranial nerve I) (Patel & Pinto, 2014) (Fig. 1.3).

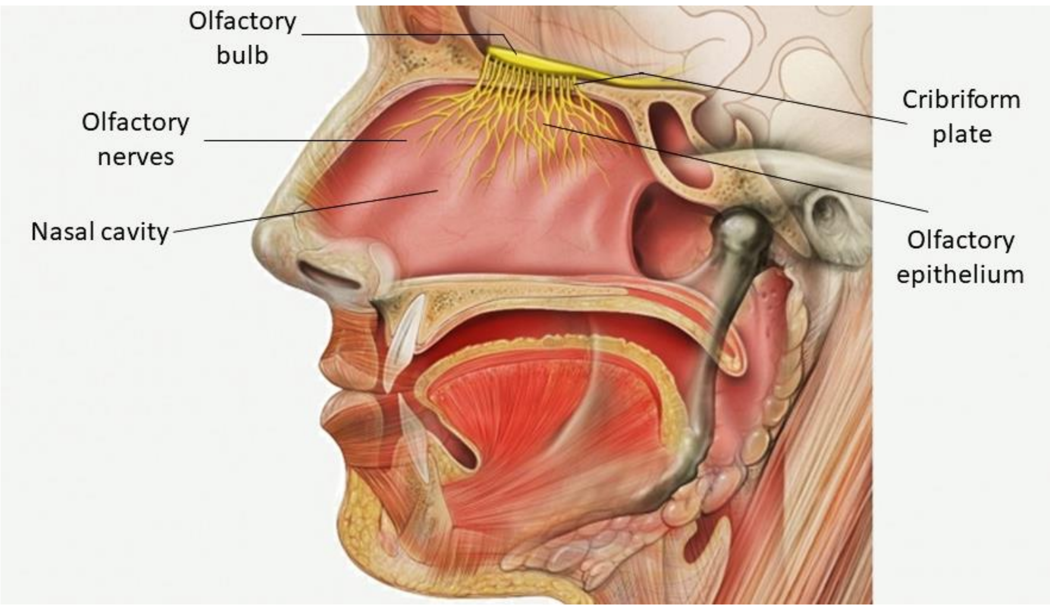

Fig. 1.2. Pictorial representation of the microanatomy of the olfactory system (adapted from Lynch, medical illustrator).

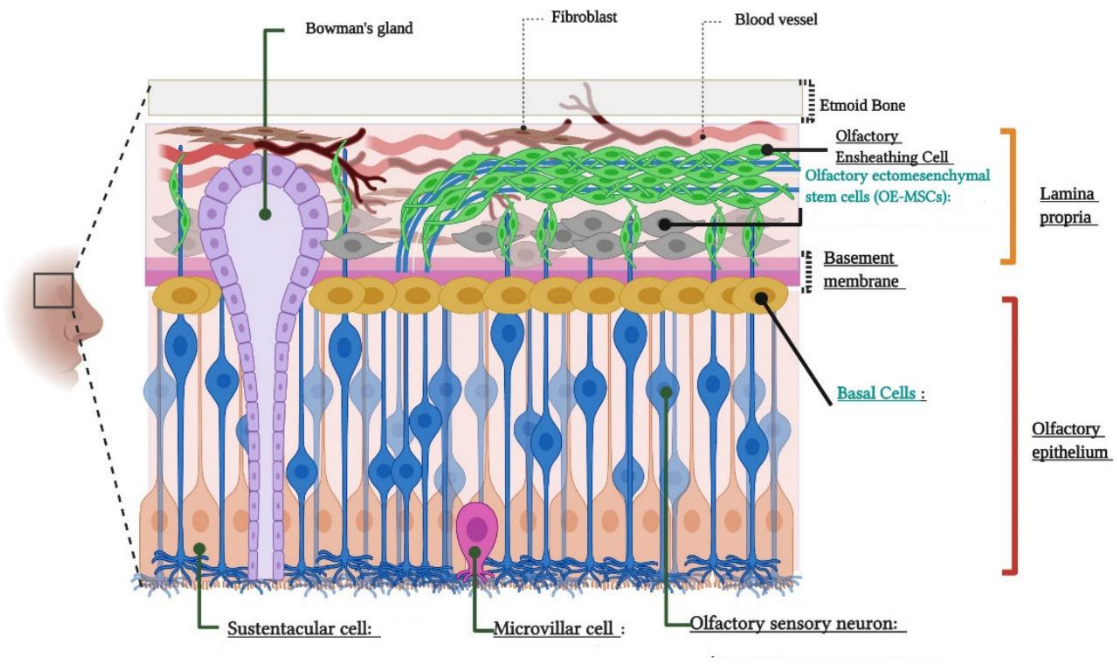

Fig. 1.3. Pictorial representation of the human olfactory mucosa (Adapted from Gomez-Virgilio et al., 2021)

1.1.2. Central structures

Olfactory bulb

In the brain, the first relay station in the olfactory system is the olfactory bulb (OB). The relatively small size of this structure compared to other animals (e.g., in mice the size of the OB is 2% of its brain volume, while in humans is about 0.1% of the brain volume; Kavoi & Jameela, 2011) has led scientists and researchers, starting from Paul Broca, to believe that humans have a poor sense of smell compared to other animals. However, despite the large difference in relative size, the absolute number of neurons is always within the same order of magnitude (i.e., around 10 million neurons) (Ribeiro et al., 2014). Because of this wrong belief, until recently, the function and importance of the olfactory bulb were largely underestimated.

The olfactory bulb receives input from the axons from the OSNs of the olfactory epithelium and sends the output through the mitral cell axons. All the input from the OSNs expressing a given receptor protein converge on a single glomerulus, thus allowing also low-intensity signals to be detected. In addition, the OB receives retrograde top-down information from higher-order brain areas in order to increase the discriminability of the odorants and the general sensitivity of the system. Moreover, it has been recently suggested that the OB already processes the valence information of the odor to select the most appropriate behavioral response (Iravani et al., 2021).

Notably, uniquely for the olfactory system, the signal can be transmitted from the OB to the other cortical areas without a thalamic relay, leading the OB to fulfil thalamic functions in the processing of other sensory stimuli. Hence, since in the OB a basal cognitive process already takes place, it can be viewed as the primary olfactory cortex, being functionally comparable to other primary sensory cortices.

The axons from the OB conjoin to form the olfactory tract, which conveys information to a set of brain areas, the piriform cortex, the entorhinal cortex, and the amygdala.

Piriform cortex

The piriform cortex is one of the most important structures in the olfactory system and is viewed as the primary olfactory cortical area (Price, 1990). In the piriform cortex an initial representation of the odorant, but also the odor object formation, takes place. More importantly, its connection to the amygdala, the entorhinal cortex, and the secondary olfactory structures affect the behavioral, cognitive, and contextual information associated with olfactory perception (Howard et al., 2009).

Entorhinal cortex

The entorhinal cortex receives input from the OB and the piriform cortex and has an output connection to the hippocampus, a key region for memory processes (Insausti et al., 2002).

Anterior cortical nucleus of the amygdala

From the olfactory bulb and the piriform cortex, the olfactory signal is sent to the amygdala and the periamygdaloid cortex for a cognitive, but also affective, evaluation of the signal. Indeed, in the amygdala seems to take place an overall emotional evaluation of the olfactory stimulus, being responsible for the coding of a combination of valence and intensity, reflecting the intensity only for emotionally salient (pleasant or unpleasant) odors (Winston et al., 2005).

Secondary olfactory cortices

The processing of the olfactory information continues in the secondary olfactory cortices: the orbitofrontal cortex (OFC), the insula, the hippocampus, the thalamus, the hypothalamus, the ventral striatum, the cingulate cortex, and the cerebellum. These areas are not specific for olfactory processing but are crucial for higher cognitive processing of odors.

In the OFC higher cognitive processes take place, creating the final conscious smell percept. The OFC is located on the ventral portion of the frontal lobe and receives inputs from the primary olfactory cortices through both the direct and indirect (via the thalamus) pathways (Price, 1990). This structure is considered a key region for secondary olfactory processing since it is responsible not only for the olfactory sensitivity ability and the discrimination tasks (Seubert, Freiherr, Frasnelli, et al., 2013) but also for the integration of information from other sensory modalities (Gottfried & Dolan, 2003).

The insula, traditionally considered the primary gustatory cortex (Veldhuizen et al., 2011), receives input from the piriform cortex, the amygdala, but also from the OFC, and it has been found to be activated by both pleasant and unpleasant odors (Rolls, 2016).

The hippocampus is a brain area strongly involved in emotion and memory processing, conveying memory information associated with odors (Price, 1990). Moreover, it seems to be involved also in the cross-modal integration of sensory stimuli (Gottfried & Dolan, 2003).

As previously mentioned, the main pathway in olfactory processing does not involve the thalamus, projecting the information directly from the olfactory bulb and the piriform cortex to the neocortex. However, it exists also an indirect pathway involving the mediodorsal thalamus, linking the primary olfactory cortex to the OFC and having the function of higher-order olfactory thalamus (Courtiol & Wilson, 2015).

The cingulate cortex, in particular the anterior part, has been found to be activated following olfactory stimulation. Hence, it seems likely it has a role in the attentional processing of odors (Soudry et al., 2011). In Fig. 1.4, a schematic representation of the primary and secondary olfactory cortices is provided.

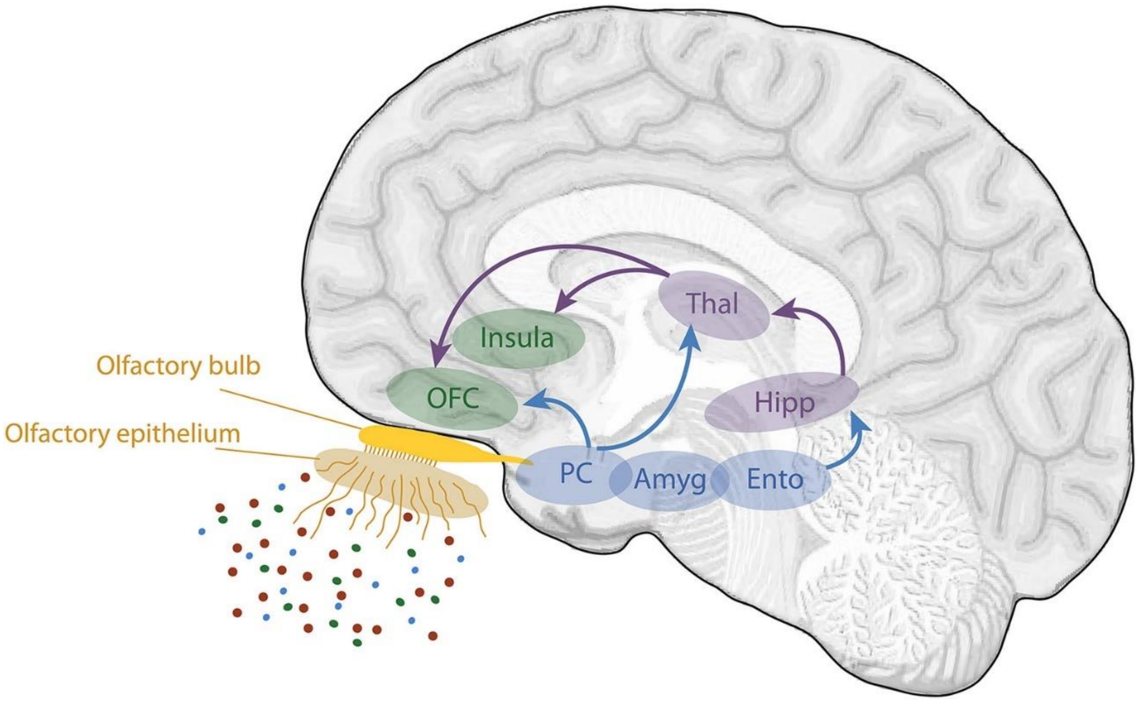

Fig. 1.4. Schematic view of the human olfactory system. The primary and secondary olfactory cortices are represented in blue and green, respectively.
Amyg, amygdala; Ento, entorhinal cortex; Hipp, hippocampus; OFC, orbitofrontal cortex; PC, piriform cortex; Thal, thalamus (from Saive et al., 2014)

1.1.3. Odorant transduction and coding

Already in the periphery, specifically in the olfactory cilia of the OSNs, the transduction of the olfactory information begins. The transduction starts when the odorant binds a specific receptor on the external surface of the cilia (Fig. 1.5). In the ciliary membranes of the OSNs, there are olfactory receptor (OR) proteins that are members of the G-protein-coupled receptor family and are encoded by a large multigene family. Hence, the binding between the odorant and the receptor can occur directly or can be mediated by the OR proteins that transport it to the receptor (Rawson, 2006).

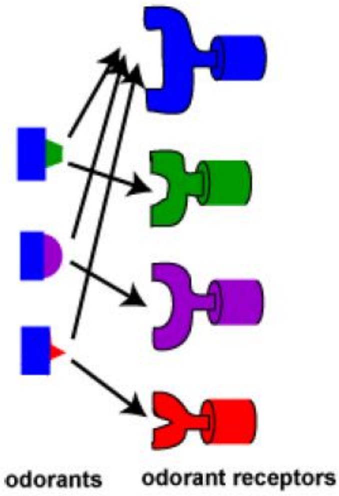

Fig. 1.5. Combinational odorant receptor coding for odors. (From Song et al., 2008)

Interestingly, despite the vast amount of OR genes (e.g., about 1500 in mice), each OSN expresses a very small number of OR genes. This notion has led to the formulation of the "one receptor – one neuron hypothesis" (Breer et al., 2017). In the same way, in humans, an individual receptor expresses only one among the approximately 350 receptors identified (Malnic et al., 2004). A single odorant can bind to multiple receptors, and a single receptor can bind to multiple odorants. Despite the receptors are distributed throughout the epithelium without a specific topography, OSNs expressing the same receptor project only on two glomeruli in the OB, one located in the medial and the other in the lateral hemisphere of the OB. Within the glomeruli, mitral and tufted cells project the information to higher brain areas. Importantly, mitral and tufted cells are subjected to inhibitory effects from higher-order brain areas through GABA (γ-aminobutyric acid)-ergic interneurons located in the OB. This feedback mechanism permits cortical brain areas to modulate olfactory processing at an early peripheral level. Hence, a unique pattern of OSN activity led to a unique pattern of mitral cell activity, which is decoded in higher brain regions as a specific odor quality, leading to a primary olfactory representation (Cleland, 2008; Rawson, 2006) (Fig. 1.6).

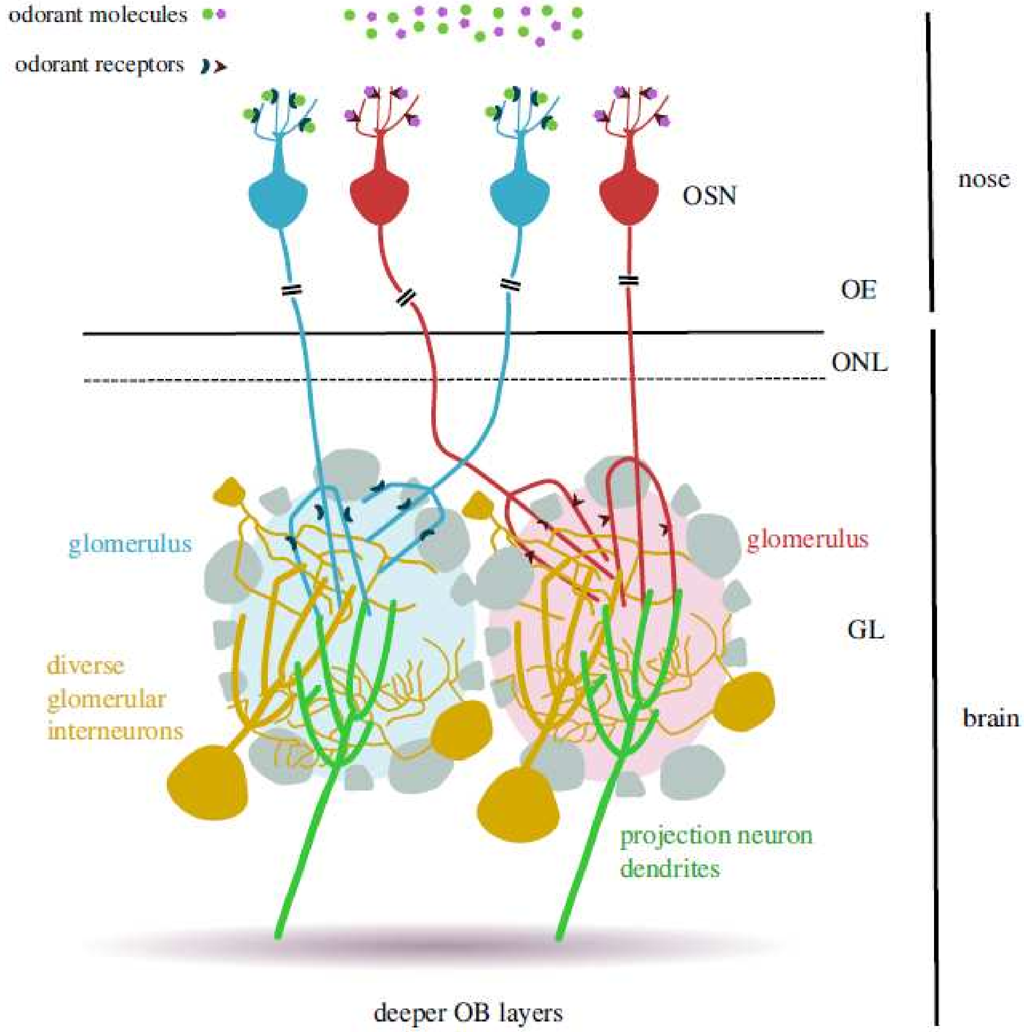

Fig. 1.6. Projection of the olfactory sensory neurons to the olfactory bulb. OSN = olfactory sensory neuron; OE = olfactory epithelium; ONL = olfactory nerve layer; OB = olfactory bulb; GL = glomerular layer. (From Dorrego-Rivas & Grubb, 2022)

However, most of the odorants we experience in our everyday life are complex mixtures of a number of individual volatile chemicals, further enhancing the complexity of precise signaling responses, leading us to a limited understanding of the mechanisms responsible for the perception of complex mixtures (Patel & Pinto, 2013; Rawson, 2006). However, following the combinational odorant receptor coding, it is reasonable to assume that changes in concentration (e.g., a higher concentration of odorants) may lead to the activation of the highest affinity as well as the lowest affinity receptors, eliciting a different quality perception of the same odorants presented at a lower concentration (Rawson, 2006). However, the combinatorial model fails to explain why, contrary to the predictions, a mixture activates a low number of glomeruli than the number of individual components in the mixture (Rawson, 2006), further highlighting the complexity of the signaling and our limited understanding of the underlying mechanisms.

Finally, another important aspect in the coding processing contributing to the quality as well as the intensity of the odorant perception is the temporal coding. The temporal coding is influenced by several factors: the properties of the odors (e.g., volatility, solubility), and characteristics of the olfactory system (e.g., nasal structure, mucus composition, airflow rate) (Rawson, 2006).

Following this brief review of the odor transduction mechanisms, it is clear how the olfactory system, through the combinatorial activity pattern, the top-down inhibitory effects from higher-order brain areas to the glomeruli, and the temporal aspects of the neural activation, turns out to be a highly sensitive and specify system, able to decode and recognize the vast number of diverse odorants that we encounter in our everyday life. Furthermore, a variety of conditions can alter or modulate the olfactory performance, and this can depend also on the properties of the odors, thus emphasizing the complexity of the olfactory experience.

1.2. Olfactory dysfunction

Our senses are crucial for everyday life and well-being. Screening of sight and hearing is performed routinely from an early age to ensure there are no impairments that may affect the quality of life. However, olfactory dysfunctions are not taken into account and their prevalence is mostly underestimated. Only recently, the sense of smell has become popular in the general population and in the media, since the COVID-19 pandemic significantly increased the prevalence of olfactory loss and dysfunction (Parma et al., 2020). Despite the negative outcomes associated with the global COVID-19 pandemic, it helped to shed light on the importance of the sense of smell and its evaluation. As a consequence of this neglect, the importance of the sense of smell is only realized when it is lost, or alterations appear. Not surprisingly, the majority of people presented with olfactory dysfunction are not aware of their impairment. However, when they have been asked about their changes in sight and hearing, they are conscious of the deterioration of these senses (Adams et al., 2017).

Despite the poor appreciation we attribute to our sense of smell, olfactory disorders affect about 22% of the general population (Desiato et al., 2020), increasing with age and with the highest prevalence in men. Olfactory dysfunction can be divided into quantitative and qualitative. Table 1.1 provides a definition of the terms used to describe olfactory disorders.

Table 1.1. Definitions of quantitative and qualitative olfactory disorder

	Normosmia	Normal olfactory function
Quantitative disorders	*Hyposmia (or "microsmia")*	Reduced olfactory function
	Functional anosmia	Reduced olfaction to the extent that the subject has no function that is useful in daily life.
	Anosmia	Absence of all olfactory function

	Specific anosmia (or "partial anosmia")	Reduced ability to smell a specific odor, but preserved ability to smell most other odors.
	Hyperosmia (or "superosmia")	Increased ability to smell odors to abnormal level (rare)
Qualitative disorder	*Parosmia (or "dysosmia", "cacosmia", "euosmia" or "troposmia")*	Distorted perception of an odor stimulus
	Phantosmia	An odor is perceived without concurrent stimulus, an "olfactory hallucination"

Quantitative olfactory disorders affect about 13-18% of the population (Hummel et al., 2017). On the other side, the prevalence of qualitative olfactory dysfunction is considerably lower, around 3.9% (Nordin et al., 2007). However, since our poor understanding of the function and importance of the sense of smell, olfactory dysfunction goes mainly unnoticed and their prevalence is underestimated (Nordin et al., 1995; Temmel et al., 2002). In general, it has been reported that people tend to overestimate their olfactory ability: when the olfactory functions are tested, in a sample of healthy individuals who reported to have normal olfaction it has been shown that about 3% presented functional anosmia and the 30% hyposmia (Oleszkiewicz et al., 2020; Oleszkiewicz & Hummel, 2019).

1.2.1. Causes of olfactory dysfunction

Following the classification used in the auditory system, an attempt has been made to classify the olfactory dysfunctions based on the location of the presumed pathology. Following this reasoning, three main categories have been detected:

1) Conductive dysfunction: blockage of odorant transmission to the olfactory epithelium
2) Sensorineural dysfunction: damage/loss of the olfactory neuroepithelium

3) Central dysfunction: damage/loss of the olfactory processing pathways of the central nervous system

However, this classification has proved to be reductive. Several conditions known to cause olfactory loss may fall into different categories, leading to an incomplete understanding of the underlying pathophysiology. In Table 1.2 are reported the main causes of olfactory dysfunctions.

Table 1.2 Main causes of olfactory dysfunctions

- Olfactory dysfunction secondary to sinonasal disease
- Post-infectious olfactory dysfunction
- Posttraumatic olfactory dysfunction
- Olfactory dysfunction associated with neurological disease
- Olfactory dysfunction associated with exposure to drugs/toxins
- Congenital olfactory dysfunction
- Olfactory dysfunction associated with aging
- Olfactory dysfunction associated with psychiatric disorders
- Other possible causes: iatrogenic damage (sinonasal and skull base surgery, laryngectomy), tumors, multiple systemic co-morbidities
- Idiopathic olfactory dysfunction

Olfactory dysfunction secondary to sinonasal disease

Sinonasal disease is the most common source of olfactory dysfunction (30%, Keller & Malaspina, 2013). This is due to the presence of oedema that obstructs the transmission of the odorant to the olfactory epithelium, with or without polyps, and/or the inflammatory component of chronic rhinosinusitis. The olfactory dysfunctions associated with sinonasal disease usually fluctuate over time and are rarely associated with parosmia or phantosmia (Hummel et al., 2017).

Post-infectious olfactory dysfunction

Upper respiratory infection (URI), such as the common cold, influenza, pneumonia, or human immunodeficiency virus, is the second cause of olfactory loss in the adult population (25%) (Keller & Malaspina, 2013). Some evidence reports a higher prevalence in women than men, with the middle-aged or elderly more affected (Deems et al., 1991; Sugiura, Yoshiaki Nakai, Midori, 1998; Temmel et al., 2002), probably because of the accumulation of insults during the lifetime and the reduced regenerative ability of the olfactory system (Hummel et al., 2017). The onset of the disorder is usually concomitant to the infection, even though some patients are unaware of the causative episode, and the olfactory impairment is rarely permanent, with about one-third of patients exhibiting a spontaneous recovery after two years (Hummel, 2000; Reden et al., 2006). The pathophysiology of the disorder is still not clear, but it is supposed to involve either damage to the olfactory epithelium or central olfactory processing pathways (Youngentob et al., 2001).

Posttraumatic olfactory dysfunction

Traumatic injuries are among the most common causes of olfactory loss (Hummel et al., 2017). Traumatic injuries can affect the nose (involving the distortion of the nasal bone, septal fractures, epithelial injuries, blood clots, oedema, or alteration in mucous characteristics), causing mechanical obstruction of odorants to the olfactory epithelium or transection of the olfactory fila crossing the cribriform plate, or the central structures of olfactory processing, through contusions or intraparenchymal hemorrhage (Hummel et al., 2017). The prognosis is poor compared to the post-infectious loss, with the recovery rate ranging between 10 to 30% of cases, depending on the severity of the injury (Doty & Yousem, 1997; Duncan & Seiden, 1995; Fan et al., 2015; Reden et al., 2006).

Olfactory dysfunction associated with neurological disease

Increasing evidence highlight the presence of a link between olfactory dysfunction and neurological diseases, such as Parkinson’s (PD) and Alzheimer’s disease (Attems et al., 2014;

Bahuleyan & Singh, 2012; Doty, 2012). In particular for PD, the presence of olfactory disturbances occurs between 4 and 6 years before the onset of motor symptoms, making the olfactory deficit a reliable marker for the diagnosis of PD (Haehner et al., 2009; Ponsen et al., 2004; Ross et al., 2008). The significance of this relationship is still not fully understood. Some evidence reported reduced activity in the hippocampus and amygdala in response to odors in individuals with PD compared to healthy controls (Westermann et al., 2008), while histological studies have found Lewy bodies in the olfactory bulb and a decreased neural population in the anterior olfactory nucleus (Attems et al., 2014; Duda, 2010).

Olfactory dysfunction associated with exposure to toxins or medications

Exposure to several toxins, pathogenic agents, chemotherapeutic agents, and other medications can lead to olfactory disturbances, resulting in both peripheral or central damages (Hummel et al., 2017).

Congenital olfactory dysfunction

Between 0.01-0.02% of the general population present congenital anosmia, i.e., they are born without the sense of smell (Croy et al., 2012). Genetic factors can be the cause of some olfactory dysfunction, leading to hypoplastic or aplastic olfactory bulbs and olfactory sulci, without any other abnormalities (Abolmaali et al., 2002; Yousem & Geckle, 1996). The first signs appear around 10 years old, but the diagnosis is made late compared to other congenital sensory impairments (usually it takes 13 years after the first signs) (Schäfer et al., 2021).

Olfactory dysfunction associated with normal aging

Epidemiological studies have consistently shown that olfactory functions decrease with age. Olfactory dysfunction is present in 62.5% of people over 80 years old, and is a predictor of 5-year mortality (Devanand et al., 2015; Gopinath et al., 2012). The causes linking olfactory dysfunction and age are multiple and varied. First of all, a wide range of physiological changes in the nose occurs that may lead to disrupted olfactory abilities, e.g., parasympathetic/sympathetic dysregulation, reduced mucosal blood flow, fibrosis in the cribriform plate, and age-related mucociliary dysfunction. In addition, a reduction in the olfactory sensory neuron regeneration may lead previous transitory insults, such as infection or exposure to toxins or medication, to become permanent damages. The reduction of the afferent input to the olfactory bulb may then lead to a reduction also in the olfactory bulb volume (Hummel et al., 2017).

Olfactory dysfunction associated with psychiatric disorders

A wealth of psychiatric conditions has been associated with altered olfactory function: mood disorders including Major Depressive Disorder with seasonal pattern (Gross-Isseroff et al., 1994; Lombion-Pouthier et al., 2006; Pause et al., 2001; Postolache et al., 1999, 2002), anorexia nervosa (Fedoroff et al., 1995; Kopala et al., 1995; Roessner et al., 2005), panic disorder (Kopala & Good, 1996) and psychosis (Corcoran et al., 2005; Hudry et al., 2002). The rationale behind this relationship lies in the assumption that the brain areas involved in odorant processing partially overlap with the brain areas involved in emotion which present an altered functioning in these pathologies. A deeper overview of the relationship between olfaction and emotion will be presented in the next paragraphs.

Other disorders associated with olfactory dysfunction

Olfactory dysfunction may also be associated with intranasal and intracranial tumors (Murphy et al., 2005), nasal surgery, endocrine disorders (e.g., Addison's disease, Turner's syndrome, Cushing's syndrome, hypothyroidism, Kallman's syndrome; Deems et al., 1991; HENKIN, 1967; Henkin et al., 1975; Henkin & Bartter, 1966; Males & Schneider, 1972), metabolic disorders (e.g., diabetes mellitus, hypertension, vitamin B12 deficiency; Gouveri et al., 2014), sinonasal and skull base surgery complications (Alobid & Mullol, 2012).

Idiopathic olfactory dysfunction

Olfactory dysfunction can be defined as idiopathic when a clear etiology is not present (Fark & Hummel, 2013). About 16% of patients present with idiopathic olfactory dysfunction. However, a multidimensional and multidisciplinary approach should be used to better disentangle the presence of idiopathic olfactory dysfunction from, for example, asymptomatic upper respiratory infections, early neurodegeneration, or a psychiatric condition (Hummel et al., 2017).

1.2.2. Consequences of olfactory dysfunction

Before examining the consequences of olfactory dysfunction, it is worth mentioning the major functions of olfaction that can then be affected by its impairment, which are (1) ingestion, (2) hazard avoidance, and (3) social communication (Stevenson, 2010).

Odors are important cues not only in alerting us to food in the environment and guiding our appetite, but they also represent a key part in the construction of the flavour percept during food consumption. This is clear when we have a cold, and the nose is blocked: food changes its taste, and the pleasure of food is missing. Indeed, up to 70% of patients with anosmia reported a decreased enjoyment of eating or drinking (Croy et al., 2014), but also an altered eating behavior that can lead to obesity, diabetes, eating disorders, cardiovascular, endocrinological or metabolic diseases (e.g., Fairburn et al., 1998; Hillson, 2014; Keller & Malaspina, 2013; van Gaal et al., 2006). All these aspects can result in a reduced quality of life, which in turn may lead to further psychological disorders, such as depressive symptoms (Croy, Nordin, et al., 2014; Orth & Robins, 2013).

Most of the patients with odor perception dysfunction report problems in the detection of spoiled and burning food, but also fire, gas, and smoke. These lead to more frequent house accidents, but also to feelings of worrying and insecurity (Croy, Nordin, et al., 2014). Furthermore, patients worry about their personal body odor, bad breath, and their children or personal hygiene (Blomqvist et al., 2004; Croy, Nordin, et al., 2014; Keller & Malaspina, 2013; Nordin et al., 2011; Temmel et al., 2002). For example, their inability to smell when they smell bad, to dose the perfume use, or to detect when a child's diaper needs to be changed, lead patients to be in a constant state of fear and worry that affect well-being and result in the development of anxiety and depressive symptoms (Croy, Nordin, et al., 2014; Schäfer et al., 2021).

Strictly related to the concerns about their personal hygiene, the social sphere is highly affected by olfactory dysfunction. About one-third of patients report that their social relations are affected by their impairment, especially in the romantic and sexual domain (Croy, Nordin, et al., 2014; Mahmut & Croy, 2019; Schäfer et al., 2019).

All these aspects, which refer to diverse domains of life, have to be taken into consideration in the assessment and evaluation of olfactory dysfunction since they play a prominent role in the well-being of the patients. Anhedonia, frustration, isolation, anxiety, and sadness are common negative feelings that occur together with olfactory loss, making clear that the sense of smell is important for functions that are vital for well-being and mental health, and it can no longer be ignored or trivialized.

Here, I reported two quotes from two anosmic patients that summarizes the consequence of smell loss:

"The sad thing, I find, is not being able to appreciate the everyday smells which we take for granted: perfume, freshly mown grass, freshly baked bread, scent of bluebells/roses/flowers in general. Living by the sea, I used to love the smell of the seaweed around the tide pools. The list is endless." (subject 0028) A patient's quote from Keller and Malaspina (2013).

"It's a weird affliction. People don't really get it. They think it's not as big a deal as it is. After all, they figure anosmics aren't disabled. We don't need seeing-eye dogs or sign language to interact with our environment. And they are right — partly. We can function without drawing attention to our plight. We can do virtually everything we could before we lost our sense of smell, except enjoy the immensely important aspects of human life that most people take for granted." (subject 0005) A patient's quote from Keller and Malaspina (2013).

1.3. The olfactory experience

What an olfactory object is and what processes enable the brain to recognize, categorize and discriminate between olfactory objects in the environment is still a matter of debate. Given the visuo-centric nature of human sensory experience, talking about olfactory objects questions the traditional view of objects as "things" that must have specific characteristics, such as being visible, solid, with a delimited position in space, opaque, and with a specific color. These assumptions cannot be satisfied in the olfactory domain, since odors are invisible, gaseous, and not connected to their source. Therefore, should odors not be considered objects?

In order to address this issue, in the following sections I will use a psychological framework to review the primary – and unique – characteristics of olfactory stimuli and the mechanisms being odor perception.

1.3.1. Bottom-up odor object perception

The perception of an odor object starts with the synthesis of the single components into a perceptual unified entity (Fig. 1.7, Panel A). Indeed, the vast majority of real-world odors are complex mixtures of different odor molecules. The olfactory system entwines these elements into perceptual units, making it impossible, even for trained experts, to distinguish more than three components in an odor mixture (Laing & Francis, 1989; Livermore & Laing, 1996). This creates a reduced amount of information needed to be processed by the brain and minimizes the risk of perceptual confusion in processing odors containing overlapping components. For example, the odor of a rose is composed of more than 400 volatile compounds (Ohloff, 1978).

A second step is to filter the information, coming from the environment, not related to the olfactory object, in a phenomenon called *odor-background segmentation* (from figure-ground segmentation, a well-known phenomenon in other sensory modalities) (Fig. 1.7, Panel B). In the olfactory domain, sensory habituation is one of the factors determining the segmentation of the stimulus of interest from the irrelevant background. For example, when considering a rose in a bouquet of flowers as an odor object, the olfactory features emerging from the other flowers and leaves constitute the background stimulus. The inhibition of this background stimulus is essential to perceive the rose odor object, and prolonged exposure to it, inducing sensory-specific habituation, allows the smell of the rose to be perceived.

The third step is the ability to recognize an olfactory object despite its changes in a real-world unpredictable environment, that is the maintenance of *object constancy*. Following the rose example, if we smell the same rose in different environmental conditions (e.g., weather conditions, wind direction, respiratory phase), we are still able to link the same olfactory experience to the same odor object, allowing *object categorization* (Fig. 1.7, Panel C). This ability to classify different stimuli into the same perceptual group, but also the same stimulus presented in different conditions, reduces the cognitive resources needed to process the odor object and optimize behavioral responses (Gottfried, 2010).

The following step requires the capability of the olfactory system to discriminate between different odor objects, or between different versions of the same odor object category (Fig. 1.7; Panel D). Experience and perceptual learning facilitate odor discrimination, promoting a flexible adaptation within the environment (Goldstone, 1998). After prolonged exposure and perceptual learning, the olfactory system is capable of perceiving dissimilarities between different varieties of roses, allowing *odor object discrimination*.

Finally, *selective attention* is a key ability in odor perception (Fig. 1.7, Panel E). In the real world, olfactory stimuli are rarely presented in isolation, instead many different odors are presented simultaneously. However, given the limited number of cognitive resources, the olfactory system needs to focus its resources toward behaviourally relevant stimuli, making the olfactory attentional selection a key ability in odor object perception. Hence, entering a flower shop requires the olfactory system to be presented with an array of different flower smells simultaneously. Selective attention allows the olfactory system to select only one odor object, the rose odor object, among the competing alternatives, for example, tulips and daisies.

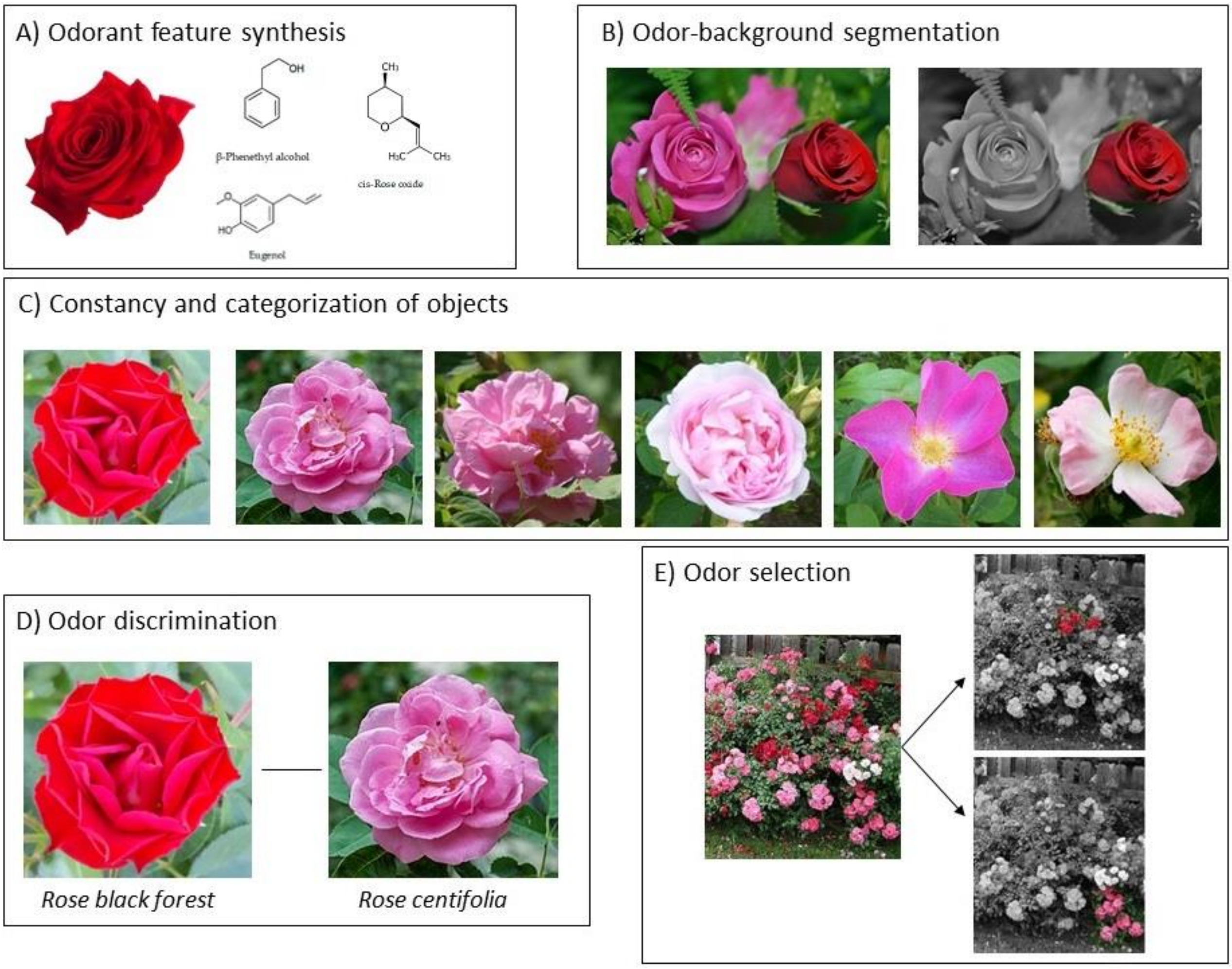

Fig. 1.7. Schematic representation of the principal mechanisms of odor object perception. **Panel A)** depicts three volatile components produced by the rose: β-Phenethyl alcohol, cis-Rose oxide, and eugenol. **Panel B)** depicts the odor-background segmentation. **Panel C)** depicts the constancy and the categorization of odor objects: despite the differences in size, shape, color, and texture, all of the objects fall inside the category "rose". **Panel D)** depicts odor discrimination: after prolonged exposure and perceptual learning, two varieties of rose (rose black forest and rose centifolia) can be perceptually discriminated. **Panel E)** depicts olfactory selective attention. Different odor objects are present at the same time (left). Attentional mechanisms allow the selection of the odor object of interest, bringing it to the perceptual foreground (right).

The characteristics of odor object perception described above underlie the fact that many of the basic principles governing visual object perception also apply to olfactory objects, enabling olfactory stimuli to be defined as objects. However, it is worth to be mentioned that a hedonic definition of an odor object has been proposed. Specifically, the idea here is that an odor object is made by not only the perceptual feature of the odor but also by the odor's pleasantness combined with the subjective state of the recipient at the moment of the perception of the odor (Yeshurun & Sobel, 2010). In this respect, the odor object is not the odor of the pear, but the combination of the pleasantness of that odor and the subjective state at which the odor is detected. Hence, in the case of hungriness, the odor of a pear is different (probably more pleasant) compared to a satiety state, despite the object being the same. However, the previously described characteristics required for the odor objects perception (i.e., synthesis, segregation, categorization, discrimination, and selection) are applicable for odors of different valence, making the two definitions compatible and non-mutually exclusive (Gottfried, 2010).

1.3.2. High-order cognitive processing of odors: the odor awareness

Olfactory perception is also influenced by higher cognitive processes, such as awareness and consciousness, that contribute shaping the olfactory experience in the real world.

As stated in the previous section, in the real world a number of olfactory stimuli are present at the same time, and people process most of them unconsciously (Sela & Sobel, 2010). In every breath we take we sniff a relatively high number of odors. However, we rarely notice all of them. Moreover, some individuals suddenly notice the food aroma of the food, the fragrance of the perfume people are wearing, or the stench coming from the bathroom, while others detect them only when it is brought to their attention. These examples make clear that there are other cognitive factors that play a role in turning an olfactory stimulus into a conscious olfactory experience, and this cognitive factor seems to be attention (Keller, 2011).

Olfactory attention is profoundly different from the other sensory modalities. Compared to vision, where attention is mainly allocated in space through the direction of the gaze toward the visual object, in olfaction spatial abilities are rudimental. Moreover, the discontinuity in the olfactory inputs can also be viewed as a limit for olfaction awareness. Indeed, in vision, for example, visual stimuli are processed continuously except for occasional blinks, while in olfaction the sensory information is acquired through single sniffs, making it difficult to detect slight changes in the olfactory environment (Sela & Sobel, 2010).

Despite the notion of odors as poorly localized in space and time, experimental evidence supports the hypothesis of the key role of attention in modulating olfaction. Attending to odors results in a reduction in the latency of early olfactory event-related potentials (OERPs) components (Krauel et al., 1998), as well as an increased amplitude for later OERPs components (Geisler & Murphy, 2000; Krauel et al., 1998; Pause et al., 1997). Moreover, activity in several brain areas results to be modulated by attention to the odors (especially the structures responsible for the earliest levels of cortical processing, such as the piriform cortex), but also in downstream structures (de Araujo et al., 2005). In addition, neural data demonstrated that paying attention to odors increases functional interactions within thalamocortical networks, specifically from the piriform cortex to the thalamus and from the thalamus to the orbitofrontal cortex (Plailly et al., 2008). This indirect olfactory pathway through the thalamus may serve as a fined tune discriminative capacity, selecting only behaviourally and biologically relevant stimuli for additional processing in the orbitofrontal cortex. This ability of the olfactory system is prompted by cognitive factors, such as attention (Plailly et al., 2008).

This evidence raised the question of whether individual differences in odor perception might depend on differences in the degree of attention individuals pay to those odors. These are metacognitive abilities that are not measurable in experimental settings but can give us unique insight into how people interact with their daily olfactory environment. The development of questionnaires aimed at measuring not only odor awareness (e.g., *the Odor Awareness Scale*; Smeets et al., 2008a), but also the general attitude toward the odors (e.g., *the Affective Impact of Odor scale*; Wrzesniewski et al., 1999), helped to untangle the role of these mechanisms in odor perception, further confirming that higher interest and higher attention to odors are related to higher familiarity ratings of odorous stimuli (Bensafi & Rouby, 2007), more affective experiences when smelling odors (Wrzesniewski et al., 1999), higher odor-related memories (Arshamian et al., 2011), better abilities to form olfactory images in our mind (Arshamian & Larsson, 2014; R. J. Stevenson & Case, 2005), but also better olfactory abilities (Nováková et al., 2014; Smeets et al., 2008a).

Given the evidence reviewed so far, it is clear how odor awareness is important in shaping the olfactory experience and having an intact sense of smell is only a prerequisite in the complex and composite realm of odor perception.

1.4. Function of emotions in olfaction

If odors can be defined as a sensation elicited by chemical substances on the olfactory system, what an emotion is remains a matter of debate.[1] From an evolutionary perspective, the primary role of emotions is to signal security or danger and motivate the individual to either approach or avoidance

[1] For the last century, scientists have debated about the nature of emotions, their definition, and their role in human life. However, providing a unified framework in the study of emotion is not the main focus of the present thesis; hence, a classical definition of emotion was adopted. For a review on the emotion debate see Adolphs et al., 2019; Lindquist et al., 2013

behavior (Lang, 1995). In addition, we can refer to "emotion" as all the responses to the anticipation or occurrence of rewarding or punishing stimuli (Russell, 2003). Importantly, an emotion is a multicomponential phenomenon, and the emotional experience is based on the coherent organization of all the components that constitute the emotion, which are the subjective and cognitive evaluation of the situation, the physiological modifications, and the behavioral responses to threat or reward (LeDoux, 2014). As animals, we perform actions to move forward a stimulus that represents a reward, such as the smell of food, a pleasant touch, or the sight of a beautiful scene, while we react to avoid or escape from threats, such as the fear evoked by the smell of a predator (Rolls, 2005). Hence, odors represent powerful cues in inferring emotion from the environment.

In this context, approach and avoidance are the two main behavioral responses that are critical for the survival of the organism and, at the same time, in the olfactory context what modulates these behavioral responses is odor valence (or pleasantness). Interestingly, it has been shown in both non-human and human infants the odor valence processing is innate, or at least part of it (Kobayakawa et al., 2007; Soussignan et al., 1997). However, if the development of odor preferences is innate or learned is still controversial (e.g., Engen et al., 1988; Schaal et al., 2000). As depicted in Fig. 1.8, two main continuous dimensions can describe emotion: valence (i.e., pleasant vs unpleasant) and arousal (i.e., high vs low, intense vs mild). Along this continuum, all discrete emotions can fall within. An individual, over time, can move through different states, from a low arousing pleasant/unpleasant state to a high arousing pleasant/unpleasant state (Kontaris et al., 2020).

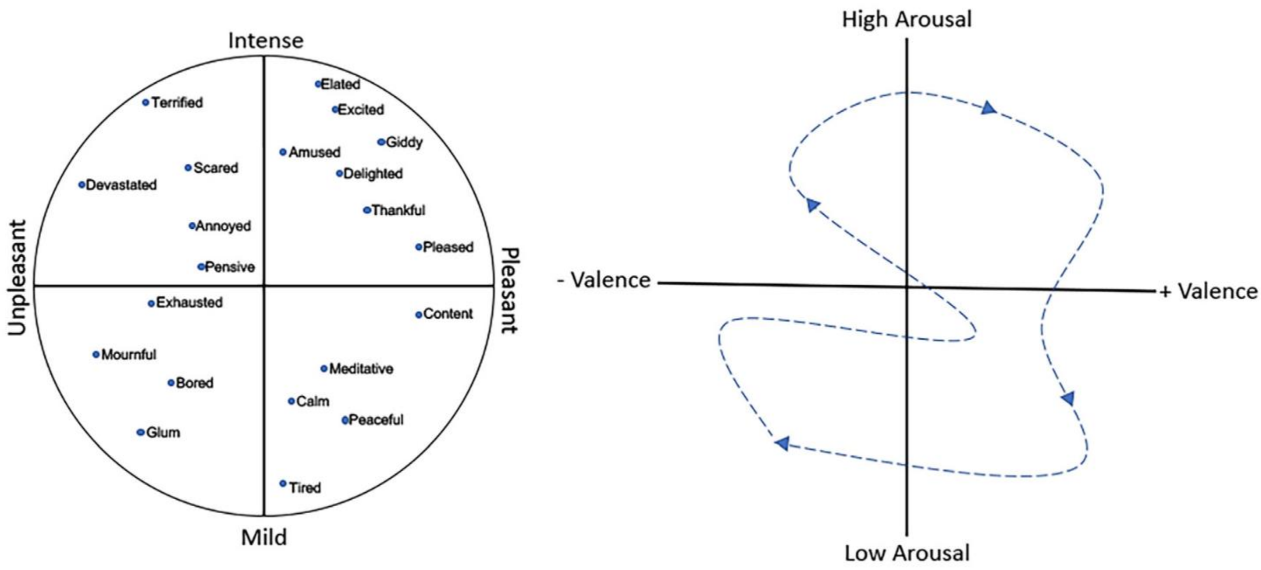

Fig 1.8. On the left there is a representation of the two-dimensional emotion plot, valence is represented in the x-axis (unpleasant vs pleasant), while arousal is represented in the y-axis (intense vs mild). On the right, there is depicted the temporal shift in the affected state (dashed arrow) showing that, over time, different states can be experienced (from Kontaris et al., 2020).

In this context, how can odors modulate emotion? And how can emotions modulate odor perception? First, pleasantness is the primary dimension of perception in both emotion and olfaction domains. Second, they share a common neural substrate. As it has been briefly reviewed at the beginning of this chapter, odor perception is a neural network-based process. Interestingly, the network involved in emotion and mood heavily overlaps with the network involved in olfaction (Fig. 1.9).

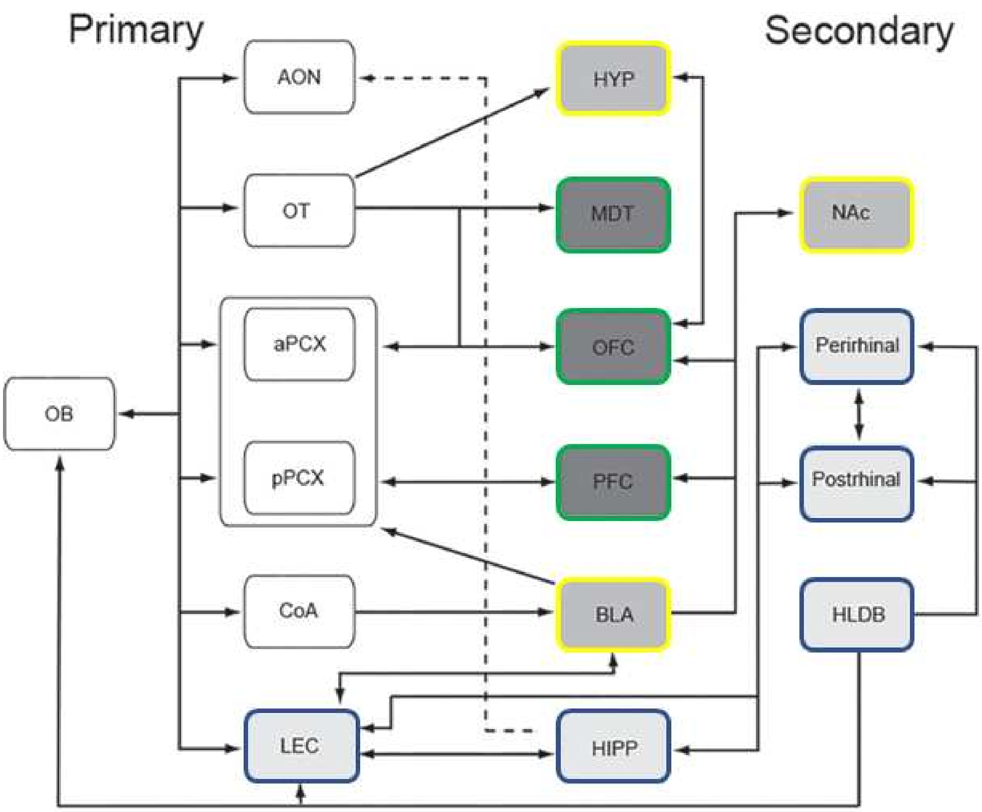

Fig. 1.9. Schematic representation of the primary (*left*) and secondary (*right*) olfactory networks. The shaded and colored regions are the same regions involved in the processing of emotion (the regions more associated with negative emotions are depicted in *blue*, the regions more associated with positive emotions are in *green*, and the regions involved both in negative and positive emotions are in *yellow*). Abbreviations: AON, anterior olfactory nucleus; aPCX, anterior piriform cortex; BLA, basolateral amygdala; CoA, cortical nucleus of the amygdala; HIPP, hippocampus; HLDB, horizontal limb of the diagonal band; HYP, hypothalamus; LEC, lateral entorhinal cortex; MDT, mediodorsal thalamus; NAc, nucleus accumbens; OB, olfactory bulb; OFC, orbitofrontal cortex; OT, olfactory tubercle; PFC, prefrontal cortex; pPCX, posterior piriform cortex. (Adapted from Kontaris et al., 2020)

This reciprocal connection results in the fact that odors can affect emotions and mood, and emotions and mood can influence odor perception. Indeed, olfactory perception is not only the basic sensory encoding of chemical substances, but it is largely driven by the subjective state at the moment of the encoding (Yeshurun & Sobel, 2010). As an example, when it asked to evaluate the pleasantness of orange syrup in fasting subjects, they rated it as pleasant; however, the rating shifted after the ingestion of glucose (Cabanac & Fantino, 1977). Interestingly, this phenomenon does not happen only with hunger, but also with emotional states and mood. Highly anxious individuals present faster response times to both positive and negative odors (la Buissonnière-Ariza et al., 2013), highly stressed individuals show better odor identification performance (Hoenen et al., 2017), whereas individuals experiencing anger report poorer olfactory identification performance (Hoenen et al., 2017). Moreover, both shy individuals and individuals with depressive symptoms present lower olfactory abilities (Herberner et al., 1989; Pollatos et al., 2007).

From this evidence, it is clear that the emotional state can influence not only the hedonic aspects of odor perception but also the individual's olfactory abilities, however, the underlying mechanisms are not fully understood yet. Instead of focusing on the role of transient emotions in modulating the olfactory experience, the study of affective disorders, which present with more stable alterations in mood, can be a useful approach to better understand this phenomenon.

1.5. Is olfaction a marker for affective disorders?

Given the prominent role of olfaction in vital aspects of human life, its modulation through emotions, and their shared neural network, whether and to what extent affective disorders can be affected by olfactory impairments is a consequent question.

Among affective disorders, the one that has received more attention is depression. Already in 1949, Mac Lean hypothesized the possible involvement of olfaction in depressive states, defining the sense of smell as part of an area of the brain with the function of controlling the visceral and emotional functions, the so-called "visceral brain", later renamed "limbic system" (MacLean, 1949). Despite the growing body of literature on the limbic system and depression, their association with olfaction had been fairly neglected for the last 15 years, when researchers started again to explore the role of olfaction in depressive disorders. However, the mechanisms underlying this relationship are far from being fully understood. Interestingly, this relation is reciprocal: not only individuals with depression present with alteration in their olfactory functions but also individuals with olfactory loss are more likely to report depressive symptoms (Croy et al., 2012; Croy, Nordin, et al., 2014; Temmel et al., 2002). Despite the relative early interest in the study of olfaction in depression, an indication of reduced olfactory abilities in depression has been already confirmed by several meta-analyses and reviews (Atanasova et al., 2008; Athanassi et al., 2021; Kohli et al., 2016; Taalman et al., 2017).

From an anatomical point of view, the first candidate "biomarker" that has been found to explain this phenomenon is the size of the OB (Negoias et al., 2010). Indeed, individuals with depression appear to present a reduction in their OB volume. More specifically, the degree of OB reduction is correlated with the severity of the disorder: greater OB reduction leads to more severe depressive symptomatology (Croy & Hummel, 2017). In addition, structural alterations in the hippocampus, cingulate cortex, habenula, and amygdala have been observed in depression (Campbell et al., 2004; van Tol et al., 2010; Yao et al., 2020), as well as functional alterations in the amygdala and orbitofrontal cortex activity. Specifically, hyperactivation in the amygdala, hyperactivation of the ventromedial OFC (an area involved mainly in anxiety and rumination), and hypoactivation of the dorsal OFC (an area involved mainly in attention and working memory) have been reported in depression (Drevets et al., 2008; Rochet et al., 2018). The relationship between morphological and functional alterations in these brain areas and reduced olfactory performance in individuals with depression is further confirmed by neuroimaging studies reporting an altered activation of those areas in response to odor presentation and odor memory tasks (Rochet et al., 2018; Rolls, 2004; Sobel et al., 1998; Zatorre et al., 1992).

However, as reviewed in the previous chapter, in shaping the olfactory experience also cognitive factors play a key role. Among the wide range of symptoms affecting individuals with depression, cognitive functions are of great relevance. Cognitive theories of depression posit that depression is characterized by cognitive biases in all aspects of information processing, including memory, attention, interpretation, and perception (Mathews & MacLeod, 2005). Specifically, individuals with depression tend to filter information from the environment according to their existing memory representations, ideas, or experiences, called schemas (Beck & Bredemeier, 2016). In this view, negative stimuli are processed preferentially, while positive stimuli are avoided, and neutral or ambiguous stimuli are interpreted in a schema-congruent manner. The hippocampus, the thalamus, and the amygdala are the brain regions proposed to be involved in the attentional and memory biases that affect depression (Disner et al., 2011). Interestingly, these are also the brain regions receiving projections from the primary olfactory system. Alterations in these brain regions could explain not only the cognitive bias but also the reduced performance in the cognitive aspects of olfactory perception, such as the identification of odors, olfactory learning and memory during depressive states.

Finally, as stated at the beginning of this chapter, among the consequences of olfactory loss, the development of depressive symptoms is one of the most common. This is not only true given the biological and neural connections between olfaction and affective disorders, but it also strongly affects the quality of life more broadly, reducing the ability to enjoy surroundings, as well as the joy of eating and tasting the quality of food (Hummel & Nordin, 2005). The alteration of olfactory functions in depression may, at least in part, be the cause of the loss of appetite, motivation to eat and anhedonia that is often present in depression, which, in turn, can cause the social isolation characteristic of depression.

Finally, among affective disorders, the vast majority of research focused their effort on investigating olfactory alterations in depression, leaving out anxiety disorders. This is particularly surprising given that almost the same brain areas involved both in depression and in olfaction are also implicated in anxiety disorders. The few studies focusing on anxiety reported conflicting results: while in a group of patients with different anxiety disorders, but also in healthy subjects with anxiety symptoms, a reduction in olfactory abilities has been found (Clepce et al., 2012; Takahashi et al., 2015), other evidence reported higher olfactory sensitivity in individuals with panic disorder (Burón et al., 2015, 2018).

Despite the growing interest in this area of research, more studies are needed to better explore the role of olfaction in anxiety, and regarding depression no clear conclusions have been made. If olfactory dysfunctions are the cause or consequence of the development of depression is still to be clarified. In addition, albeit the prominent role of attention both in olfactory perception and in depression, no study so far investigated its role in the relationship between depression and olfactory abilities. Elucidate these aspects can improve not only our understanding of complex phenomena such as depressive disorders and olfaction, but also develop more specialized treatments and possibly identify potential predictive biomarkers of depression.

CHAPTER 2

Smelling emotions: The role of body odors

In the previous chapter, we focused on decoding and processing of olfactory stimuli present in the environment, also called "common odors". These stimuli help individuals in localizing food sources, spoiled food, or the presence of gas leaks, which are all essential survival functions, but can also indicate the presence of odor objects not relevant for survival, such as the odor of the flowers. If common odors are produced by inanimate objects, another category of odors, called "body odors", refers to olfactory stimuli able to convey biologically relevant information. Body odors are produced by human beings and allow communication between conspecifics, being able to convey not only genetic and individual characteristics, such as gender, age, and reproductive state, but also psychological and transient states, such as the emotional status of the individual.

In the following sections, the role of body odors in the communication of emotions will be reviewed and a focus will be put on the advantages of this form of communication.

2.1. Human social behavior

Humans, like most mammals, are a social species in which social relationships are essential not only to wellbeing, but also to survival. A number of theorists over the years have posited that human behavior is driven by the motivation to approach rewards and the motivation to avoid threats. These motivations create dispositions for action: positive emotions typically prime approach-related behavioral drives, with negative emotions activating avoidance-related behaviors (Bradley & Lang, 2000; Carver & Scheier, 1990; Davidson et al., 1990; Frijda, 1986). The so-called approach and avoidance motivational systems are independent and separate, but they interact in orienting responses to emotional stimuli and in influencing ongoing affect (Lang et al., 1998). Moreover, it suggested that these two systems have partially distinct neural substrates that exert distinct influence on action: the Behavioural Activation System (BAS) and the Behavioural Inhibition System (BIS) (Corr, 2004; McNaughton & Gray, 2000). BAS is thought to control approach behavior in response to reward cues through the dopaminergic activity in the mesolimbic system, whereas BIS is thought to reflect avoidance behavior and is sensitive to signals of threat and punishment via noradrenergic and serotoninergic activity in the septohippocampal system (Graeff, 1994; Smillie, 2008).

More recently, this model has been applied to the domain of social motivation (Gable, 2006; Gable & Strachman, 2008). Social interactions simultaneously offer both incentives and threats. According to this model, approach social goals (e.g., “to make friends”) and avoidance social goals (e.g., “to not be lonely”) represent dispositional constructs that stimulate appetitive and aversive behavior, respectively (Gable & Gosnell, 2013). It is reported that stronger social approach motivation is related to more satisfaction toward social life and less loneliness. On the other side, stronger social avoidance motivation is associated with less satisfaction, more loneliness and insecurity, more anxiety, and negative social attitudes (Gable, 2006). In this view, social relationships not only promote adaptive behavior through promoting social support, companionship, intimacy, and avoiding potential threats, but they are also linked to health and wellbeing (S. Cohen, 2004). A meta-analysis conducted by Holt-Lunstad and colleagues (2010) reported that social relationships influence the risk of mortality as other well-established risk factors such as smoking behavior and obesity status. In particular, individuals with adequate social relationships have a 50% greater likelihood of survival compared to those with poor or insufficient social relationships (Holt-Lunstad et al., 2010). Aside from health and wellbeing, social isolation and loneliness are also associated with poor psychological health and the development of psychopathological symptoms (Cacioppo & Patrick, 2008; House et al., 1988; Whisman, 2001). These observations have been also confirmed by a longitudinal study reporting that social isolation and loneliness predict mortality (Steptoe et al., 2013), in a way that can be compared to high blood pressure, obesity or smoking. Moreover, feelings of loneliness also affect mental health and cognitive functioning. Loneliness not only increases depressive symptoms, perceived stress, fear of negative evaluation, anxiety, and anger, and diminishes optimism and self-esteem (Cacioppo et al., 2006), but also induces cognitive decline and dementia (Gow et al., 2007). Therefore, as a social species, humans avoid loneliness as a basic drive for phylogenetic survival.

The need for social bonds is reflected in the brain structure of primates, which have larger brains than the minimum size needed to live. Indeed, the hypothesis of a "social brain" has been put forward by the fact that social life is the only thing that differentiates primates from all other species, possibly explaining the expansion of the neocortex in primates (Dunbar & Shultz, 2007b). Specifically, the increase in the size of the neocortex in primates can be explained by social complexity, which refers to, for example, group size, coalition frequency, social learning frequency and male mating strategies. Indeed, it has been repeatedly reported a correlation between brain size and social group complexity, probably due to the cognitive demands of pair-bonding, which is reflected in the need for coordinating one's behavior with that of one's mate, an ability that requires perspective-taking (Dunbar, 2009). Importantly, in anthropoid primates, relationships extend to non-reproductive bonds: friendship is a phenomenon unique to humans and intrinsically related to our neocortex size.

Following this line of reasoning, the need for social relationships essential in humans requires not only larger brains, but also specialized neural networks for the processing of social information (Adolphs, 2010). For example, human facial expressions are processed by different brain areas compared to common visual objects: the "fusiform face area" is specifically activated by faces and has a role in processing facial expressions (Ganel et al., 2005), and the memory for faces is a specialized mechanism independent from the hippocampus (D. M. Smith & Bulkin, 2014). In addition, empathy, a prominent emotion in social communication, involves specialized neuronal relays, different from non-social emotions (Singer & Lamm, 2009).

2.2. Human chemosignals as a medium in social communication

Along with the increasing interest in olfactory functions in the last years, novel discoveries on the role of odors in human communication have further highlighted the function of this sense in human social life. In particular, humans can communicate not only with their facial expressions or gestures, voices or touch, but also with chemicals emitted from their bodies (Semin & de Groot, 2013). In contrast to other sensory-based forms of communication, the olfactory “messages” are usually unintentionally released by the emitter and processed unconsciously by the perceiver. The messages are composed of chemicals, called chemosignals, contained in body odors (Parma et al., 2017; Semin et al., 2019).

Compared to visual and acoustic stimuli, social communication through olfactory modality presents some advantages, which are related to the intrinsic nature of the signal (Wyatt, 2003). Indeed, molecules can easily move across physical barriers, and they can persist for a long time allowing social information to be transmitted over long distances and to persist even after the sender[2] is no longer in the place. Besides this ability, olfactory communication is totally effortless for the sender and it requires very low energy for the receiver to decode the information. Since chemical communication is based on a mixture of molecules it can be extremely specific but at the same time, it can transmit different types of signals (Parma et al., 2017; Pause, 2012, 2017). Finally, chemosensory signals are mainly processed subconsciously by the human brain, thus not requiring conscious processing (Lundström & Olsson, 2010; Pause, 2012).

[2] In the present thesis, the “sender” is who produces the chemicals, while the “receiver” is who receives the chemical message.

In the following sections, an overview of the findings related to chemosensory communication will be provided. The term “pheromones” is avoided given the still-present debate on whether human chemosignals can be defined as pheromones. Hence, the terms chemosignals, body odors or social odors will be used interchangeably in the following sections.

2.2.1. Production of chemosignals

The human body produces a wide range of chemicals that could be interpreted as signals. In the human skin, there are three types of glands: the apocrine glands (which are thought to play a major role in social communication), the sebaceous glands (which produce most of the lipids in the skin) and the eccrine glands (involved in the regulation of the temperature). The apocrine glands, mostly located in the axillae and pubic regions, but also in ears wax, eyes, and nipples, become functional around puberty and their activity is regulated mainly by psychophysiological reactions (Fig. 2.1). They produce small quantities of milky lipid- and protein-rich fluid which is odorless: this fluid is then metabolized by bacteria producing volatile and nonvolatile substances, meaning odorant acids, sulfanylalkanols and steroids, that are the precursors of the sweat odor (Doty, 2010; Lundström & Olsson, 2010; Parma et al., 2017). Hence, the secretions of these glands are initially odorless. After the incubation with the bacteria present in the armpit area the characteristic sweat odor is produced (Leyden et al., 1981; Starkenmann, 2017).

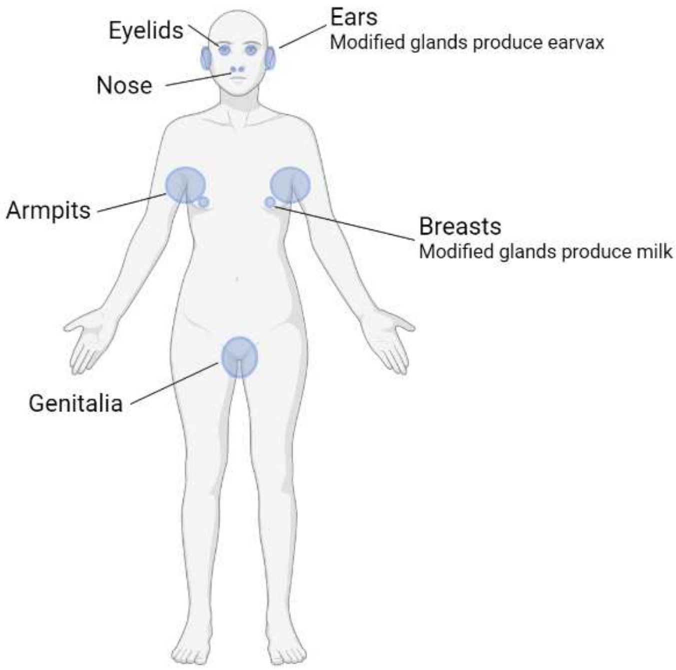

Fig. 2.1. Distribution of apocrine glands (highlighted in blue) on the whole human body.

The typical cutaneous environment, characterized by a cool, acid and desiccated habitat, represents the perfect niche for unique sets of microorganisms, defining the so-called *skin microbiome* (Grice & Segre, 2011). In addition, hair follicles, sebum from the sebaceous glands, and the high density of sweat glands in the axillary areas determine the perfect condition for the growth of bacterial colonization. In particular, the axillary area is mainly colonized by Corynebacterium, Staphylococcus, Streptococcus and b-Proteobacteria, all organisms that grow in areas of high humidity.

Despite the exact composition of the apocrine sweat being still unknown, what is clear is that the microbial activity undoubtedly leads to the development of the characteristic sweat odor (Fredrich et al., 2013). Moreover, the axillary microbiome, in combination with endogenous (e.g., sex, age, and individual host factors) and exogenous (e.g., cosmetics, detergents) characteristics contributes to creating the individual body odor (Fig. 2.2.).

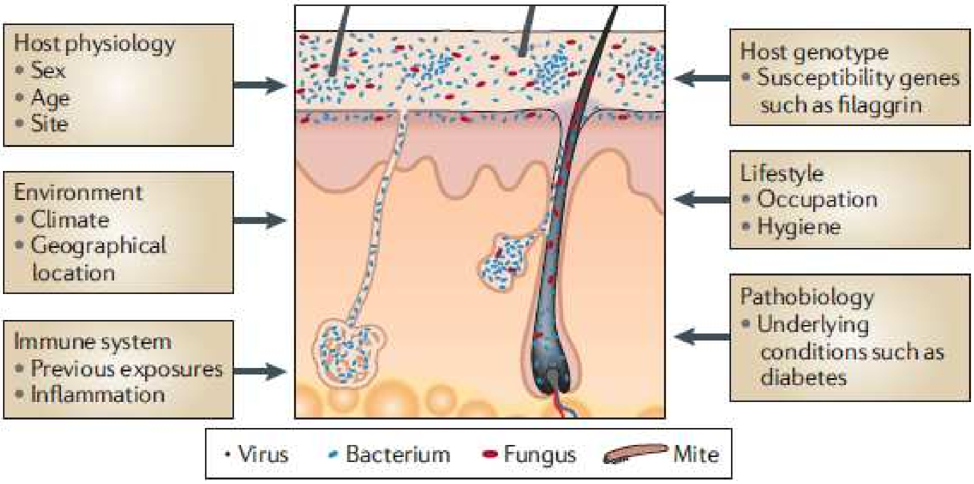

Fig. 2.2. Factors contributing to variation in the skin microbiome (adapted from Grice & Segre, 2011)

2.2.2. Inter- and intraindividual variation in body odor

Each individual present a broad variability of acids and this pattern is stable, unique, and carries information regarding the genetic identity of the individual, like a fingerprint (Kuhn & Natsch, 2009; Roberts et al., 2005). Moreover, besides the genetic influence, sweat odor is also affected by multiple factors among which we can mention diet, reproductive state, diseases, sexual orientation, emotional state and personality (Havlíček et al., 2017; Havlicek & Lenochova, 2008).

Genetic factors can, at least in part, explain odor individuality. Experimental evidence in support of this hypothesis arises from twin studies, showing that the hand odors of monozygotic twins were more easily discriminable than the ones from dizygotic twins (Wallace, 1977), but also the axillary odor of monozygotic twins was more easily matched than odors from dizygotic twins, even though twins were living apart (Roberts et al., 2005). This evidence suggests that our odor is relatively stable throughout life, as an “odor fingerprint”. However, on the other hand, human body odor can be shaped by the environment as well as by intrinsic factors.

Gender and age are stable factors that affect body odor quality. For instance, humans are able to assign men’s and women’s body odor to the correct gender categories in a frequency higher than chance and, generally, men’s body odor is judged as stronger and less pleasant (Doty et al., 1978;

Hold & Schleidt, 1977; Schleidt, 1980; Sorokowska et al., 2012). In addition, these differences are also confirmed by chemical analysis of the sweat samples obtained from men and women (Penn et al., 2007). Regarding age, humans can successfully discriminate, label and select the odor of old individuals (75-95 years old) when it is compared to the odor of younger individuals (Mitro et al., 2012). Moreover, a positive correlation has been found between the estimated age of strangers' body odor and their actual age (Sorokowska et al., 2012).

Some authors suggests that the diet is the most important environmental factor affecting body odors (Havlicek & Lenochova, 2008). Twin studies, again, helped in demonstrating this effect: humans were no longer able to discriminate hand odors of monozygotic twins when they underwent a different diet and this was difficult even for trained dogs (Hepper, 1988; Wallace, 1977). However, little is known yet on the impact of specific foods on body odors (Havlíček et al., 2017).

Another salient factor, connected to the gender, shaping our body odor, is the hormonal influences. The endocrine system controls several physiological processes and has a prominent role in motivation: hormone release is regulated by the hypothalamus, a structure involved in the motivational processes along with, among others, the orbitofrontal cortex and the amygdala (Schultheiss, 2013). In addition, apocrine glands are affected by hormones, mainly to communicate motivational states to other individuals, but also to indicate the reproductive status. Ovulation, in humans, is usually thought to be a concealed phenomenon. However, body odor gives important cues in identifying the reproductive status of the women, thus contributing to successful reproduction. Several pieces of evidence reported higher hedonic and attractiveness ratings of body odor of women in the follicular phase, but not for women using hormonal contraception (Gildersleeve et al., 2012; Kuukasjärvi et al., 2004; Singh & Bronstad, 2001). These results highlight the role of steroid hormones in shaping body odor, supposedly as a result of the amount or the ratios of estrogen and progesterone.

Linked to the role of hormones in modulating body odors, several studies have investigated if sexual orientation has an impact on body odor, however, no clear conclusions have been made yet. One study, investigating both heterosexual and homosexual men and women body odor pleasantness in groups of heterosexual and homosexual men and women, reported a complex pattern of findings but, overall, it seemed that the odor of homosexual men was perceived as less pleasant for all the group except for homosexual men (Martins et al., 2005). On the other side, another study investigating only the attractiveness of the odor of homosexual and heterosexual men in a group of heterosexual women reported that the odor of homosexual men was found to be more appealing than those of heterosexual men (Sergeant et al., 2007). Hence, it appears that sexual orientation can affect body odor, however, more research is needed to explore the underlying mechanisms linking sexual orientation to body odor.

Among the interindividual factors responsible for body odor variation is personality. When we meet a new person, we tend to attribute a range of psychological characteristics based on their appearance or on tiny clues from their behavior. Body odor can contribute to making the "first impression". Neuroticism and dominance can be detected by strangers (adults but also prepubertal children) only by smelling the axillary odor, and women appear to be more accurate than men (Sorokowska, 2013a, 2013b; Sorokowska et al., 2012). Dominance recognition can be due to the higher level of testosterone in people with dominance traits. Regarding neuroticism, the mechanism behind this association is not clear yet, but a possible explanation could lie in the emotional state, particularly anxiety, that characterizes individuals with neuroticism traits and that can impact the quality of the body odor (Albrecht et al., 2011; Fialová & Havlíček, 2012). The role of emotional states in shaping body odors will be reviewed in detail in the next paragraph.

Finally, body odor can be shaped also by health status. Already ancient medical authorities, such as Hippocrates and Galen, stated the importance of odors in medical diagnostics. Now we know that the changes in body odor can be due to altered metabolism or to a direct effect of infectious agents (Havlíček et al., 2017). Moreover, oncological patients present specific odor profiles that can be detected by trained dogs from breath or urine samples, in particular from patients suffering from lung, bladder, and prostate cancer (Moser & McCulloch, 2010).

Hence, each human has an individual odor that is stable across the lifespan. However, the volatile compounds present in the body odor are for the most part the result of metabolic activity, making the body odor vary according to a variety of intrinsic and extrinsic factors. Body odor contains a wide range of information about the sender that is processed by the receiver, modulating his/her perception, the physiological and neurophysiological state, and the behavior.

2.2.3. The role of chemosensory communication

In the previous sections, we underlined the factors that affect the quality of body odor. Given the amount of information these signals are carrying, what is the role of these odors in perceivers and in social communication? To summarize the literature on body odor communication, the principal types of body odors that affect everyday life are (1) romantic partner's body odor, (2) familiar or significant others' body odor, (3) strangers' body odor, and (4) own body odor.

Mate selection and romantic partner body odor

Body odor is an important source of information in mate selection, judged as even more important than physical attractiveness itself (Sergeant et al., 2005), especially for women (Havlicek et al., 2008; Herz & Cahill, 1997; Herz & Inzlicht, 2002). First, individuals tend to select potential partners with a dissimilar major histocompatibility complex (MHC) type to their own (Boehm & Zufall, 2006; Restrepo et al., 2006). The MHC is a gene complex that regulates T-cell activity, and therefore is involved in immune recognition. Hence, maintaining a high MHC polymorphism allows individuals to resist a wide range of pathogens, helping the survival of the species. In humans, this mechanism is mediated by the human leukocyte antigen (HLA). People commonly prefer the body odor of others with dissimilar HLA (Jacob et al., 2002; Santos et al., 2005; Thornhill et al., 2003; Wedekind et al., 1995; Wedekind & Füri, 1997). In addition, at a neural level, the body odor of donors with similar HLA is processed faster and requires more neutral responses (as measured with chemosensory event-related potentials, CSERPs) than the odor of people with dissimilar HLA, indicating avoidance behavior to preventing inbreeding (Pause et al., 2006).

In addition, body odor is involved in the process of physical attraction. Women reported preferring the body odor of symmetric men, an indication of physical health. Further, women's ratings of male physical attractiveness and ratings of male body odor attractiveness result to be highly correlated (Foster, 2008; Roberts et al., 2011). When in a romantic relationship, women's attention to other men's body odor is reduced (Lundström & Jones-Gotman, 2009). In addition, exposure to the body odor of a romantic partner reduces the autonomic response (i.e., reduced skin conductance) and the subjective evaluation of a stressful situation (Granqvist et al., 2018), improves sleep efficiency (Hofer & Chen, 2020), and provides a source of general comfort (Mahmut & Croy, 2019).

All in all, body odors appear to be essential in human mate choice, but also in the attractiveness of potential partners, and this phenomenon seems to be more pronounced in women.

Familiar or significant others' body odor

Kin recognition is the first function of body odors in structuring social relations in many species (Mehdiabadi et al., 2006). Being able to recognize family members and in-group members is of great importance to favorite prosocial behavior and to avoid predation from out-group members (Dunbar & Shultz, 2007a; Olsson et al., 2005). Experimental evidence reported that familiar members can be recognized by smelling their body odor: newborns are able to recognize their mother's odor, mothers and fathers can recognize their siblings' odor, siblings can recognize each other, but also strangers can match family members by smelling their body odor (Porter & Schaal, 2003; Porter & Winberg, 1999). Among the familiar body odor category, friends' odor can be included as well as kin and family members' odors. Indeed, it has been reported that smelling a friend's odor activates the same brain regions involved in familiar stimuli processing (Lundström et al., 2008). This result suggests that not only genetic, but also experience, is important in chemosensory communication.

Related to familiar body odor, another area in which human body odors are particularly relevant is mother-infant bonding. Mothers can successfully recognize their infant's body odor already one day after birth (Kaitz et al., 1987; Russell, 1983), and it is perceived as very pleasant and rewarding (Croy et al., 2017). This is also confirmed by the activation of reward-related brain areas in the mothers when smelling the infant's odor (Lundström et al., 2013; Nishitani et al., 2014), possibly as a priming effect motivating them for infant's care. At the same time, newborns can detect the mother's axillary odor, but also the breast skin's odor and the milk odor (Porter & Schaal, 2003; Schaal et al., 2004). In addition, newborns show a preferential orientation toward the mother's breast odor right after birth (Varendi et al., 1994), and 4-month-old infants look at human eyes for a significantly longer time when they are presented with the maternal odor compared to a nonsocial odor (Durand et al., 2013). Moreover, it has been recently shown that maternal body odor, compared to control olfactory stimuli, enhances selectively the categorization of salient visual signals (e.g., faces but not cars) response in 4-month-olds (Leleu et al., 2020; Rekow et al., 2020, 2021, 2022).

This early chemosensory communication between kin members but, specifically, between mother and infant, fosters the development of secure attachment, from one side, and motivates the caring for the infants, from the other side. In addition, it is another proof of the automatic processing of these types of social signals, which do not necessarily require conscious processing.

Strangers' body odor

Chemosensory communication involves the exchange of information between oneself and someone different from self. As it has been reviewed in the previous sections, the "other" can be someone with shared genetic features, a friend, without any genetic relationship but familiar due to learning and experience, or a stranger, with no genetic or learned bonds, and therefore potentially dangerous. Confirming this view, when smelling strangers' body odor neuroimaging studies reported in the perceiver an activation of the same brain areas involved in the perception of fearful faces or negative emotional stimuli, such as the inferior frontal gyrus and the amygdala, but also insular regions (Lundström et al., 2008; Morris et al., 1998; Whalen et al., 1998). In addition, they are also consciously perceived as more unpleasant and intense than a friend's body odor (Cecchetto et al., 2016; Lundström et al., 2008; Übel et al., 2017). These results suggest that strangers' body odor induces feelings of fear and disgust, being processed as potentially dangerous cues.

Own body odor

In the processing of discrimination between ourselves and the external world, the recognition of our own body odor has a prominent role. Humans are constantly, but mostly unconsciously, smelling themselves. This behavior is mainly achieved through self-face-touching and hand sniffing. Recently, it has been shown that this behavior is highly frequent, appearing about 20 times per hour (Perl et al., 2020). Behavioral evidence reported that humans, and even children, are able to recognize their own body odor from the odor of others (Hold & Schleidt, 1977; Mallet & Schaal, 1998; McBurney et al., 1976; Schleidt, 1980).

Self-smelling provides information both on others they have been in contact with, and on themselves. Humans commonly touch people whom they have close relationships, but also complete strangers, with the most common situation being handshaking. Indeed, after handshakes people tend to smell their hands more often than the non-shaking hand (Perl et al., 2020), mainly to obtain social information coming from the body odor. On the other side, humans smell their hands also to obtain information on intrinsic sources. As a conscious behavior, sniffing themselves can be associated to look at themselves in the mirror. Both behaviors are due to the need of verifying their aspect (if they "look good") as well as their own odor (if they "don't smell bad"). In addition, it can also provide a sense of *self*, subconsciously being a reassuring behavior serving to reduce stress and anxiety (Perl et al., 2020).

2.3. Chemosensory communication of emotions

In addition to the wide variety of stable and transient factors that can affect body odor, the emotional state is a dynamic state that can be transmitted to perceivers. As stated in the previous paragraphs, as a social species, for humans is of great relevance to be aware of the emotional state of the conspecifics. This is a phenomenon that is widely known also in other species, where animals facing stressful or dangerous situations produce chemicals that warn conspecifics about the current threat, triggering in them defensive behaviors. In humans, the study of analogous effects started only at the beginning of this century. Chen and Haviland Jones (2000) have been the first to study this phenomenon. In this first study, the authors addressed the question of whether people could correctly identify body odors produced in happy or fearful conditions. Specifically, happy body odor was collected from axillary pads while participants viewed a funny movie, conversely, the fearful odor was collected while they watched a frightening movie. Afterward, unrelated people were asked to select the "odors of people when they are happy" or to select the "odors of people when they are afraid" first in a 3-choice task, with two male or two female odors plus the control odor, then in a 6-choice task, with all the conditions. Results revealed that women were able to identify above-chance happy body odors collected from both male and female donors, while men only for female body odor. In addition, fearful body odors were correctly identified by both men and women only when the odors were collected from male donors, but not from female donors (Chen & Haviland-Jones, 2000). Similarly, Ackerl and colleagues (2002), using only fearful and neutral body odors (i.e., body odors collected during the viewing of frightening and non-frightening movies, respectively), reported that women were successful in discriminating between body odors collected in different emotional conditions. Moreover, fearful odors were also rated as more intense, and less pleasant than control odors (Ackerl et al., 2002).

After this first evidence, a number of studies confirmed these results, showing that human body odor is shaped by the emotional state of the donors, and these changes can be perceived by the receivers (Pause, 2004; Pause et al., 2009; Prehn et al., 2006). More importantly, individuals are not only able to discriminate between body odors produced in different emotional situations, but they also partially reproduce the affective, behavioral, perceptual and neutral state of the sender, in a phenomenon called *emotional contagion* (Hatfield et al., 1993). This effect can occur unconsciously and automatically (Semin, 2007).

From the increased interest in the study of emotion communication through body odor, the literature focused on the transmission of "negative emotions" (i.e., fear, stress or anxiety; de Groot & Smeets, 2017), while only recently new attention has been put also in the communication of "positive emotions" (i.e., happiness or sexual arousal; de Groot, Smeets, Rowson, et al., 2015; Iversen et al., 2015; Richard Ortegón et al., 2022; Zhou et al., 2011; Zhou & Chen, 2009) since happiness does not carry evolutionary salient information as fear.

From these studies, the emerging picture is that exposure to fear or anxiety body odor increases the perceptive abilities in order to detect potentially dangerous signals. Fearful body odor enhances vigilance (e.g., Chen et al., 2006; de Groot et al., 2012; de Groot, Smeets, & Semin, 2015), reduces the perceptual acuity for safety signals, such as happy faces (Pause et al., 2004; Zernecke et al., 2011), but increases the attention to threat signals, such as fearful and angry faces (Adolph et al., 2013; Mujica-Parodi et al., 2009; Zhou & Chen, 2009), but also for ambiguous signals, such as neutral facial expressions (Rubin et al., 2012). In addition, anxiety body odor affects also job performance: in a study performed on dentist students, it has been reported that the students' performance was significantly lower when exposed to anxiety body odors (Singh et al., 2018). Secondly, the fearful and anxiety body odors activate the motor system: in the context of anxiety body odor, the startle reflex is augmented, indicating an automatic preparation for action (Pause et al., 2009; Prehn et al., 2006). In addition, from a neural point of view, fearful and anxiety body odor induces higher event-related potentials (ERPs) (e.g., Adolph et al., 2013; Pause et al., 2010) and increased amygdala activity (Mujica-Parodi et al., 2009). Finally, to further confirm the emotional contagion hypothesis, it has been reported that fearful body odor elicited, in the receiver, facial expressions of fear or general negative affect (measured by the activity of the *medial frontalis* muscle and of the *corrugator supercilia*; de Groot et al., 2012, 2014a, 2014b; de Groot, Smeets, & Semin, 2015; de Groot, Smeets, Rowson, et al., 2015), as well as increased state anxiety (Albrecht et al., 2011). It is worth mentioning that, despite the first reports on body odor detection, recent studies consistently reported that humans present difficulties in correctly identifying the emotions conveyed by odors (Ackerl et al., 2002; Mujica-Parodi et al., 2009; Pause et al., 2004, 2010; Prehn-Kristensen et al., 2009; Zhou & Chen, 2009). Nevertheless, they presented coordinated responses that match the emotional state of the sender.

Regarding the communication of positive emotions, literature is scarce. The few studies available reported that women are able to distinguish between happy body odor and fear body odor or control odor (Chen & Haviland-Jones, 2000; Zhou & Chen, 2011), even though they were less accurate compared to the identification between fear body odor and control odor (Zhou & Chen, 2011). However, happy body odor appeared not to influence the perception of ambiguous stimuli (Zhou & Chen, 2009). On the other side, it has been demonstrated that happy body odor induced in the receiver a facial expression of happiness and a global processing style typical of happiness states (de Groot et al., 2015), and also increased creativity and reduced heart rate (Ortegón et al., 2022).

To sum up, induced emotional states of fear or anxiety shape the quality of the body odor. The body odor, once it is perceived by the receiver, generates a complex pattern of behavioral, physiological and neural responses that partially resemble the modification observed in the sender, presumably to prime the system to sensitively detect harm in the environment. In addition, odors are able to transfer not only negative states but also positive affect.

2.3.1. Chemosensory communication in affective disorders

Among mental disorders, depression and social anxiety are the most common and are both characterized by impaired social functioning. Social anxiety is characterized by intense fear and avoidance of social situations (Hofmann & Bögels, 2006; Rapee & Spence, 2004), and it has been proposed to be associated with increased activity of the defensive motivational system (Nusslock et al., 2015). Social anxiety is characterized also by abnormal processing of social threat information, with the presence of information-processing biases in attending to, interpreting and remembering social information (Hirsch & Clark, 2004). In particular, in the maintenance of the disorder, avoidance behaviors play a crucial role since they do not allow the extinction of fear of social situations (Stangier et al., 2006; Wells et al., 1995).

Conversely, depressive disorders are characterized by anhedonia, apathy and psychomotor retardation, which seem to be associated with hypoactivation of the appetitive motivational system (Henriques & Davidson, 1990; J. L. Stewart et al., 2010), resulting in a reduced propensity for approach-related action tendencies. This hypoactivation results in reduced motivation to respond in social interactions, altered empathic responses and the inability to find effective solutions for interpersonal problems (Kupferberg et al., 2016). Importantly, these dysfunctions persist even after remission of the depressive symptoms: indeed, social anhedonia is a core feature of depression and is characterized by the decreased enjoyment and interest in pleasant social interactions due to a reduced drive for approach behaviors and social affiliation (Kupferberg et al., 2016). Social impairment is so pervasive that both social anxiety disorder and depression are considered among the 5 most impairing psychiatric disorders (Alonso et al., 2004).

In the study of the approach-avoidance model in the domain of social motivation, researchers have focused predominantly on the acoustic and visual aspects of human social interaction, and only recently they have directed their attention to another relevant aspect, that is olfaction. As reviewed in the previous paragraphs, compared to other modalities, the transmission of social information through chemosignals has several advantages related to the intrinsic nature of the signal (Wyatt, 2003). For example, molecules can easily move across timely and physical barriers allowing the signal to be transmitted over long distances and to persist even after the sender is no longer in the place.

Despite the ability of body odors to convey emotional information, their role as a context in the processing of emotional stimuli is still widely unknown. However, it is particularly relevant in all conditions in which social interaction and emotional processing are impaired, such as affective disorders. To date, only a few studies have investigated the neural processing of chemosensory stimuli in social anxiety and all of them focused on fear or anxiety chemosignals. Accordingly, socially anxious individuals report enhanced startle reactivity (Pause et al., 2009) and faster processing of chemosensory anxiety signals compared to healthy controls (Pause et al., 2010) and this effect is similar to those obtained with threatening visual stimuli (i.e., Kolassa & Miltner, 2006; Mühlberger et al., 2009). When visual (fearful faces) and olfactory (chemosensory anxiety signals) stimuli were presented together, high social anxious individuals show enhanced motivated attentional allocation (LPP) and larger startle responses than healthy controls (Adolph et al., 2013). With respect to depression, to our knowledge, no studies have investigated whether depressed individuals report reduced sensitivity toward chemosensory signals, according to the hypothesis that depression is characterized by a reduced drive for approach behaviors and social signals (Kupferberg et al., 2016). Furthermore, there are no studies, to date, providing information regarding the processing of happiness chemosignals in patients with affective disorders. Determining if there is dysregulation also in the processing of happiness chemosignals could shed light on the complex interplay between the two motivational systems in the development and course of an affective disorder.

PART II:

The experiments

CHAPTER 3

Processing of human body odors[3]

3.1. Abstract

Across phyla, chemosignals are a widely used form of social communication and increasing evidence suggests that chemosensory communication is present also in humans. Chemosignals can transfer, via body odors, socially relevant information, such as specific information about identity or emotional states. However, findings on neural correlates of processing of body odors are divergent. The aims of this meta-analysis were to assess the brain areas involved in the perception of body odors (both neutral and emotional) and the specific activation patterns for the perception of neutral body odor (NBO) and emotional body odor (EBO). We conducted an activation likelihood estimation (ALE) meta-analysis on 16 experiments (13 studies) examining brain activity during body odors processing. We found that the contrast EBO versus NBO resulted in significant convergence in the right middle frontal gyrus and the left cerebellum, whereas the pooled metaanalysis combining all the studies of human odors showed significant convergence in the right inferior frontal gyrus. No significant cluster was found for NBOs. However, our findings also highlight methodological heterogeneity across the existing literature. Further neuroimaging studies are needed to clarify and support the existing findings on neural correlates of processing of body odors.

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3.2. Introduction

As a social species, humans depend on social communication to create and maintain social relationships and attain well-being and health (Pause, 2017). Along with extensively studied forms of social communication used by human beings, such as the visual (e.g., facial expressions or gestures) and acoustic (e.g., voices) modalities (Semin & de Groot, 2013), the olfactory modality has recently garnered attention. In contrast to other sensory-based forms of communication, the olfactory "messages" are usually unintentionally released by the emitter and processed unconsciously by the perceiver. The messages are composed of chemicals, called chemosignals, contained in body odors (Parma et al., 2017; Semin et al., 2019).

The human body delivers a wide range of chemicals that can be interpreted as signals. To date, investigators primarily focused on sweat chemicals produced in the axillary areas (Doty, 2010). Human sweat odors result from the combined activity of skin glands and bacteria. Among skin glands, the apocrine type, mostly located in the axillary and pubic regions, is thought to play a major role in social communication. The apocrine glands, which become functional around puberty, produce small quantities of milky lipid- and protein-rich odorless fluid. This fluid is then metabolized by bacteria producing volatile and nonvolatile substances such as sulfanylalkanols and steroids, which are the precursors of the sweat odor (see Parma et al., 2017 for a review). It has been shown that each individual presents a broad variability of odorant acids and that this pattern is unique and stable over time, reasonably due to genetic influence, as suggested by monozygotic twins studies (Kuhn & Natsch, 2009; Roberts et al., 2005) and studies on major histocompatibility complex (MHC)-associated mate choice (Havlicek & Roberts, 2009). Growing evidence (see Havlíček et al., 2017; Havlicek & Lenochova, 2008) suggests that, besides genetic influence, other internal and external factors, such as diet, hormonal variations, and health status, could influence the variability of body odors.

The above-mentioned factors have to be considered when collecting sweat to study human body odors. Even though there is still no consensus about a standard way to collect body odors, and the sampling procedure can be quite heterogeneous across studies (see Parma et al., 2017 for a review of the applied experimental setups), there are some aspects that are usually kept constant: 1) the removal or standardization of all the external possible confounders related to hygiene, diet, and behaviors that can affect body odor (e.g., avoiding second-hand smoking, physical exercise, and stressful situations); 2) the collection of the sweat from the armpits through a sterile cleaned cotton pads (or gauze or cotton t-shirt) to prevent contamination; 3) the storage of the samples at freezing temperature below −24°C to prevent the bacteria from continuing to metabolize and degrade the substrate. Indeed, even though bacterial activity is fundamental to produce volatile molecules, the experimental protocols applied prior, during, and post-collection of body odors are particular important to refrain bacteria to excessively grow and to produce malodors, that can negative affect the experimental procedure (Mujica-Parodi et al., 2009; Parma et al., 2017).

The literature on human body odors can be divided in two sections: the transmission of emotional states and the transmission of information related to the identity of the individual. Researchers have examined whether humans can communicate emotions such as fear or anxiety (see de Groot & Smeets, 2017 for a recent review), happiness (e.g., Zhou & Chen, 2009; de Groot et al., 2015), disgust (e.g., Zheng et al., 2018), aggression (e.g., Mutic et al., 2017) and competition (Adolph et al., 2010). Individuals exposed to emotional body odors (EBOs) exhibit behavioral effects, such as increased startle response (Adolph et al., 2013; Prehn et al., 2006), biased identifications or judgments (Dalton et al., 2013; Wudarczyk et al., 2016; Zernecke et al., 2011), higher risk-taking behavior (Haegler et al., 2010), generation of emotional facial expressions (de Groot et al., 2012; de Groot, Smeets, Rowson, et al., 2015; Kamiloğlu et al., 2018) or lower practice performance (Singh et al., 2018).

Besides emotional states, evidence suggests that human body odors can also transmit information related to the identity of an individual. Studies showed that not only are mothers able to discriminate and prefer the odor of their own baby (Kaitz et al., 1987; Porter & Moore, 1981; Russell et al., 1983), but that humans in general can distinguish the odor of a kin or a friend's odor from that of strangers' (Lundström & Jones-Gotman, 2009; Olsson et al., 2006; Wallace, 1977; Weisfeld et al., 2003). Moreover, the investigation of odor preference conjectured that pleasantness rating of human body odors may be affected by genetics (e.g., Jacob et al., 2002; Kromer et al., 2016; Pause et al., 2006; but see for a critical review Havlicek & Roberts, 2009), the gender (Martins et al., 2005), the age (Mitro et al., 2012), the sexual orientation (Martins et al., 2005), the health status (Olsson et al., 2014; Regenbogen et al., 2017), the ethnicity (Parma et al., 2019), and the personality traits (Sorokowska et al., 2012) of the body odor of donors, however, further research is needed to confirm and clarify the results. Finally, as with emotional chemosignals, neutral body odors (NBOs) also seem to affect perceivers' behavior (Cecchetto et al., 2020; Cecchetto, Lancini, Rumiati, et al., 2019). Interestingly, these effects were observed although the participants could not differentiate the odors, suggesting that they can induce behavioral effects outside of conscious access.

With the interest in human chemosignals, neuroimaging studies examining the neural correlates of processing of olfactory social signals are accumulating. Lundström et al. (2008) was the first study to demonstrate that human body odors engage cortical areas that are not typically active during processing of common odors, as the occipital cortex, the angular gyrus, and the anterior and posterior cingulate cortex. Further investigations revealed that different brain areas are participating in the processing of different body odors. Strangers' body odors activate the inferior frontal gyrus (IFG) and the amygdala (Lundström et al., 2009), whereas a friend's odor activates the retrosplenial cortex (Lundström et al., 2009). Regarding emotional communication, the anxiety-related body odors was investigated through different experimental designs, which revealed heterogeneous brain networks. One study reported the fusiform gyrus, insula, precuneus, cingulate cortex, thalamus, dorsomedial prefrontal cortex, and cerebellum (Prehn-Kristensen et al., 2009), whereas another study the activation of the amygdala (Mujica-Parodi et al., 2009). On the other hand, Wudarczyk et al., (2015) showed that the exposure to anxiety-related chemosignals during fearful faces increased activity in left insula and left middle occipital gyrus extending to the fusiform gyrus. The exposure to anxiety chemosignals during a task priming social exclusion (Cyberball task) showed reduced activation in hippocampus, middle temporal gyrus, superior temporal gyrus and IFG compared with the neutral chemosensory condition (Wudarczyk et al., 2015). Body odors produced during an emotion of disgust activated the fusiform face area, amygdala, and orbitofrontal cortex (OFC; Zheng et al. 2018), whereas body odors produced during a condition of imaginary aggression activated the thalamus, hypothalamus, and insula (Mutic et al., 2017).

Due to the multitude of brain regions associated with different aspects of human body odors processing, there has not yet been a consensus regarding consistent involvement of specific brain regions in processing of body odors. Hence, we conducted a meta-analysis examining studies of brain activity elicited in response to experimental manipulations of human body odors in order to uncover brain areas 1) specifically involved in the processing of NBOs and of EBOs and 2) consistently evoked across all types of human body odors (both neutral and emotional).

3.3. Material and Methods

Literature search

Literature search was performed on January 2020 on PubMed and PsycINFO using the following search string: (fMRI AND chemosignals) OR (fMRI AND human body odors) OR (fMRI AND body odor) OR (fMRI AND social odor) OR (fMRI AND chemosensory) OR (fMRI AND chemosensory signals) OR (fMRI AND sweat) OR (fMRI AND chemosensory cues) OR (fMRI AND chemosignaling) OR (fMRI AND chemosensory communication). Additionally, three more studies were tracked through the screening of one recent book chapter on human body odors (Parma et al., 2017). The protocol of the meta-analysis was registered on the Open Science Framework (https://osf.io/uvghb/).

Inclusion and exclusion criteria

Studies were included if they met the following criteria: 1) the receivers were healthy human participants, normosmic, and nonsmoking; 2) involved human body odors acquired form the armpit region on absorbent material; 3) they were functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) studies; 4) 3D coordinates of peak activations in stereotactic space of the Montreal Neurological Institute (MNI) or Talairach were reported; 5) reported on whole brain analysis; 6) they reported original data (i.e., secondary analysis were excluded). Two independent authors (C.C., E.D.B.) performed the search and the selection, with discrepancies resolved through discussion.

ALE meta-analysis

Three meta-analyses were conducted using the GingerALE 2.3.6 software (http://www.brainmap.org/ale/; Eickhoff et al., 2009): 1) one analysis was conducted on the contrast EBO > NBO and, when available on NBO > EBO; 2) another individual analysis was conducted on NBO > control odor (CO) and on CO > NBO; 3) finally, to better highlight the network involved in body odor perception, we computed a pooled meta-analysis combining all the studies using human odors. Stereotactic coordinates (x, y, z) were extracted from the studies. Coordinates in the MNI152 standard space were converted into the Talairach space using the GingerALE foci converter tool. Activation likelihood estimates were calculated for each voxel by modelling each coordinate of reported activation foci using a Gaussian probability function. The full-width half-maximum of the Gaussian function used to blur the foci was calculated using the sample size for each experiment (Eickhoff et al., 2009). The clusters were formed using permutation testing (2000 permutations), with a correction for multiple comparisons (using the cluster-wise method integrated in GingerALE, $P < 0.05$) and an uncorrected P-value at $P < 0.001$. For each cluster from each analysis, we report the region labels, Talairach coordinates, the peak ALE P-value and the cluster volume.

3.4. Results

Selection and excluded studies

As shown in the PRISMA flowchart (Figure 3.1), the string produced 780 records that were screened in order to exclude reviews, book chapters, studies that were not performed on healthy human participants, studies that did not use real human sweat odors, and studies which did not include fMRI or PET measurements. Of the remaining 21 studies, 5 were excluded because they were duplicates.

Of the remaining 16 records, the full text was evaluated: 1 study (Radulescu & Mujica-Parodi, 2013) was excluded because it was a reinvestigation of the dataset used in Mujica-Parodi et al., 2009; Lübke et al. (2014) and the first study presented in Mujica-Parodi et al. (2009) were excluded because ROI analyses were performed and the coordinates of whole-brain analysis were not available; Wudarczyk et al. (2015) was excluded because the contrasts "chemosensory anxiety cues-chemosensory sports cues" and vice versa were not significant. Therefore, our meta-analysis included 16 experiments (from 13 studies; Cecchetto et al., 2020; Cecchetto, Lancini, Bueti, et al., 2019; Lundström et al., 2008, 2009, 2013; Mujica-Parodi et al., 2009; Mutic et al., 2017; Prehn-Kristensen et al., 2009; Regenbogen et al., 2017; Wudarczyk et al., 2016; Zheng et al., 2018; Zhou et al., 2011; Zhou & Chen, 2008).

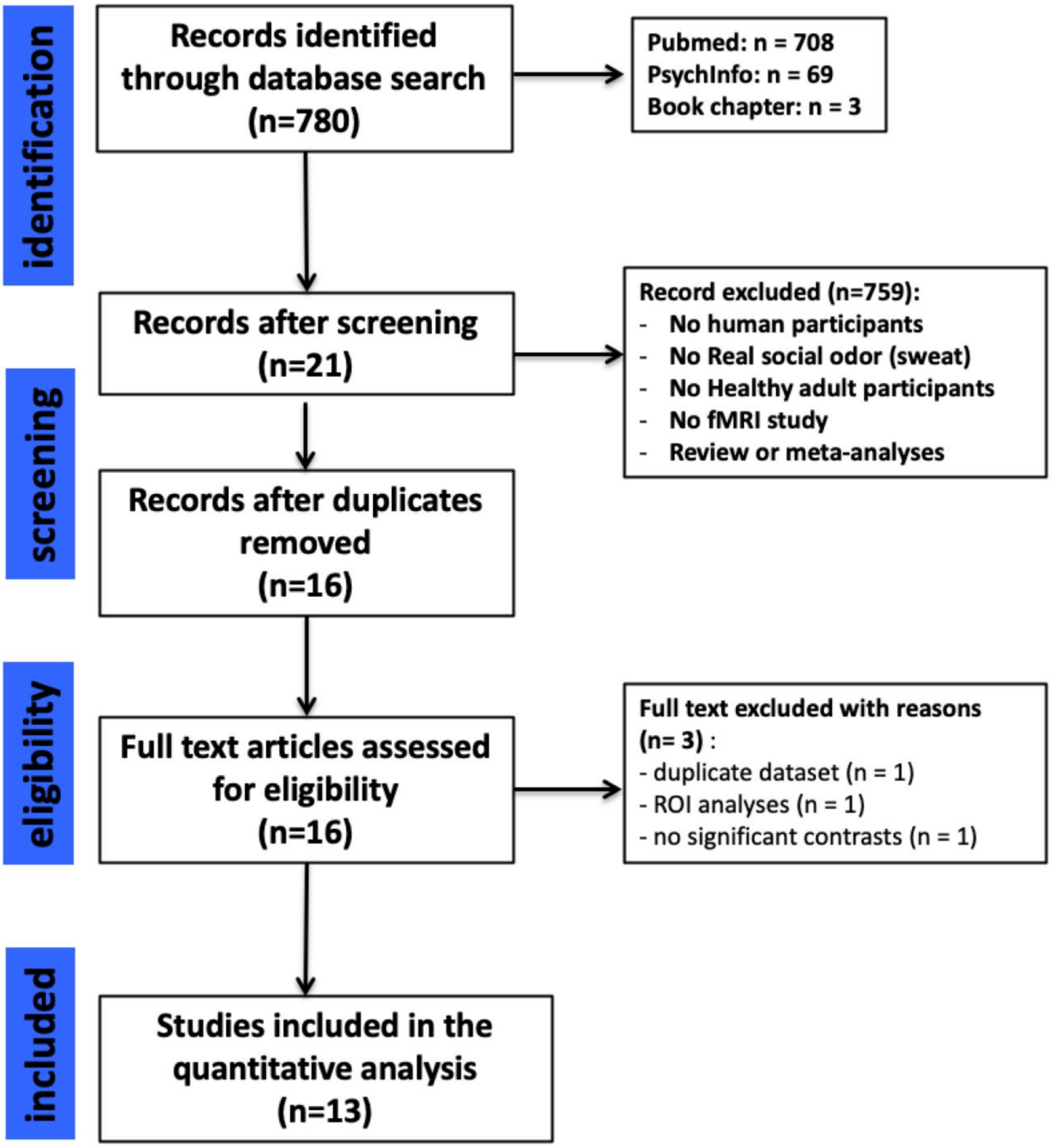

Fig. 3.1. Prisma flow-chart illustrating the selection process of the present meta-analysis.

Characteristics of included studies

The 13 included studies (see Table 3.1), published between 2007 and 2020, are 2 PET studies (Lundström et al., 2008, 2009) and 11 fMRI studies (Cecchetto et al., 2020; Cecchetto, Lancini, Bueti, et al., 2019; Lundström et al., 2013; Mujica-Parodi et al., 2009; Mutic et al., 2017; Prehn-Kristensen et al., 2009; Regenbogen et al., 2017; Wudarczyk et al., 2016; Zheng et al., 2018; Zhou et al., 2011;

Zhou & Chen, 2008). They reported data of 291 (231 females) healthy, nonsmokers, heterosexual, and normosmic participants, between the age of 20 and 32. The sweat odors presented were collected from a total of 262 donors. In six studies (Cecchetto, Lancini, Bueti, et al., 2019; Mutic et al., 2017; Wudarczyk et al., 2016; Zheng et al., 2018; Zhou et al., 2011; Zhou & Chen, 2008), the donors were only males, in three studies (Cecchetto et al., 2020; Lundström et al., 2008, 2009) only females, and in three studies (Mujica-Parodi et al., 2009; Prehn-Kristensen et al., 2009; Regenbogen et al., 2017) of both gender. In one case (Lundström et al., 2013), the sweat odor was collected from infants of 3–6 weeks old. The sampling methodology applied in the 13 studies varies widely. Regarding the medium of sampling, six studies used cotton pads sewn in tight cotton-t-shirt (Cecchetto et al., 2020; Lundström et al., 2008, 2009; Mutic et al., 2017; Regenbogen et al., 2017; Zheng et al., 2018), two studies used just cotton pads (Prehn-Kristensen et al., 2009; Wudarczyk et al., 2016), two studies used rayon/polyester pads (Zhou et al., 2011; Zhou & Chen, 2008), one study gauze sponges (Mujica-Parodi et al., 2009), and two studies (Cecchetto, Lancini, Bueti, et al., 2019; Lundström et al., 2013) used cotton t-shirts that were later cut in the axillary areas. In all studies, donors were asked to follow hygiene, dietary, and behavioral restrictions the 2 days before the sampling day, such as using only free-parfum body products provided by the experimenters. Additionally, in Mujica-Parodi et al. (2009), donors had their underarms shaved and washed with a nonionic detergent before the application of the pads.

In five studies (Cecchetto et al., 2020; Cecchetto, Lancini, Bueti, et al., 2019; Lundström et al., 2008, 2009, 2013), the sweat odor was collected in a neutral condition and presented to the participants, through an olfactometer, masked by a common odor (Cecchetto et al., 2020; Cecchetto, Lancini, Bueti, et al., 2019) or in the natural composition (Lundström et al., 2008, 2009, 2013). In two of these studies (Lundström et al., 2008, 2009), the odor was collected during sleeping time for 7 consecutive nights, while in the other two studies (Cecchetto et al., 2020; Cecchetto, Lancini, Bueti, et al., 2019), the odor was sampled for 12 consecutive hours during the day. In the study involving infants, body odor was collected for two consecutive nights after the partum (Lundström et al., 2013). In one study (Regenbogen et al., 2017), the sweat odor was collected for 5 h after the injection of an endotoxin, so during a sickness condition, and after the injection of placebo, so during a healthy condition. In seven studies (Mujica-Parodi et al., 2009; Mutic et al., 2017; Prehn-Kristensen et al., 2009; Wudarczyk et al., 2016; Zheng et al., 2018; Zhou et al., 2011; Zhou & Chen, 2008), the sweat odor was collected twice: once during an emotional situation (e.g., stress, anxiety, sexual, disgust, aggression) and once during an exercise or neutral situation for the control condition. In three of these studies (Zheng et al., 2018; Zhou et al., 2011; Zhou & Chen, 2008), odor was sampled while donors were watching a 20 min emotional or neutral video. In Mujica-Parodi et al. (2009) and Mutic et al. (2017), also the sampling lasted for 20 min but during a skydiving activity or a mental calculation task for the emotional condition and physical activity for the neutral condition. In Prehn- Kristensen et al. (2009) and Wudarczyk et al. (2016), the odors were collected for 60 min prior to an oral examination or during physical activity. In six of these emotional task studies, authors reported to control the successful of emotion induction through skin conductance measure (Zhou et al., 2011; Zhou & Chen, 2008), self-rating questionnaires (Mutic et al., 2017; Wudarczyk et al., 2016), cortisol level (Mujica-Parodi et al., 2009; Prehn-Kristensen et al., 2009; Wudarczyk et al., 2016). Interestingly, Mujica-Parodi et al. (2009) performed gas chromatography mass spectroscopy as well as calculations using Henry's law to control the used collection and delivery methods resulted in the presentation of sweat molecules.

The tasks used to investigate human body odor effect differed across the 13 studies: while in 8 studies the investigated brain activity was just associated to odor perception (Lundström et al., 2008, 2009, 2013; Mujica-Parodi et al., 2009; Prehn-Kristensen et al., 2009; Regenbogen et al., 2017; Zhou et al., 2011; Zhou & Chen, 2008), the other studies explored the effects of human body odors on associated tasks including moral decision-making (Cecchetto, Lancini, Bueti, et al., 2019), encoding-recognition of faces (Cecchetto et al., 2020), emotion recognition (Wudarczyk et al., 2016), emotional stroop task (Mutic et al., 2017), and food judgment (Zheng et al., 2018). Notably, all studies included ratings of the perceptual features of the odor conditions to ensure that the odor categories were perceived similar and that participants were not able to consciously distinguish between them. All studies found no significant differences between the body odors and the control odors except for Regenbogen et al. (2017), which found body odors being rated as less pleasant than the control odor but equally intense, and Zhou et al. (2011), in which the sexual sweat was perceived as more intense and less pleasant than the neutral sweat, however, these perceptual differences were statistically controlled in the analysis of the brain activity.

Table 3.1. Characteristics of the studies included in the meta-analysis

Study ID	Study	Receivers				Donors				Odor condition	Task	Sensory modalities
		Subjects	**Total**	**M/F**	**Age (SD)**	**Subjects**	**Total**	**M/F**	**Age (SD)**			
1	Lundström et al. 2007	healthy controls	15	0/15	23 (2.9)	participants and close friend	30	0/30		odor-free baseline, odor control, self BO, friend BO, and stranger BO	odor perception	olfactory
2	Zhou and Chen 2008	healthy controls	19	0/19	23.4 (0.8)	healthy subjects	3	3/0	28 (1.7)	sexual BO, neutral BO, sex pheromone (PSP), PEA as a non-social control	odor perception	olfactory
3	Lundström et al. 2009	healthy controls	12	0/12	24 (2.8)	participant's biological sister	12	0/12	23 (4)	participant's biological sister BO, participant's close friend BO, odor control	odor perception	olfactory
						participant's close woman friend	12	0/12	22 (2.7)			
4	Mujica-Parodi et al. 2009	healthy controls	16	8/8	22 (3)	healthy subjects	40	20/20		stress BO, exercise BO	odor perception	olfactory
5	Prehn-Kristensen et al. 2009	healthy controls	28	14/14	22.1 (2.9)	healthy subjects	49	28/21	24.3 (3.9)	anxiety BO, sport BO	odor perception	olfactory
6	Zhou et al. 2011	healthy controls	19	0/19	23.4 (0.93)	healthy subjects	6	6/0		sexual BO, neutral BO + sex pheromone androstadienone (ANDR) and phenyl ethyl alcohol (PEA) as non-social control	odor perception	olfactory

7	Lundström et al. 2013	healthy controls	30	0/30		primiparous' neonatal	15		3-6 weaks	neonatal BO	odor perception	olfactory
		nulliparous	15		22.1 (1.9)							
		primiparous	15		28.6 (4.1)							
8	Wudarczyk et al. 2016	healthy controls	24	14/10	24.33 (2.91)	healthy subjects	10	10/0	26.40 (3.75)	anxiety BO, sport BO	emotional recognition task	olfactory + visual
9	Mutic et al. 2017	healthy controls	18	9/9	26.61 (4.48)	healthy subjects	16	16/0	25.23 (3.75)	exercise BO, aggression BO	emotional stroop task	olfactory + visual
10	Regenbogen et al. 2017	healthy controls	30	15/15		healthy subjects	18	9/9	23.41 (3.62)	sick BO, healthy BO	odor and face perception	olfactory + visual
11	Zheng et al. 2018	healthy controls	16	0/16	21	healthy subjects	14	14/0	19.8	disgust BO, neutral BO, neutral odorants, disgust odorants	food judgment task	olfactory + visual
12	Cecchetto et al. 2019	healthy controls	28	0/28	23.7 (4.2)	healthy subjects	10	10/0	26.3 (3.6)	neutral BO	moral decision-making task	olfactory + visual
13	Cecchetto et al. 2020	healthy controls	36	0/36		healthy subjects	27	0/27	22.11 (4.32)	neutral BO	incidental-encoding task	olfactory + visual
		BO	19		24.21 (2.84)							
		MASK	17		26 (5.61)							

ALE results

The first analysis focused on the contrast EBO > NBO, and, if available, NBO >EBO (Experiments 2, 4–6, 8–10, 12–13; see Table 3.2). This included 51 foci and a minimum cluster size of 440 mm3. The analysis revealed two significant clusters in the right middle frontal gyrus (MFG) and in the left cerebellum (Table 3.3, see Figure 3.2). The second meta-analysis examined the contrast NBO > CO and CO > NBO (1, 3, 7, 14–16; see Table 3.2). The analysis included 32 foci; the minimum cluster size was 488 mm^3. No significant clusters were found. Finally, we jointly analyzed all the studies using human odors (studies included in Table 3.2). This included 89 foci and a minimum cluster size of 520 mm^3. The analysis revealed one significant cluster in the right IFG (Table 3.3, see Figure 3.2).

Since the study by Lundström et al. (2013) is the only one using infant body odors instead of adult body odors, we performed a sensitivity analysis after excluding this article. Given the contrast proposed in this article (NBO > CO), the sensitivity analysis was narrowed to the NBO > CO, CO > NBO analysis and pooled metaanalysis only. The result was consistent with the results of the main meta-analysis. In particular, for the contrast NBO > CO and CO > NBO the minimum cluster size was 464 mm^3, and no significant clusters were found. For the pooled meta-analysis, the minimum cluster size was 664 mm^3, and the analysis revealed one significant cluster in the right IFG (Center of mass: x = 32.6, y = 37.5, z = 0.4; peak: x = 30, y = 28, z = 4; peak ALE P-value = 0.009; Cluster volume = 816 mm^3).

Table 3.2. Description of contrasts reporting a direct comparison between body odors and control condition or between emotional and neutral body odor in each included study

Exp. ID	Study	Method	Contrasts	# of foci	Statistical threshold
1	Lundström et al. 2007	PET	Conjunction analysis: all BO conditions (Stranger, Friend, and Self) > Baseline condition	5	p < 0.001 uncorrected for a whole-brain search volume
2	Zhou and Chen 2008	fMRI	omnibus F test: sexual BO > neutral BO > controls	2	p < 0.0005 uncorrected
3	Lundström et al. 2009	PET	81onjunction analysis: kin detection > control (sister vs friend + sister vs baseline)	10	p < 0.001 uncorrected for a whole-brain search volume
4	Mujica-Parodi et al. 2009	fMRI	stress BO > exercise BO	4	p < 0.001 uncorrected
5	Prehn-Kristensen et al. 2009	fMRI	anxiety BO > sport BO	29	whole brain analysis; p = 0.001; uncorrected
6	Zhou et al. 2011	fMRI	sexual BO > neutral BO	1	p < 0.0005 uncorrected
7	Lundström et al. 2013	fMRI	neonatal BO > odorless air	6	p < 0.05 whole-brain analyses corrected using a false discovery rate (FDR)
8	Wudarczyk et al. 2016	fMRI	anxiety BO > sport BO	5	Monte Carlo simulations p = 0.001 uncorrected
9	Wudarczyk et al. 2016	fMRI	sport BO > anxiety BO	1	Monte Carlo simulations p = 0.001 uncorrected
10	Mutic et al. 2017	fMRI	aggression BO > exercise BO	4	p < 0.05 whole-brain analyses family-wise error (FWE)
11	Regenbogen et al. 2017	fMRI	sick BO > healthy BO	6	p < 0.05 whole-brain analyses family-wise error (FWE)
12	Zheng et al. 2018	fMRI	BO (disgust + neutral) > odor (disgust + neutral)	2	p < 0.005 uncorrected
13	Zheng et al. 2018	fMRI	odor (disgust + neutral) > BO (disgust + neutral)	3	p < 0.005 uncorrected
14	Cecchetto et al. 2019	fMRI	masked BO > masker	2	p < 0.05 whole-brain analyses family-wise error (FWE)
15	Cecchetto et al. 2019	fMRI	masker > masked BO	6	p < 0.05 whole-brain analyses family-wise error (FWE)

16	Cecchetto et al. 2020	fMRI	BO (odor > air) > mask (odor > air)	3	$p < 0.05$ whole-brain analyses family-wise error (FWE)

Table 3.3. Significant clusters for the comparison between emotional body odor (EBO) and neutral body odor (NBO) and the pooled meta-analysis combining all the studies.

Contrast	Cluster	Site	Region	BA	Center of mass			Peak			Peak ALE value	Cluster volume
					x	y	z	x	y	z		
EBO > NBO	1	L	Cerebellum		-9.4	-31.4	-20.4	-10	-30	-20	0.016	576 mm^3
	1	L	Cerebellum					-12	-38	-22	0.009	
	2	R	Middle frontal gyrus	11	33	39.9	-1	32	40	-2	0.015	456 mm^3
All BO > Baseline	1	R	Inferior frontal gyrus	45	32.7	37.8	0.3	30	28	4	0.009	784 mm^3

Note: Talairach coordinates for the two ALE meta-analysis with significant results for all human body odors > baseline; Emotional body odors > Neutral body odors. L: left; R: right; BA: Broadman Area.

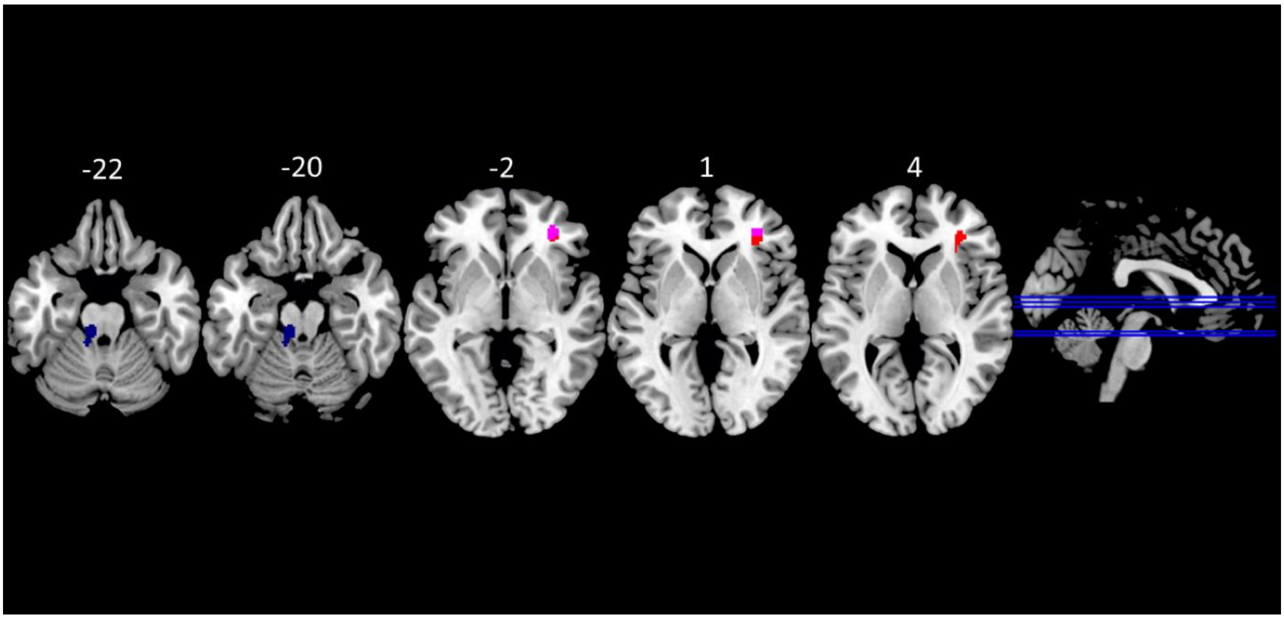

Fig. 3.2. Localization of significant clusters (FDR, $P < 0.05$) in the ALE analysis (superimposed on a ch2bet template using MRIcroN) for the contrast EBO > NBO (blue color) and for the pooled analysis combining all the studies using human odors (red color). Violet color represents neural overlapping regions. The left side of the image indicates the left side of the brain, and the right side of the image indicates the right side of the brain. The numbers represent the z-value of slice according to the MNI stereotactic reference system.

3.5. Discussion

The aims of this ALE meta-analysis were: 1) to explore the specific brain regions associated with the perception of the NBOs and of the EBOs and 2) to evaluate the areas involved in the perception of human body odors (both neutral and emotional).

Our findings emphasize that neuroimaging literature on human body odors is still limited, particularly with regards to NBO. Furthermore, studies used heterogeneous methodologies and produced mixed results. These limitations are consistent with the preliminary nature of this meta-analysis that, to the best of our knowledge, is the first to evaluate the neural correlates of human body odors. Nevertheless, the results indicated that the right MFG and the left cerebellum emerged specifically in the contrast EBOs versus NBOs, whereas no significant convergence was found for the NBOs. Moreover, the right IFG resulted from the pooled meta-analysis combining all the studies using human body odors (both neutral and emotional). The areas for which we report significant convergence have all been previously related to many cognitive processes. Therefore, it is difficult to draw specific interpretations without running the risk of reverse inference bias (Poldrack, 2006). For instance, the right MFG, emerged in the contrast emotional versus NBOs, has been found in a variety of cognitive tasks such as phonological processing (Tan et al., 2005), semantic priming (Laufer et al., 2011), emotion regulation (Vrtička et al., 2011), and in the wider network of chemosensory processing (Seubert, Freiherr, Djordjevic, et al., 2013). The MFG is generally considered to be part of the Dorsal Attention Network (with the temporoparietal junction, ventral frontal cortex, frontal operculum, and anterior insula) where it presumably acts as a "circuit-breaker," interrupting ongoing processes and reorienting the attention toward more relevant stimuli (Corbetta et al., 2008). In the neuroimaging of body odors processing, in particular, the activation of MFG was reported in Mutic et al. (2017) for the processing of aggression chemosignals, suggesting a possible implication of this area in attentional processing of possible danger. Given our findings cover different emotional chemosignals, we speculate a more general role in reorienting an individual's attention, which would need to be substantiated by further studies.

The contrast EBOs versus NBOs also highlights a significant convergence in the left cerebellum. Although the cerebellum is mostly recognized for its role in motor function, its connections to the midbrain and the limbic system have supported its involvement in emotion and emotion regulation (Schutter & van Honk, 2005). Specifically, the involvement of the cerebellum was shown for a wide range of emotion related domains, such as perception and recognition, encoding, experience and regulation of emotions, emotional learning, and emotional aspects of speech (for a review see Adamaszek et al., 2017). Importantly, the cerebellum, in particular the vermis, which is connected to the brain stem, hypothalamus, limbic areas such as amygdala, hippocampus, and sensory cortices, may act as an interface between the sensory stimuli, emotional states, and motor responses (Clausi et al., 2017). Interestingly, the cluster in the left cerebellum has been found at a single study level in five studies (Lundström et al., 2009; Mujica-Parodi et al., 2009; Prehn-Kristensen et al., 2009; Regenbogen et al., 2017; Wudarczyk et al., 2016). Though findings related to the cerebellum are difficult to interpret given that this area has been mostly associated with motor control, they highlight the need for further investigations into its role in human body odor perception.

The pooled meta-analysis combining all the studies using human odors resulted in a significant convergence in the right IFG. The right IFG has been implicated in a wide range of experimental tasks such as fine movement control (Liakakis et al., 2011), inhibition and attentional control (Hampshire et al., 2010; Hampshire & Owen, 2006) and target detection (Hampshire et al., 2009). This area has also been linked to several tasks more related to social cognition, such as the ability to understand others' intentions (de C. Hamilton & Grafton, 2008; Iacoboni et al., 2005; Liu et al., 2016; for a recent meta-analysis see Adolfi et al., 2017), the empathic response (Baird et al., 2011; Shamay-Tsoory et al., 2009), and the perception of facial expressions (e.g., Adolphs, 2002;

Hennenlotter et al., 2005; Jabbi & Keysers, 2008; van der Gaag et al., 2007). The IFG is also considered an important hub in the human mirror neuron system (Gallese et al., 2004), hence implicated in the basic aspects of social communication. Interestingly, Lübke et al. (2014), a study that was not included in our meta-analysis, also found activation in the right IFG. In this study, individuals with high versus low social openness evoked higher activation in this area during the perception of neutral human body odors. Conversely, in our meta-analysis, four included studies specifically contributed to the right IFG cluster: three of these brought the contrast EBO versus NBO (sexual body odor: Zhou & Chen, 2008; anxiety body odor: Prehn-Kristensen et al., 2009; Zhou et al., 2011), one (Regenbogen et al., 2017) involved sick body odor (in contrast to healthy body odor) which could not be considered either emotional nor totally neutral. Therefore, since there were no studies using completely NBOs among those we included, our findings cannot be generalized to all types of body odors (both neutral and emotional) and must be interpreted with caution.

The present meta-analysis has several limitations. First of all, the number of included experiments is limited (n = 16), emphasizing that investigation of human body odors is a recent field. As such, single experiments could be given disproportionate weighting. Furthermore, the modalities of the collection of the body odors and the odor presentation (with an olfactometer or not) were different and several tasks were used. Besides the sampling methods, body odors, as olfactory stimuli, required the use of an MRI compatible olfactometer to deliver the odor in a controlled fashion. Unfortunately, olfactometers are still not common as available laboratory devices (Lundström et al., 2010). All these constraints contribute to the scarcity of neuroimaging literature on body odors and to the differences in experimental setups, as researchers scramble to adapt to the available resources. Even if researchers are careful during the sampling and preserving of body odors, it is clear that the field needs common guidelines for body odor collection and presentation. However, across all studies included in this meta-analysis, there was an evaluation of the perceptual features of the odor conditions to ensure that the differences between conditions were not mediated by differences in perceptual attributes. Importantly, participants evaluated the stimuli as perceptually similar, or, in the case differences were found (in 2 of 13 studies), these were controlled in the statistical analysis removing the possible confounding effect. Finally, due to the small number of available studies, two imaging methods (PET and fMRI) were pooled together, which might have influenced our results. These aspects might account for the lack of significant results regarding the NBOs, as most of the previous imaging literature has been focused on the EBOs and only five studies were available for the specific analysis of the NBOs. Moreover, among these five studies, the heterogeneity was very high: some studies presented the body odors masked with a common odor (Cecchetto et al., 2020; Cecchetto, Lancini, Bueti, et al., 2019), and three studies presented the body odors of kins, friends, and strangers (Lundström et al., 2008, 2009, 2013). Also, to increase the consistency across the included studies, only those involving real human sweat have been included. Indeed, it has been shown that the ecological validity of studies investigating single molecules is limited (Pause, 2017) and there is no consensus about which molecules are more involved in the transmission of social information (Ferdenzi et al., 2019; Pause, 2017).

In conclusion, despite the several limitations, we provide a preliminary mapping of brain areas responsive to human body odors. These results offer new insight into the neural correlates of processing of body odors and underscore the need of further neuroimaging investigations.

CHAPTER 4

The investigation of olfactory meta-cognitive abilities in affective disorders

4.1. Study 1: The Social Odor Scale: Development and initial validation of a new scale for the assessment of social odor awareness[4]

4.1.1. Abstract

The degree of attention individuals pay to olfactory cues (called odor awareness) influences the role of odors in everyday life. Particularly, odors produced by the human body (i.e., social odors) are able to carry a wide variety of information and to elicit a broad spectrum of emotional reactions, making them essential in interpersonal relationships. Hence, despite the assessment of awareness toward social odors is crucial, a proper tool is still lacking. Here, we designed and initially validated the Social Odor Scale (SOS), a 12-item scale designed to measure individual differences in awareness towards different social odors. In Study 1.1, an exploratory factor analysis (EFA; KMO test: MSA = 0.78; Bartlett's test: $\chi^2(78) = 631.34$, $p < 0.001$; Chi-squared test: $\chi^2(42) = 71.84$, $p = 0.003$) suggests that the three factors structure was the model that best fit with the Italian version of the scale. The confirmatory factor analysis (CFA) supports a second-order model with one higher-order factor

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representing social odor awareness in general and three lower-order factors representing familiar, romantic partner, and stranger social odors. The final version of the scale presented a good fit (RMSEA = 0.012, SRMR = 0.069, CFI = 0.998, TLI = 0.997). In Study 1.2, CFA was performed in the German version of the scale confirming the validity of scale structure. Study 1.3 and 1.4 revealed that SOS total score and its subscales were positively correlated with other validated olfactory scales, but not with olfactory abilities. Moreover, SOS was found to be related to the gender of the participants: women reported to be more aware to social odors and, specifically, to familiar social odors than men. Overall, the results indicated that SOS is a valid and reliable instrument to assess awareness toward social odors in everyday life.

4.1.2. Introduction

The prominent role of odors in people's life is well known (McGann, 2017), however not all humans pay attention to odors in the environment in the same way (Smeets et al., 2008). There are individuals that spontaneously notice the food aroma or the fragrances of flowers, whereas others become aware only after drawing their attention to them. This meta-cognitive ability has been called "odor awareness", reflecting the degree to which individuals catch olfactory cues and let them guide and affect their attitudes and actions (Smeets et al., 2008). Odor awareness was found to be related to both the self-rated sense of smell (the better participants ranked their ability to smell, the better their olfactory awareness) and to olfactory abilities (people who reported to be less aware of odors had a significantly poorer olfactory performance than individuals claiming a higher odor awareness) (Smeets et al., 2008).

Odor awareness is relevant not only for the examples described before but also for odors, especially body odors, conveying socially relevant messages. Indeed, as in other species (Wyatt, 2005), increasing evidence suggests that the chemicals produced by the human body are essential in interpersonal relationships (Roberts et al., 2020; Semin et al., 2019). Essentially, each individual presents a typical body odor that, as for physical appearance, reflects personal stable characteristics or transient events (e.g., personality, sex, age, health, and even transient emotional states; de Groot & Smeets, 2017; Havlíček et al., 2017). These odors are perceived by other people and affect their reaction: they become social odors (Ferdenzi et al., 2019; Smeets et al., 2020). For example, the "smell of sickness" (i.e., sweat collected during a sickness condition) can influence social desirability (Regenbogen et al., 2017) or the "smell of fear" (i.e., sweat collected during a fearful condition) can affect behavior (de Groot & Smeets, 2017; Singh et al., 2018).

The processing of social odors mostly occurs without the allocation of attention, modulating individuals' behaviors unconsciously (Dal Bò et al., 2020; Lundström & Olsson, 2010; Parma et al., 2017; Pause, 2012). However, it has been demonstrated that humans are able to partially distinguish familiar to unfamiliar social odors consciously (Lundström et al., 2008, 2009; Schäfer et al., 2020; Übel et al., 2017). The degree to which odors are important in social contexts can change across individuals. For instance, Sorokowska and colleagues (2018), analysing the odor awareness toward interpersonal situations of individuals from 44 countries, demonstrated that social odors are more strongly related to individuals' characteristics, i.e., gender, age, and education, than cultural or country factors (Sorokowska et al., 2018).

Despite the growing body of literature documenting the importance of human social odors on everyday social interactions (Roberts et al., 2020), a proper and specific tool that measures individual differences in the awareness toward social odors is still missing. Indeed, existing questionnaires, which for example assessed the awareness toward odors (the Odor Awareness Scale, OAS; Smeets et al., 2008), or the importance that people give to the sense of smell (the Individual Significance of Olfaction scale, ISO; Croy et al., 2010), or the attitudes toward odors in everyday life (the Odours in Everyday Life Questionnaire, OELQ; Cupchik et al., 2005), include both items that assess the perception of common odors and the perception of bodily odors in interpersonal situations. Recently, the Body Odor Disgust Scale (BODS; Liuzza et al., 2017) was developed. However, as specified in its name, it refers exclusively to the emotion of disgust. Yet, previous literature has shown that social odors are able to carry a wide variety of information and to elicit a broad spectrum of emotional reactions (e.g., attractiveness, fear, safety) (de Groot & Smeets, 2017; Ferdenzi et al., 2020; Granqvist et al., 2019).

Given the lack of a tool that specifically assesses social odor awareness, we present here a series of studies designed to develop and validate a new scale called Social Odor Scale (SOS). By reviewing the previous literature on social odors and the existing olfactory scales (Croy et al., 2010; Cupchik et al., 2005; Liuzza et al., 2017; Smeets et al., 2008) we could identify four types of social odors that occur in individuals' everyday life. First, romantic partner odor: social odors play an important role in mate selection by affecting desirability (Havlicek & Roberts, 2009; Regenbogen et al., 2017; Roberts et al., 2011; Singh & Bronstad, 2001) with this process being only partially subconscious, as both men and women seem aware of using odors in their mate choice (Havlicek et al., 2008). Second, odors of familiars or significant others: these social odors provide a feeling of security and familiarity and help the relationship maintenance (Granqvist et al., 2018; Hofer et al., 2018; Hofer & Chen, 2020; Mahmut & Croy, 2019; McBurney et al., 2006). Familiar social odors include odors from significant others, family members, and friends (Croy et al., 2019; Ferdenzi et al., 2010; Lundström et al., 2008; R. Porter et al., 1983; Schäfer et al., 2020). Third, stranger's body odors: these odors are processed as a dangerous and threatening stimulus and they are rated as more unpleasant and intense than a friend's body odor (Cecchetto et al., 2016; Lundström et al., 2008; Übel et al., 2017); and finally, fourth, own social odor: people can discriminate their own body odor from the odors of others and thus constantly smell themself as a reassuring behavior to obtain information on individuals with whom there has been contact which in turn provides information about the self (Gergely & Watson S, 1996; Perl et al., 2020). The SOS has been specifically developed to measure the level of attention participants pay to the four types of social odors (own, familiar, romantic partner, and stranger) and thus we expected a four-factor questionnaire.

In Study 1.1 an Exploratory Factor Analysis (EFA) and a Confirmatory Factor Analysis (CFA) were conducted to assess and confirm the factor structure of the Italian version of the scale. In Study 1.2 the CFA was replicated on the German version of the SOS. In Study 1.3 we measured the association between the SOS and the actual olfactory abilities measured with the Sniffin' Sticks test (Hummel et al., 1997). In Study 1.4 we investigated the relationship between the SOS and demographic variables and self-reported olfactory abilities.

4.1.3. Study 1.1: Exploratory Factor Analysis and Confirmatory Factor Analysis on the Italian version

Study 1.1 was designed to investigate the factor structure of the Italian version of the scale through the exploratory factor analysis (EFA) and to test the validity of the proposed model through the confirmatory factor analyses (CFA).

Materials and methods

Item construction

Four types of social odors were identified by reviewing the previous literature and the existing olfactory scales (Croy et al., 2010; Cupchik et al., 2005; Liuzza et al., 2017; Smeets et al., 2008): individual body odor, familiar and unfamiliar body odor, romantic partner body odor, and body odor of strangers. Items were designed to assess the awareness of body odors (the person's tendency to pay attention to odors), behavior (avoidance or approach), and emotions (e.g., annoyed, attracted, aroused) related to body odors. Each item was formulated as a personal statement. Initially, a pool of 30 items was created: 20 items were formulated by revising and rephrasing items from other chemosensory scales: the OELQ (Cupchik et al., 2005), the OAS (Smeets et al., 2008), the BODS (Liuzza et al., 2017), and the ISO (Croy et al., 2010). Other 10 specific scenarios, in which the individual could be affected by body odors, were set. Finally, the authors reviewed this pool to have 6 items for each type of body odors. The criteria were appropriateness (meaning that each item correctly described a scenario in which the specific body odor was involved), comprehensibility (meaning that each item was clear and easily understandable by readers), and redundancy (meaning that each item was not too similar to the other items). These 24 items were then presented to three experts, who were not part of the project, who agreed that each item was appropriate, clear, and not redundant. Their judgment was only qualitative.

For each item, participants had to rate to what extent they agree or disagree with each of the statements presented. The scoring was obtained using a 5-point Likert scale (0 = I totally disagree, 1 = I mostly disagree, 2 = I neither agree nor disagree, 3 = I mostly agree, 4 = I totally agree).

Participants

The survey was presented online using the Qualtrics survey platform (Qualtrics XM Platform). Participants between 18 and 45 years old were recruited via social media, word of mouth, and during classes at the University of Padua and the University of Pisa. A total of 533 Italian-speaking participants took part in this study. Participants were excluded if they were diagnosed with COVID-19 (Parma et al., 2020) and if they were pregnant or breastfeeding. Moreover, we excluded participants who did not answer correctly to the control item that was included to control the tendency of some participants to answer items without reading the content (Meade & Craig, 2012; Shamon & Berning, 2020). Therefore, the final sample was composed of 343 participants (259 women, 78 men, 6 did not specify their gender), between 18-45 years (mean = 24.8; SD = 5.5).

The present study was conducted with the adequate understanding and digital consent of the participants in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee, University of Padua (prot. no. 3667).

Statistical analyses

Data were cleaned using the software R (R Team, 2017) and analyzed with JASP (JASP Team, 2020). The sample was randomly split into two datasets of approximately equal size and with equal number of men and women: the Exploratory Factor Analysis (EFA, N = 171) was performed on one half, the Confirmatory Factor Analysis (CFA, N = 172) was performed on the other half. CFA was performed with the software R using the packages "lavaan" (Rosseel, 2012).

Results and discussion

The initial Kaiser–Meyer–Olkin (KMO) test results of 0.79, and the Bartlett's test of sphericity results of $\chi^2(276) = 1313.24$, $p < 0.001$, indicating that the data are adequate for factor analysis. Based on the eigenvalues and the scree plot, three possible models were found: with 3, 4, or 5 factors. These three models were explored with EFA which were conducted using a minimum residual estimation method and applying an Oblimin rotation. See Table 1A of Appendix A for the initial factor loading of the first EFA. To assure a good quality of the SOS scale, we established two criteria for the selection of items. First, items with low loading values (below 0.40) were progressively removed from the scale. Second, items with loading values above 0.40 in more than one component of the matrix, and therefore not specific to a single factor, were progressively deleted (Corner, 2009; Costello & Osborne, 2005; Kline, 2014; Yong & Pearce, 2013). We first explored the 4 factors solution, which was in line with our hypothesized subscales. With this solution, the first factor was specific for the romantic partner body odor, the second for the familiar body odor, the fourth for the stranger body odor, whereas the third factor retained items that were not specific for the own body odor. For that reason, we also explored the 3 and 5 factors solutions. After Oblimin rotation, the structure that best fit the data was the 3 factors solution: KMO test: MSA = 0.78; Bartlett's test: $\chi^2(78) = 631.34$, $p < 0.001$; Chi-squared test: $\chi^2(42) = 71.84$, $p = 0.003$. In total, 11 items were deleted and 13 were preserved (Table 4.1). Factor 1 contained 5 items and was loaded by romantic partner social odor items (called "PAR"), Factor 2 contained 4 items and was loaded by familiar social odor items (called "FAM"), Factor 3 contained 4 items and was loaded by stranger social odor items (called "STR").

Table 4.1. Oblimin-rotated factor matrix (minimum residual method) of the 13 items.

Item n°	Factor 1: PAR	Factor 2: FAM	Factor 3: STR	Uniqueness
7		0.683		0.480
10		0.588		0.545
11		0.662		0.514

12		0.790		0.424
13	0.514			0.510
15	0.592			0.674
16	0.840			0.316
18			0.445	0.740
19			0.678	0.539
20			0.543	0.708
23			0.470	0.761
24	0.718			0.393
14	-0.436			0.817

The second-order confirmatory factor analysis (CFA) was performed to test the validity of the proposed 3-factor model and to examine if the three factors fitted the general concept of "social odor awareness". As the items presented a non-normal distribution assessed with the Shapiro-Wilk test (all ps < 0.05), the diagonally weighted least squares (DWLS) was used for the CFA (Bolker et al., 2009; Mindrila, 2010). The CFA provided the following goodness of fit indices: RMSEA (root mean square error of approximation) value was 0.038 (90% CI [0.000, 0.063]), SRMR (standardized root mean square residual) value was 0.077, CFI (Confirmatory Factor Index) value was 0.979, TLI (Tucker Lewis Index) value was 0.974. Although the model yielded a good fit to the data, the Factor 1 presented a poor reliability (McDonald's ω coefficient = 0.66). Analysing the percentage of variance of each item that was explained by the factor, assessed by the squared standardized loadings of items, it was revealed that the item 14 poorly explained the Factor PAR ($R^2 = 0.105$). For that reason, item 14 (see Table 1A in Appendix A) was removed from the scale and the CFA was conducted again. The final version of the scale presented a good fit (RMSEA = 0.012, SRMR = 0.069, CFI = 0.998, TLI = 0.997), as shown in Fig 4.1. Moreover, all the factors presented a good reliability (Factor PAR: McDonald's ω = 0.77, Factor FAM: McDonald's ω = 0.84, Factor STR: McDonald's ω = 0.70; Total: McDonald's ω = 0.80). See Table 4.2 for the inter-factor correlations of each item. The Italian translation of the SOS is available in the table 2A of Appendix A.

Table 4.2. Inter-factor correlation and median of the final version of the Italian scale

Item n°	FAM	STR	PAR	Total
13			0.46	0.59
15			0.42	0.24
16			0.70	0.48
24			0.67	0.53
7	0.62			0.60
10	0.65			0.59
11	0.73			0.58
12	0.68			0.57
18		0.38		0.28
19		0.48		0.27
20		0.40		0.29
23		0.38		0.33
Median	0.67	0.39	0.56	0.52

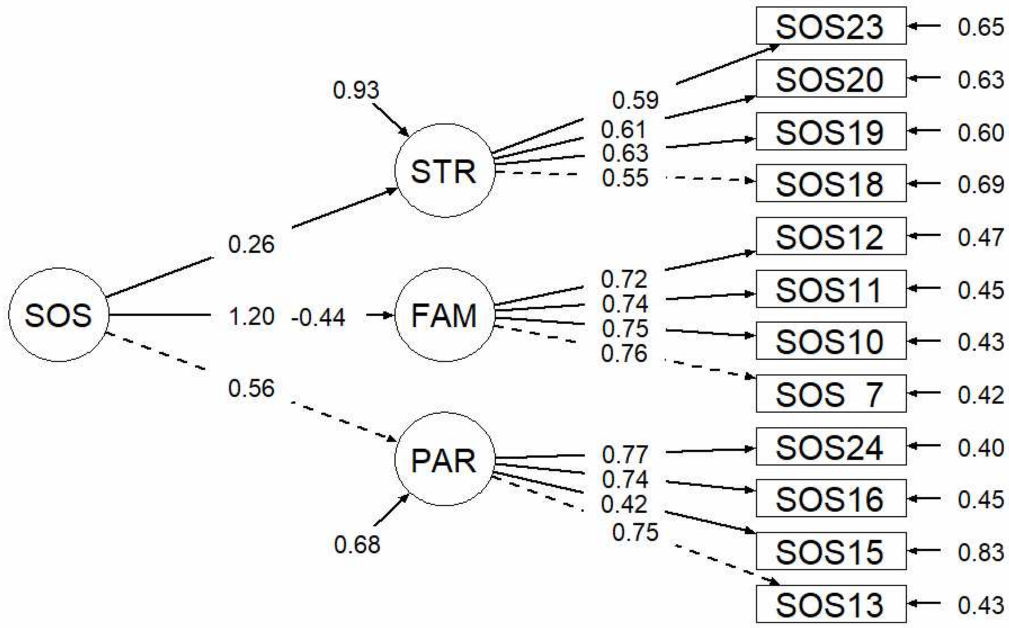

Fig. 4.1. Factorial map of the CFA results for the SOS. CFA, confirmatory factor analysis; FAM, familiar social odor; PAR, romantic partner social odor; STR, stranger social odor

4.1.4. Study 1.2: Confirmatory Factor Analysis of the German version

Study 1.2 was designed to investigate the factor structure of the German version of the scale through the confirmatory factor analysis (CFA) and to clarify if it matches the previously found factor structure.

Materials and methods

Participants

The Italian version of the SOS questionnaire was translated in German by an official Italian – German translator (the German translation of the SOS is available in the Table 2A in Appendix A). Then, two native German speakers revised and approved the translation. The survey was presented online using the Qualtrics survey platform. Participants were recruited via social media, word of mouth and during classes at the University of Graz, University of Klagenfurt, and the Medical University of Vienna. A total of 359 German-speaking participants took part in this study. Inclusion and exclusion criteria were the same as Study 1.1. The final sample was composed of 211 participants (169 women, 36 men, 6 did not specify their gender), between the ages of 18-45 years (mean = 23.4; SD = 5.5).

Statistical analyses

CFA was performed similar to Study 1.1 aiming to evaluate whether the three-factor structure with 12 items found for the Italian version of the questionnaire can be replicated in the German version.

Results and discussion

The CFA provided the following goodness of fit indices: RMSEA value was 0.024 (90% CI [0.000, 0.052]), SRMR value was 0.065, CFI value was 0.988, the TLI value was 0.984. Although the model yielded a good fit to the data, the reliability of the three factors is slightly lower than the original Italian version: Factor PAR, McDonald's ω = 0.73, Factor FAM, McDonald's ω = 0.71, Factor STR, McDonald's ω = 0.61, Total, McDonald's ω = 0.70. See Table 4.3 for the inter-factor correlations of each item. See Table 3A of Appendix A for the final version of the German SOS scale and Table 4A of Appendix A for the English translation of the scale, which has not been validated.

Table 4.3. Inter-factor correlation of the final version of the German scale

Item n°	FAM	STR	PAR	Total
13			0.41	0.49
15			0.38	0.24
16			0.62	0.49
24			0.59	0.48
7	0.47			0.37
10	0.29			0.33
11	0.56			0.36

12	0.56			0.34
18		0.42		0.35
19		0.36		0.21
20		0.33		0.19
23		0.45		0.25
Median	0.51	0.39	0.50	0.35

4.1.5. Study 1.3: Association with the actual olfactory abilities

Study 1.3 was designed and pre-registered as part of a broader project that aims to explore if the awareness of body odors is related to the olfactory ability, awareness, and imagery, as well as to several psychological characteristics (https://osf.io/htdmw). We reported here the data related to the first part of the project (Hypothesis a) which had the aim of investigating whether social odor awareness is predicted by olfactory abilities as measured by Sniffin' Sticks test (Hummel et al., 1997).

Participants, materials and procedure

Participants that were involved in previous projects that included the Sniffin' Sticks test (Hummel et al., 1997) at the University of Padova and at the University of Graz were contacted through emails and were asked to perform the SOS online (hosted by Qualtrics XM Platform). We initially contacted and invited 58 Italian and 104 Austrian participants between 18 and 35 years old. Exclusion criteria were chronic rhinitis or other conditions that may affect their ability to perceive odors, smoking, pregnancy or breastfeeding, presence of any severe somatic or neurological conditions, use of psychotropic drugs (including antidepressants, antipsychotics, anxiolytics and mood stabilizers) and being under a psychological therapy at the moment of the recruitment, presence of severe psychotic symptoms (i.e., hallucinations and/or delusions), presence of suicidal thoughts, incapability to understand and to give an informed consent for the experiment. Due to recent reports (Parma et al., 2020), all participants who were diagnosed with COVID-19 within the last 3 months before participating were excluded. A total of 57 participants (43 Italian and 13 Austrian) agreed to take part in this study. They were 43 women and 14 men, between the ages of 18-44 years (mean = 23.9; SD = 4.1).

Sniffin' Sticks test

The computer-testing version of the Sniffin' Sticks test was performed (Burghart Instruments, Wedel, Germany; Hummel et al., 1997). The test is composed of three subtests assessing three different olfactory functions: 1) the odor detection threshold was determined for n-butanol with 16 stepwise dilutions, using the single staircase technique based on a three-alternative forced choice task (3AFC); 2) the odor discrimination was assessed over 16 trials again using a 3AFC task: for each discrimination step, three pens were presented in random order, two containing the same odor and the third containing the target odor; 3) the odor identification was measured by presenting 16 common odors, each presented with four verbal descriptors in a multiple forced-choice format (three distractors and one target). A total score (TDI) above 30.5 is considered to be within the normosmic range, whereas under 16.5 indicates the presence of anosmia (Hummel et al., 1997). According to these criteria, two anosmic participants were excluded. In order to obtain a wide variability of olfactory abilities related to social odor awareness, hyposmic participants were not excluded. The final sample was composed of 51 normosmic and 6 hyposmic.

Statistical analyses and results

Statistical analyses were pre-registered at the Open Science Framework (OSF, (https://osf.io/htdmw, Hypothesis a). Data was cleaned and analyzed using the software R (R Team, 2017). As control, a t-test (*t.test* function, *stats* package) was performed in order to assure that there were no differences between the two groups (Italian and Austrian) in terms of SOS total score. No significant differences were found between the Italian and the Austrian samples on the total score of the SOS [$t(55) = 0.67$, $p = 0.50$], for this reason we merged the two samples for all following analyses.

For the SOS total score a multiple regression model with TDI score as fixed factor was performed using the *lmer* function (*lme4* package). Gender, sexual orientation, and age were fitted as random intercepts. A second multiple regression model including discrimination, identification, and threshold scores was performed on the SOS total score. In order to dealing with singular fit, one random intercept and one TDI subscores at a time was removed from the model, and the resulting model was compared with the initial one on the basis of the AIC criterion (Bolker et al., 2009), using the *anova* function (*lmerTest* package; Kuznetsova et al., 2017). In the final models, all random intercepts were removed, so linear regressions using the *lm* function were performed. For both models, no significant predictors were found (all $F < 0.40$, all $p > 0.52$). Additionally, the Bayesian equivalent of the two above regression models were performed using JASP (JASP Team, 2020). For both models, results showed Bayes factors BF_{10} between 0.31 and 0.27 indicating anecdotal evidence for H_0 (Lee & Wagenmakers, 2013). These results suggest that SOS scores are not related to olfactory abilities measured with the Sniffin' Sticks test, however further investigations are needed.

4.1.6. Study 1.4: Relationship between SOS scale and demographic and olfactory measures

Study 1.4 was designed to clarify whether SOS scores are associated with demographic variables and other olfactory scales.

Materials and methods

Participants

Participants of Study 1.4 were taken from Studies 1.1, 1.2, and 1.3 who next to the SOS questionnaire completed additional scales. This dataset consisted of 286 participants from Study 1.1, 172 from Study 1.2, and 57 from Study 1.3. All these participants performed correctly all the 4 control items that were included among the proposed scales. Specifically, for Study 1.4, 12 participants were removed because they did not specify the gender. The final sample was composed of 503 participants (321 Italian, 182 Austrian; 396 women). Besides the SOS scale, participants were asked to complete the OAS, the AIO, the VOIQ and to answer some questions regarding socio-demographic information: age, gender, sexual orientation (collected on a 7-points Likert scale ranging from 0 = "Exclusively heterosexual" to 6 = "Exclusively homosexual"), smoking habits ("Do you smoke?", "If yes, how many cigarettes per day?"), for women only, questions regarding the use of hormonal contraception and menstrual cycle. Demographic information can be found in Table 4.4.

Table 4.4. Demographic characteristics and questionnaires scores by the language of the participants.

N = 503	**Italian participants (N = 321)**	**Austrian participants (N = 182)**	**t and p values**
Female gender %	78	80	$\chi^2 = 0.05$, p = 0.82
Age	24.41 (4.84)	23.93 (5.94)	t = -0.92, p = 0.36
SOS	29.43 (7.05)	29.90 (6.16)	t = 0.75, p = 0.45
SOS Familiar	12.30 (3.45)	12.80 (2.88)	t = 1.75, p = 0.08
SOS Partner	9.83 (3.29)	9.81 (3.20)	t = -0.07, 0.94
SOS Strangers	7.29 (3.08)	7.28 (2.87)	t = -0.05, p = 0.96
OAS	115.33 (15.99)	115.56 (16.30)	t = 0.15, p = 0.88
AIO	2.21 (0.49)	2.23 (0.48)	t = 0.61, p = 0.54
VOIQ	57.51 (13.49)	56.09 (13.02)	t = -1.15, p = 0.25

Notes: Data are mean (Standard Deviation) of continuous and percentage (%) of categorical variables.

Self-reported olfactory measures (OAS, AIO, VOIQ)

To assess the relation between the SOS and the more general olfactory skills to environmental odors, participants were administered direct measures of self-reported olfactory function. Specifically, the Olfactory Awareness Scale (OAS; Smeets et al., 2008) a 34-item questionnaire that evaluates the person's tendency to pay attention to odorants in the environment. The Affective Importance of Odor scale (AIO; Wrzesniewski et al., 1999) an 8-item questionnaire developed to study the role of odors in every-day life and, in particular, the impact of good and bad odors in affecting liking and memory for places, things and persons. The Vividness of Olfactory Imagery Questionnaire (VOIQ) measures the olfactory representation ability (Gilbert et al., 1998) presenting 16 scenes with different odors; here participants evaluate the vividness of the imagined odor using a 5-point scale ("1 - perfectly realistic and as vivid as the actual odor" to "5 - No odor at all, you only know that you are thinking of the odor").

Statistical analyses

Data were cleaned and analysed using the software R (R Team, 2017). Partial Pearson's correlations (*rcorr* function, *Hmisc* package) and t-test (*t.test* function, *stats* package) were performed to investigate the association between demographic variables and the SOS scores. A p value of .05 was the cut-off for significance. The Benjamini–Hochberg procedure was applied to control the false discovery rate (FDR) where needed (Hochberg & Benjamini, 1990).

Results

Demographic variables

The correlation analysis between the SOS total score and age did not yield a significant relationship (SOS total: $r = 0.04$; STR: $r = 0.12$; PAR: $r = 0.09$; FAM: $r = -0.07$). There was also a significant difference between women and men in the SOS total score [$t(501) = 3.04$, p (uncorr) = 0.002, p (FDR corr) = 0.005, $d = 0.33$] and in the FAM subscale [$t(501) = 5.11$, p (uncorr) < 0.001, p (FDR corr) < 0.001, $d = 0.56$]. No significant differences between gender and the other three subscales (ps > 0.05) were found. There were no significant correlations between sexual orientation and the SOS total score (ps > 0.05). Moreover, we investigated whether smoking habits were associated with lower scores of the SOS scale. For each participant, we gave 0 score if they reported not to be smokers, in case of smoking habits we reported the number of cigarettes smoked per day. However, no significant correlation was found between smoking habits and SOS scale ($r = 0.07$, $p = 0.13$).

Effects of reproductive state

Since previous studies have shown that olfactory perception, in particular for social odors (Lundström et al., 2006), is affected by menstrual cycle phase (Nováková et al., 2014; Pause et al., 1996) and by the use of hormonal contraception (Kollndorfer et al., 2016), we analyzed the differences in the SOS scores related to these variables. There were no significant differences in the SOS score between women using hormonal contraception and those not using it [$t(383) = 0.79$, $p = 0.43$)]. To investigate the effect of the menstrual phase, the cycle length of each woman not taking hormonal contraception was standardized to a 28-day cycle by adjusting the follicular phase of each woman with respect to the length of her normal menstrual cycle (Garver-Apgar et al., 2008). The group was then classified into the follicular (starts on the first day of menstruation and ends with ovulation; < 15 days; n = 142) or luteal (latter phase of the menstrual cycle; ≥ 15 days; n = 143) (Olatunji et al., 2020; Song et al., 2017).

Even though the difference of the SOS total score was not significant [$t(283) = 1.80$; $p = 0.07$, p-FDR = 0.10, $d = 0.21$], there was a trend toward significance for the STR subscale [$t(283) = 2.27$; p (uncorr) = 0.02, p (FDR corr) = 0.06, $d = 0.27$; Fig 4.2], with women in the follicular phase reporting higher awareness for stranger odors ($M = 7.79$, $SD = 2.79$) than women in the luteal phase ($M = 6.97$, $SD = 3.31$). No significant differences were found for FAM and PAR subscales (ps FDR corr > 0.05).

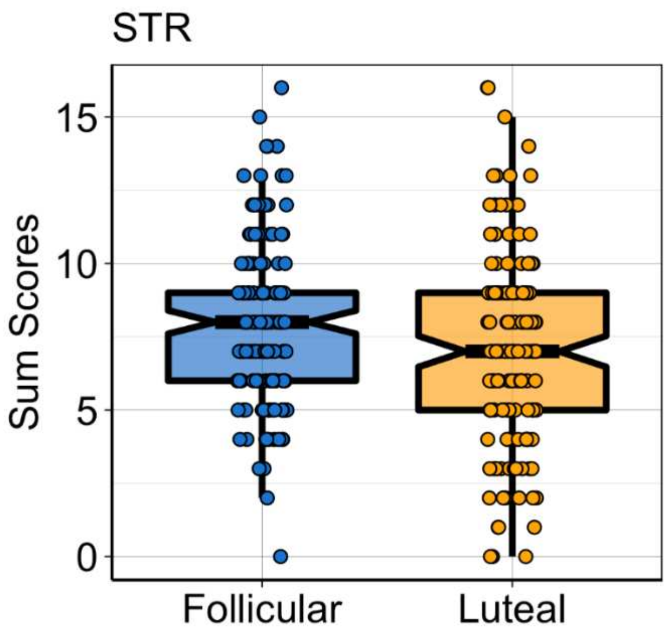

Fig. 4.2. Data distribution for Stranger Social Odor subscale. Boxplots depict the median (horizontal black line) and quartile ranges of the distribution, whiskers indicate maximum and minimum values, coloured dots represent data distribution.

Olfaction measures

The correlation analyses between the SOS and its three subscales and the olfactory measures (OAS, AIO, and VOIQ) confirmed that the scale has a good correlation with measures of awareness of olfactory stimuli and the affective response to them. Indeed, the total score of the SOS was significantly positively correlated, with medium/large effect sizes, with the OAS ($r = 0.64$, $p < 0.001$), with the AIO ($r = 0.47$, $p < 0.001$), and the VOIQ ($r = 0.36$, $p < 0.001$). Some subscales of SOS were also significantly positively correlated, with medium/large effect sizes, with the OAS (FAM: $r = 0.59$, $p < 0.001$; PAR: $r = 0.36$, $p < 0.001$; STR: $r = 0.40$, $p < 0.001$), with the AIO (FAM: $r = 0.46$, $p < 0.001$; PAR: $r = 0.32$, $p < 0.001$), and with VOIQ (FAM: $r = 0.36$, $p < 0.001$). Other subscales were correlated, but with small effect sizes, with the AIO (STR: $r = 0.22$, $p < 0.001$), and with VOIQ (PAR: $r = 0.19$, $p < 0.001$; STR: $r = 0.21$, $p < 0.001$). See Fig 4.3.

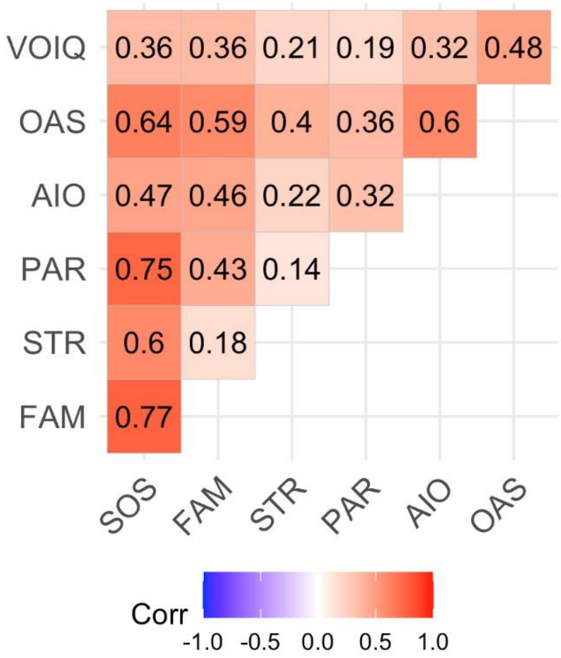

Fig. 4.3. Graphical display of the correlation matrix between OAS, AIO, and VOIQ scores and the SOS score and its subscales. Positive correlations are displayed in red and negative correlations in blue colour. Colour intensity is proportional to the correlation coefficients. Correlation coefficients are displayed inside the boxes.

4.1.7. General discussion

Despite the growing body of literature documenting the importance of human social odors on everyday social interactions (Roberts et al., 2020) as well as the presence of alteration of social odor perception in neuropsychiatry diseases (Pause et al., 2009, 2010) and neurodevelopmental disorders (Endevelt-Shapira et al., 2018; Parma et al., 2013), the attention humans pay to social odors has been largely neglected in the available measurements of odor awareness. Having a proper scale developed to assess social odor awareness is thus extremely relevant for the understanding of social odor processing and the social related behavior.

Here, we have developed and validated across 4 studies a new questionnaire called Social Odor Scale (SOS) designed to specifically assess social odor awareness. Initially, we hypothesized a four-factor structure of the SOS, as the scale was developed to measure the level of attention participants pay to the four types of social odors (own, familiar, romantic partner, and stranger) that occur in individuals' everyday life. From the exploratory factor analysis, the factors extracted did not completely match our initial hypothesis, indeed there was no statistical support for the subscale regarding the own body odor. For that reason, we adjusted the model according to a 3-factor structure: Familiar Social Odors, Romantic Partner Social Odor, Stranger Social Odor. The CFA confirmed the validity of the second-order model with one higher-order factor and three lower-order factors. The higher order factor represents social odor awareness as a whole, whereas the obtained three lower-order factors represent the awareness of Familiar Social Odors, Romantic Partner Social Odor, and Stranger Social Odor. The results of Studies 1.1 and 1.2 indicated that this new scale had a good validity and an overall good reliability to measure social odor awareness in Italian and Austrian samples.

Contrary with our hypothesis, in Study 1.3 it was found that the olfactory abilities did not predict the score on the SOS questionnaire. Results on the relation between odor awareness and olfactory performance are mixed. Indeed, even though some studies reported a positive relation between odor awareness and olfactory performance (Nováková et al., 2014; Smeets et al., 2008a), when age is controlled, this positive association disappeared (Nováková et al., 2014). Similarly, both in adults and in children, no association has been found between odor identification performance and self-reported odor awareness (Demattè et al., 2011; Ferdenzi et al., 2008). Our result is in line with the notion that people with undetected anosmia or hyposmia do not consciously perceive their impairment and, therefore, are able to correctly read and recognize social cues, maybe with the integration from other sensory modalities (Oleszkiewicz et al., 2020). Hence, it seems that the olfactory metacognitive abilities associated with social odors are not linked to the actual olfactory performance.

In Study 1.4, the final aim was to clarify whether SOS scores are associated with demographic variables and other widely used olfactory scales (i.e., OAS, AIO, and VOIQ). Results showed that women paid more attention to social odors and, in particular, to familiar body odors than men. This result is in line with studies showing a gender difference in various metacognitive abilities related to odors. For instance, women reported higher odor awareness (Demattè et al., 2011), higher interest in the sense of smell (Seo et al., 2011), and higher importance of olfaction (Croy et al., 2010; Havlicek et al., 2008) than male. This is in addition to an overall better olfactory performance (Doty & Cameron, 2009). Among women, there was no effect of oral contraception use in social odor awareness measured with the SOS. Moreover, albeit there is only a trend toward significance, women in the follicular phase reported a numerically higher awareness for stranger social odors (i.e., higher SOS stranger subscale) than women in the luteal phase. Accordingly, previous works reported higher sensitivity toward body odors during the follicular phase, compared with the luteal one (Endevelt–Shapira et al., 2019; Navarrete-Palacios et al., 2003). Our results highlight the need of further studies to better clarify the role of the reproductive menstrual phase in social odors' processing.

Finally, the SOS total score and its subscales were found to be closely related to all the olfactory measures taken into account. This result further validates the SOS and confirms its role as a new measure of odor awareness. Indeed, human's ability to pay attention to social odor is a particular component of the general awareness toward olfactory contents that, as presented by our results, is modulated by specific individual characteristics (i.e., age, gender and reproductive state). However, further studies are warranted to investigate how the SOS scale relates to the actual perception of social odors (in particular stranger, familiar and partner social odors) to provide stronger evidence in favour of the scale's validity.

In the present work some limitations have to be acknowledged. First, the SOS questionnaire has been performed online, limiting the experimental control toward the respondents. However, we included in the survey control items to assess that participants properly read the items' content. Moreover, SOS scores reflect self-perceived behavior rather than behavior itself and should be affected by response bias, an issue relative to all assessments involving self-reports. Secondly, participants were relatively young and most of them were female, making it impossible to generalize the current results to the general population. However, as it is widely reported that olfactory abilities decline with age (Hummel et al., 2007; Oleszkiewicz et al., 2019), we included only participants with an age between 18 and 45 years to have a homogeneous sample and to minimize the impact of age on the scoring on the SOS.

Future works should relate the SOS to the actual abilities to perceive body odors, as well as to the behavioral and physiological responses to them. This multimodal assessment could be helpful to achieve a better understanding of the relation between self-reported responses, cognitive processes, physiological and behavioral measurements of body odor-related responses. Moreover, SOS should also be examined in clinical populations characterized by social impairments, such as depression and social anxiety, increasing our understanding of these complex disorders. Certainly, addressing these issues may help further clarify the role of social odors in humans.

In conclusion, the SOS was developed to fill the gap left by the existing scales that neglected the multifaceted functions of body odors in social interactions. The SOS is useful to assess the social awareness toward three types of social odor (familiar, romantic partner and stranger body odor) that are relevant in our everyday life. Odors and social odors were found to be altered in several neurological and psychiatric diseases including Alzheimer (Mercer et al., 2018), Parkinson (Stephenson et al., 2010) and Autism (Endevelt-Shapira et al., 2018; Parma et al., 2013), affective disorders (Pause et al., 2009, 2010; Taalman et al., 2017) and schizophrenia (Pause et al., 2008), the use of this questionnaire will provide a useful assessment tool which may help to disentangle the role of such alterations in neuropsychiatric conditions.

4.2. Study 2: Olfactory meta-cognition in individuals with depressive and anxiety symptoms: the differential role of common and social odors[5]

4.2.1. Abstract

Diminished olfactory functioning has been reported in depression, whereas evidence in anxiety disorders is still controversial. Olfactory meta-cognitive abilities (i.e., olfactory awareness, imagery and reactivity, and the importance of odors) are essential in shaping olfaction. Few studies examined these meta-cognitive abilities in relation to depressive, anxiety, and social anxiety symptoms and none of them considered the awareness of social odors (i.e., body odors).

This pre-registered study examined the relationship between olfactory meta-cognitive abilities and symptoms of depression, general anxiety, and social anxiety in 429 individuals. Self-report measures of symptoms of depression, general anxiety, and social anxiety, along with self-report olfactory meta-cognitive scales, were collected using an online survey. Linear regression analyses revealed that olfactory awareness and importance of common odors were significantly directly predicted by symptoms of general anxiety, while affective importance to odors was negatively predicted by symptoms of depression. Regarding social odors, higher symptoms of depression and lower symptoms of social anxiety predicted increased awareness.

Symptoms of anxiety seem to be associated with higher levels of common odor awareness, corroborating the importance of olfactory functions in anxiety. In addition, results on social odors seem to reflect dysfunctional social behaviour that characterised symptoms of depression and social

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[5] *Published:* Dal Bò, E., Gentili, C., Castellani, A., Tripodi, C., Fischmeister, F. P. S., & Cecchetto, C. (2022). Olfactory meta-cognition in individuals with depressive and anxiety symptoms: The differential role of common and social odors. *Journal of Affective Disorders, 308*, 259-267. doi: 10.1016/j.jad.2022.04.071

anxiety. Hence, the assessment of meta-cognitive abilities may represent a useful tool in the prevention and assessment of depressive, anxiety and social anxiety symptoms.

4.2.2. Introduction

Among mental disorders, the most common are depressive and anxiety disorders, both widely spread among the global population (World Health Organization, 2017). Olfactory dysfunctions have been found to be strongly associated with mental health disorders, in particular with depression and anxiety (Kamath et al., 2018; Kohli et al., 2016; Mattos et al., 2017; Moberg et al., 1999; Taalman et al., 2017).

To date, the vast majority of studies investigating the relationship between olfaction and psychiatric disorders have focused primarily on depression, schizophrenia, and neurological diseases, analyzing almost exclusively the olfactory perception (e.g., Atanasova et al., 2008). In anxiety disorders, studies investigating olfactory perception are scarce and the results are contradictory (e.g., Burón et al., 2015, 2018; Clepce et al., 2012; Kopala & Good, 1996). Regarding depression, there is consistent evidence showing that individuals with depression present a decreased performance in odor identification, discrimination, and olfactory threshold (e.g., Colle et al., 2020; Croy, Symmank, et al., 2014; Croy & Hummel, 2016; Kohli et al., 2016; Negoias et al., 2010; Sivam et al., 2016; Taalman et al., 2017) and the negative relationship between depression and olfactory perception has been confirmed by several meta-analyses (Kohli et al., 2016; Taalman et al., 2017). One of the hypotheses proposed to explain the mutual relationship between olfactory perception and depressed mood suggests that olfactory perception is diminished due to a reduction of attention to odors that leads to a decreased olfactory receptor turnover rate. Depression, indeed, is characterized by a general drop of attention, and this seems to affect olfactory processing too (Croy, Symmank, et al., 2014; Croy & Hummel, 2016). In return, enhancing attention to odors improves olfactory functioning, as can be seen in daily olfactory training, which has been found to be effective in improving olfaction (Damm et al., 2014; Hummel et al., 2009; Schriever et al., 2014; for a meta-analysis, see Sorokowska et al., 2017).

Despite this evidence, it is still widely unknown whether depressive and anxiety symptoms are also associated with reduced attitude toward odors. Indeed, considerable variability has been found in various meta-cognitive measures that assess how people interact with their daily olfactory environments. These are, for example, the "odor awareness" (Smeets et al., 2008), which refers to the degree to which individuals tend to pick up olfactory stimuli and rely on them to guide their selective attitudes and actions; the "social odor awareness" which measures the degree of attention individuals pay to odors related to social interactions (Dal Bò et al., 2021); the "affective impact of odors" (Wrzesniewski et al., 1999), which indicates how odors affect the liking and memory for places, things and persons; and the "olfactory imagery", the ability to form olfactory images in our mind (Arshamian & Larsson, 2014; Stevenson & Case, 2005). These olfactory attitudes or abilities are related to the level of objective olfactory perception: people who reported to be less aware of odors also had significantly poorer olfactory performance than individuals claiming a higher odor awareness (Nováková et al., 2014; Smeets et al., 2008a). Moreover, individuals with high olfactory awareness reported better odor recognition memory and identified more odors spontaneously than individuals with low awareness (Arshamian et al., 2011). Furthermore, individuals with higher olfactory imagery abilities perceived odors as more familiar and reported lower levels of anhedonia than individuals with low olfactory imagery (Bensafi & Rouby, 2007). Hence, olfactory imagery, odor awareness, and attitudes toward odors in everyday life are essential in shaping the personal olfactory experience, and a better understanding of the role of the meta-cognitive abilities in affective disorders is crucial. Indeed, as previously shown, olfactory meta-cognitive abilities are able to moderate the olfactory experience and can represent an indirect index of the real olfactory performance (Nováková et al., 2014; Smeets et al., 2008). On the other hand, they could constitute an initial warning of a reduction in olfactory experience that could lead to a reduction in olfactory performance. The early detection of signs of vulnerability could be essential in the prevention of olfactory disorders and, consequently, affective disorders.

To our knowledge, only a few studies investigated olfactory meta-cognitive abilities in relation to symptoms of depression or anxiety (Burón et al., 2013, 2015, 2018). Individuals with anxiety symptoms reported being more sensitive and reactive to odors than individuals with depressive symptoms (Burón et al., 2013). Similar results have been found in two other studies focusing on panic disorder: here patients are reported to be more sensitive, reactive, and aware of odors compared to healthy controls (Burón et al., 2015, 2018). Odor imagery, however, has not been investigated in relation to depressive or anxiety symptoms up to now. Furthermore, olfactory meta-cognitive abilities have been studied so far focusing on common odors, even if the study of social odors (i.e., body odors conveying socially relevant messages) is of great relevance, especially for psychological disorders characterized by social impairment, such as social anxiety and depression. To date, few studies have analyzed the processing of body odors in social anxiety, reporting that social anxious individuals presented preferential processing for these types of odors (Adolph et al., 2013; Pause et al., 2009, 2010), so one might hypothesize that these people will also have a higher tendency to pay attention to these odors.

Given the literature reviewed so far, the main goal of the present study was to investigate olfactory reactivity, imagery, and awareness toward common and social odors in otherwise healthy individuals with depressive and anxiety symptoms. A deeper understanding of the meta-cognitive aspects of olfactory processing in these individuals may help to understand the initial mechanism that caused the altered olfactory abilities (Croy & Hummel, 2016) and might be useful as a possible future marker of vulnerabilities. In this pre-registered study, we hypothesized that individuals with depressive symptoms would report lower olfactory awareness, reactivity, and imagery. On the contrary, individuals with anxiety symptoms, particularly those with social anxiety, are supposed to show higher olfactory awareness, reactivity, and imagery. As an additional exploratory aim, we included measures of individual differences in approach and avoidance tendencies since previous studies have shown that olfaction guides the behaviour to approach reward and to detect and avoid threats (Gottfried et al., 2002). Moreover, we assessed the levels of alexithymia, a psychological construct that describes individuals with difficulties in identifying and describing subjective feelings and an externally oriented thinking style (Sifneos, 1973). Alexithymia has been shown to predict high levels of anxiety and depression (e.g., Berardis et al., 2008; Fietz et al., 2018; Honkalampi et al., 2000), and it has been associated with altered psychophysiological reactions to odors (Cecchetto et al., 2017). We hypothesized that individual differences in these constructs could interact with anxiety and depressive symptoms in modulating meta-cognitive olfactory abilities.

4.2.3. Materials and methods

Participants and procedure

Participants were anonymously recruited through an online survey on the Qualtrics XM platform, shared through social media and direct emails through a snowballing procedure in which participants were asked to invite friends to participate in the study. The survey aimed at Italian or German native speakers between 18 and 45 years old. This low age cut-off was chosen to minimize variability due to olfactory decline related to ageing (Oleszkiewicz et al., 2019). Given that specific effect sizes to run power analysis were not available, we chose to use the rule of thumb by Green (1991) to inform our minimum sample size. Planned multiple linear regressions included eight predictors, thus the recommended minimum sample size was set to 114 (Green, 1991). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The present study was approved by the local Ethics Committee, University of Padua (prot. no. 3667).

The online survey was opened between June and November 2020. A total of 959 started the survey, which was completed by 649 individuals. 110 participants were excluded because they did not answer correctly to one of the 4 control items included to control the tendency of some participants to answer items without reading the content (Meade & Craig, 2012; Shamon & Berning, 2020). Other exclusion criteria were pregnancy or breastfeeding, presence of somatic, neurological, or psychiatric conditions, diagnosis of COVID-19 (Parma et al., 2020), and failure to report gender. Following these exclusion criteria, the final sample consisted of 429 participants.

Following the acceptance of the informed consent, participants answered questions regarding demographic information [age, gender, and sexual orientation (collected on a 7-points Likert scale ranging from 0 = "Exclusively heterosexual" to 6 = "Exclusively homosexual")] and then completed the questionnaires regarding the olfactory meta-cognitive abilities and the psychological variables of interest.

Self-report psychological questionnaires

Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996; Italian version by Ghisi et al., 2006). The BDI-II is a reliable and valid self-report questionnaire that is used to assess the severity of current depressive symptoms in the past two weeks. Specifically, the BDI-II is composed of 21 items, each based on a four-point Likert scale and scores range from 0 to 63, with the higher scores indicating greater depressive symptoms.

Anxiety symptoms were assessed using the Beck Anxiety Inventory (BAI; Steer & Beck, 1997; Italian version by Sica & Ghisi, 2007). The BAI is a self-report questionnaire composed of 21 anxiety symptoms. Respondents have to rate how much each of these symptoms bothered them in the past week, from 0 ("not at all") to 3 ("severely, I could barely stand it") and the score ranges from 0 to 63, with the higher scores indicating greater anxiety symptoms.

Social anxiety was investigated using the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987). The LSAS is a 24-item questionnaire rating on a 4-point scale the fear and avoidance experienced in a range of social and performance situations. Scores range from 0 to 144, with higher scores indicating greater social anxiety symptoms.

Furthermore, given that olfaction guides the behaviour to approach reward and to detect and avoid threats (Gottfried et al., 2002), approach and avoidance tendencies were assessed. Participants completed the BIS/BAS scale Carver & White, 1994; Italian version by Leone et al., 2002), a 20-item questionnaire that evaluates how people typically react to certain situations and, specifically, their behavioral inhibition (BIS scale; i.e., concern over and reactivity to aversive events) and behavioral activation (BAS scale; i.e., responsiveness to incentives, drive, and fun-seeking).

Finally, given the tight relationship between olfaction and emotions (Soudry et al., 2011), emotional competence was assessed through the measure of alexithymia levels. Participants completed the Bermond–Vorst Alexithymia Questionnaire, form B (BVAQ-B; Bermond & Oosterveld, 1994) which consists of 20 items rated on a 5-point scale with total scores ranging from 20 to 100; participants with a score above 53 are considered alexithymic.

Self-report olfactory questionnaires

The Odor Awareness Scale (OAS; Smeets et al., 2008) is a 34-item questionnaire that evaluates a person's tendency to pay attention to odorants in the environment. The OAS covers topics such as food and drink, civilization, nature, and man. The OAS total score is calculated by the addition of the items (range from 32 to 158), with higher scores indicating higher odor awareness.

The Affective Impact of Odor scale (AIO; Wrzesniewski et al., 1999) is an 8-item questionnaire developed to study the role of odors in every-day life and, in particular, the impact of good and bad odors in affecting liking and memory for places, things and persons.

The Vividness of Olfactory Imagery Questionnaire (VOIQ; Gilbert et al., 1998) measures the olfactory representation ability presenting 16 scenes with different odors. People evaluate the vividness of the imagined odor using a 5-point scale ("1 - perfectly realistic and as vivid as the actual odor" to "5 - No odor at all, you only know that you are thinking of the odor").

The Social Odor Scale (SOS; Dal Bò et al., 2021) evaluates the awareness of social odors in everyday life. The SOS is composed of 12 items rated on a 5-point scale, with a total score ranging from 0 to 48, with the higher scores indicating higher attention toward social odor.

Statistical analysis (pre-registration)

Hypotheses and analyses were pre-registered on June 24, 2020 (https://osf.io/htdmw; hypotheses b) and c). Hypothesis a) was applied in Study 1 of the present Chapter). Data were cleaned and analyzed using the software R (R Core Team, 2017). Descriptive analyses of the experimental measures were run using t-tests (*stats* package; R Core Team, 2017). Dependent variables were the questionnaires regarding the olfactory meta-cognitive abilities: OAS, AIO, VOIQ, and SOS. For each dependent variable, separate linear mixed models (LMMs) were computed, using the lmer function, with the same fixed predictors (BDI-II, BAI, LSAS, BVAQ, BIS, BAS, gender, and sexual orientation) and with age and language as random factors. Due to overfitting, the models were re-shaped as linear regression, using lm function (*stats* package; R Core Team, 2017), with the previous random factors included as predictors. To explore the interaction between emotional competence and the level of anxiety, social anxiety and depression, these predictors were put in interaction. All continuous variables were centred and scaled, and collinearity was tested by calculating the Variance Inflation Factors (VIF) with the vif function of the *car* package (Fox et al., 2019). All factors showed low collinearity with values below 2.

The initial model for each dependent variable was:

~ (BDI-II + BAI + LSAS) * (BIS + BAS + BVAQ) + Gender + Sexual orientation + Age + Language

To ensure that each predictor improved the models' fit, models were simplified using the step function (stats package; R Core Team, 2017), which relies on the AIC criterion (Bolker et al., 2009). Factors that did not significantly improve the models' fit were removed. AIC values of the initial and final models were calculated using the anova function (*stats* package, R Core Team, 2017). The

Kolmogorov–Smirnov test was utilized to assess the normality of standardised residuals. Simple slope analysis was conducted to interpret the interactions using the *interactions* package (Long, 2019).

4.2.4. Results

Description of the sample

The final sample size was 429 (see Table 4.5 for sample characteristics). Italian and German speakers did not differ for gender distribution [$\chi2(1) = 0.001$, $p = 0.99$], age [$t(213.88) = -0.43$, $p = 0.66$], LSAS [$t\ (253.39) = -0.43$, $p = 0.81$], BDI-II [$t(279.84) = -1.65$, $p = 0.10$], BVAQ [$t(236.18) = 1.65$, $p = 0.10$], BIS [$t(282.6) = 1.57$, $p = 0.12$], SOS [$t(312.94) = 0.82$, $p = 0.41$], OAS [$t(264.29) = -0.28$, $p = 0.78$], VOIQ [$t(281.24) = -1.52$, $p = 0.13$], AIO [$t(268.15) = 0.90$, $p = 0.37$], but they differed for BAI [$t(312.58) = -2.36$, $p = 0.02$] and BAS [$t(288.44) = 2.46$, $p = 0.01$]. For this reason, the language of the participants was included in the initial model as predictor.

Table 4.5. Characteristics of the total sample.

Sample	N = 429
Gender	330 women (76.9%)
Language	289 Italian speakers (67.4%)
Age	M = 24.08 (5.10)
OAS	M = 115.20 (16.23)
AIO	M = 2.20 (0.49)
SOS	M = 29.58 (6.76)
VOIQ	M = 56.68 (13.70)
BVAQ	M = 48.38 (9.18)
BIS	M = 25.83 (5.45)
BAS	M = 44.73 (8.47)

BDI-II	M = 10.23 (7.79),
% above cut-off	8%
BAI	M = 10.88 (8.80)
% above cut-off	17.7%
LSAS	M = 41.13 (22.44)
% above cut-off	20.3%

Notes: OAS = Odor Awareness Scale (Smeets et al., 2008); AIO = Affective Impact of Odors scale (Wrzesniewski et al., 1999); SOS = the Social Odor Scale (Dal Bò et al., 2021); VOIQ = Vividness Olfactory Imagery scale (Gilbert et al., 1998); BVAQ = Bermond-Vorst Alexithymia Questionnaire (Bermond and Oosterveld, 1994); BIS/BAS = Behavioral Activation System and the Behavioral Inhibition System (Carver and White, 1994); BDI-II = Beck Depression Inventory-II (Beck et al., 1996); BAI = Beck Anxiety Inventory (BAI; Steer and Beck, 1993); LSAS = Liebowitz Social Anxiety Scale (Liebowitz et al., 1985); % of individuals above the cut-off.

Effects of anxiety, social anxiety and depression on olfactory metacognitive abilities

See Table 4.6 for the final model of each olfactory meta-cognitive questionnaire. OAS was significantly predicted by Gender [F(1, 416) = 20.68, p < 0.001], showing that odor awareness was higher for women than men, and by Age [F(1, 416) = 11.00, p < 0.001], indicating that odor awareness was higher in older participants. Then, OAS was positively predicted by BAI [F(1, 416) = 4.19, p = 0.041; Fig. 4.4.A] and BAS [F(1, 416) = 16.21, p < 0.001], showing that odor awareness increased with the increasing of anxiety and approach tendency. Odor awareness was negatively predicted by BVAQ [F(1, 416) = 11.34, p < 0.001], indicating that odor awareness decreased in participants with higher alexithymia. See Fig. 1A in Appendix A for main effects of BAS, BVAQ, and Age. The model also revealed a significant interaction between LSAS and BVAQ [F(1, 416) = 11.07, p < 0.001; Fig. 4.5]. An enhanced social anxiety predicted lower odor awareness in individuals with low (-1 SD) alexithymia (simple slope = -0.14, SE = 0.07, t = -1.90, p = 0.06) but not average (p = 0.50) and high (p = 0.35) alexithymia.

AIO was significantly predicted by Gender [F(1, 419) = 8.23, p = 0.004], showing that women reported higher affective responses to odors. Then, AIO was positively predicted by BAI [F(1, 419)

= 8.99, p = 0.003], and BAS [F(1, 419) = 10.22, p = 0.001], showing that participants with higher scores in BAI and BAS presented higher affective responses to odors. Finally, AIO was negatively predicted by BVAQ [F(1, 419) = 16.09, p < 0.001], in which higher alexithymic scores predicted lower affective responses to odors, and by BDI-II [F(1, 419) = 4.75, p = 0.029], indicating that the affective responses to odors decreased in participants with higher depressive symptoms. See Fig. 2A in Appendix A for main effects of BAI, BDI-II, BAS, and BVAQ. The model also revealed a significant interaction between LSAS and BIS [F(1, 419) = 5.535, p = 0.019; Fig. 4.6A] and a significant interaction between BDI-II and BIS [F(1, 419) = 4.216, p = 0.041; Fig. 4.6B]. An enhanced social anxiety predicted lower affective responses to odors in individuals with high (+1 SD) BIS scores (simple slope = -0.13, SE = 0.07, t = -1.95, p = 0.05) but not average (p = 0.84) and low BIS scores (p = 0.21). On the other side, higher depressive scores predicted lower affective responses to odors in individuals with low (simple slope = -0.24, SE = 0.09, t = -2.67, p = 0.01) and average (simple slope = -0.13, SE = 0.06, t = -2.18, p = 0.03) BIS scores, but not higher BIS scores (p = 0.66).

For VOIQ scores, age was a significant predictor [F(1, 419) = 8.01, p = 0.005], older individuals presented higher VOIQ scores, as well as the language of participants [F(1, 419) = 6.90, p = 0.009], showing that participants answering in Italian present higher VOIQ scores. Finally, BAS was a significant predictor for VOIQ [F(1, 419) = 13.24, p < 0.001], individuals with higher BAS scores presented higher VOIQ scores. See Fig. 3A in Appendix A for the main effects of BAS and Age. Finally, the model also revealed a significant interaction between BAI and BIS [F(1, 419) = 4.16, p = 0.042; Fig. 4.6C]. An enhanced general anxiety predicted higher olfactory imagery abilities in individuals with high (+1 SD) BIS scores (simple slope = 0.13, SE = 0.06, t = 2.18, p = 0.03) but not average (p = 0.64) and low BIS scores (p = 0.36). Since the Kolmogorov–Smirnov test was significant (p < 0.05), indicating that the residuals were not normally distributed, observations with values plus or minus 3 Median Absolute Deviation (MAD) from the median were removed (14 observations). The linear regression analysis was conducted again without these extreme values. The residuals were normally distributed (Kolmogorov–Smirnov test $p > 0.05$) and the new model showed that VOIQ score was significantly predicted by the BAS score [$F(1, 404) = 13.67$, $p < 0.001$], the age [$F(1, 404) = 7.45$, $p = 0.007$] and the language of the participants [$F(1, 404) = 9.04$, $p = 0.003$], as well as by an interaction between LSAS and BVAQ [$F(1, 404) = 4.26$, $p = 0.04$]. SOS was significantly predicted by Gender [$F(1, 420) = 5.75$, $p = 0.017$], showing that women reported higher social odor awareness than men. Moreover, SOS was negatively predicted by LSAS [$F(1, 420) = 5.82$, $p = 0.016$; see Fig. 1B] and BVAQ [$F(1, 420) = 14.40$, $p < 0.001$] and positively predicted by BDI-II [$F(1, 420) = 7.25$, $p = 0.007$; see Fig. 4.4C] and BAS [$F(1, 420) = 27.02$, $p < 0.001$]. See Fig. 4A in Appendix A for main effects of BAS and BVAQ.

Table 4.6. Summary of the linear regressions on OAS, AIO, VOIQ, and SOS. Significant differences are marked in bold. SE = standard error.

OAS	**Estimate**	**SE**	**t value**	**Pr(>|t|)**
(Intercept)	-0.008	0.097	-0.081	0.936
BAI	0.109	0.053	2.046	**0.041**
LSAS	-0.038	0.056	-0.673	0.501
BIS	0.063	0.056	1.117	0.265
BAS	0.211	0.052	4.026	**< 0.001**
BVAQ	-0.162	0.048	-3.368	**< 0.001**
Gender	-0.507	0.111	-4.548	**< 0.001**
Sexual orientation	-0.049	0.029	-1.646	0.101
Age	0.151	0.045	3.317	**< 0.001**
Language	0.194	0.110	1.762	0.079
BAI×BIS	0.081	0.049	1.642	0.101
BAI×BVAQ	0.069	0.049	1.404	0.161
LSAS×BVAQ	0.104	0.047	2.232	**0.026**
Residual standard error: 0.901 on 416 degrees of freedom				

Multiple R-squared: 0.21, Adjusted R-squared: 0.187

F-statistic: 9.215 on 12 and 416 DF, p-value: < 0.001

AIO	**Estimate**	**SE**	**t value**	**Pr(>|t|)**
(Intercept)	0.099	0.057	1.739	0.083
BAI	0.178	0.059	2.998	**0.003**
LSAS	-0.012	0.058	-0.204	0.839
BDI-II	-0.134	0.062	-2.180	**0.029**
BIS	0.093	0.058	1.606	0.109
BAS	0.147	0.46	3.196	**0.001**
BVAQ	-0.194	0.048	-4.011	**< 0.001**
Gender	-0.320	0.111	-2.353	**0.019**
LSAS×BIS	-0.119	0.051	-2.353	**0.019**
BDI-II×BIS	0.104	0.05	2.053	**0.041**

Residual standard error: 0.919 on 419 degrees of freedom

Multiple R-squared: 0.173, Adjusted R-squared: 0.155

F-statistic: 9.723 on 9 and 419 DF, p-value: < 0.001

VOIQ	**Estimate**	**SE**	**t value**	**Pr(>|t|)**
(Intercept)	-0.205	0.98	-2.083	**0.038**
BAI	0.025	0.055	0.452	0.651
BIS	-0.086	0.054	-1.585	0.114
BAS	0.201	0.055	3.693	**< 0.001**
BVAQ	-0.091	0.050	-1.800	0.072
Gender	-0.176	0.119	-1.481	0.139
Age	0.135	0.048	2.831	**0.009**
Language	0.309	0.118	2.627	**0.009**
BAI×BIS	0.107	0.052	2.039	**0.042**
BAI×BVAQ	0.087	0.045	1.938	0.053

Residual standard error: 0.965 on 419 degrees of freedom

Multiple R-squared: 0.088, Adjusted R-squared: 0.069

F-statistic: 4.551on 9 and 419 DF, p-value: < 0.001

SOS	**Estimate**	**SE**	**t value**	**Pr(>|t|)**
(Intercept)	0.064	0.051	1.261	0.208
BAI	0.104	0.059	1.766	0.078
LSAS	-0.124	0.052	-2.412	**0.016**
BDI-II	0.159	0.059	2.693	**0.007**
BAS	0.240	0.046	5.199	**< 0.001**
BVAQ	-0.180	0.048	-3.795	**< 0.001**
Gender	-0.266	0.111	-2.397	**0.017**
Age	0.089	0.046	1.939	0.053
BAI×BVAQ	0.082	0.042	1.966	0.050

Residual standard error: 0.915 on 420 degrees of freedom

Multiple R-squared: 0.178, Adjusted R-squared: 0.163

F-statistic: 11.39 on 8 and 420 DF, p-value: < 0.001

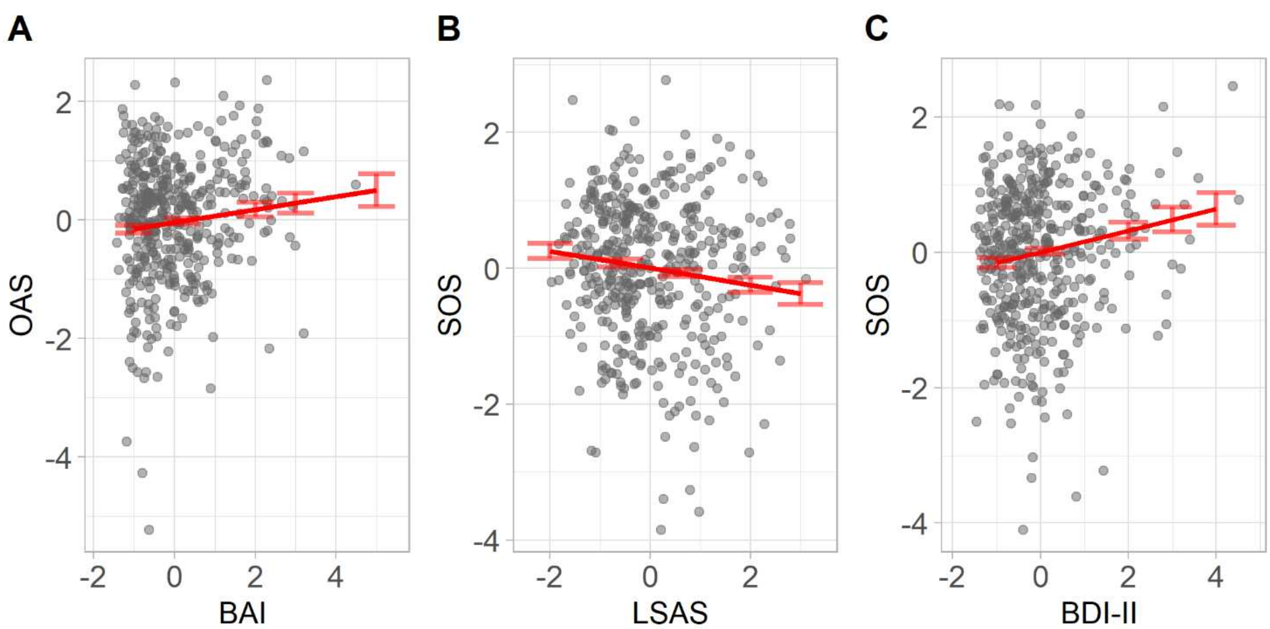

Fig. 4.4. Main effects of anxiety on (A) odor awareness, main effect of (B) social anxiety and (C) depression on social odor awareness. Black dots represent data distribution, red line is the fit of the main effect.

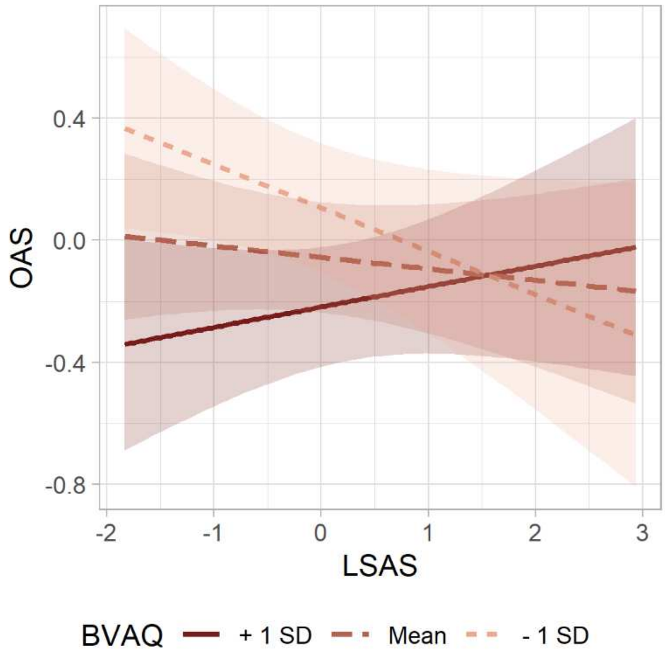

Fig. 4.5. Interaction effects of social anxiety and alexithymia on odor awareness. *Notes*. Predicted lines are plotted at +1 SD, Mean, and -1 SD values of alexithymia.

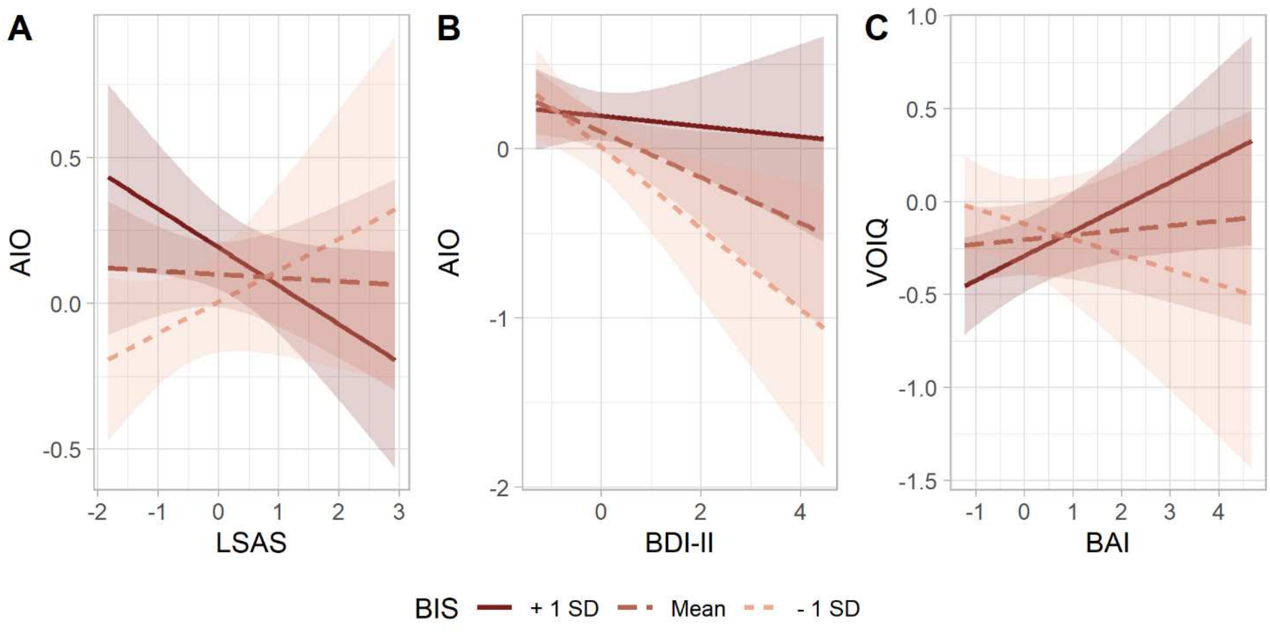

Fig. 4.6. (A) Interaction effects of social anxiety and behavioral inhibition system on the importance of odors. (B) Interaction effects of depression and behavioral inhibition system on the importance of odors. (C) Interaction effects of general anxiety and behavioral inhibition system on the olfactory imagery abilities. *Notes*. Predicted lines are plotted at +1 SD, Mean, and -1 SD values of alexithymia.

4.2.5. Discussion

The aim of this pre-registered study was to clarify whether anxiety and depressive symptomatology are associated with altered olfactory meta-cognitive abilities. Based on previous literature on objective olfactory perception (e.g., Clepce et al., 2012; Croy, Symmank, et al., 2014; Croy & Hummel, 2016; Kohli et al., 2016; Taalman et al., 2017), we hypothesized that individuals with depressive symptoms would report lower olfactory awareness, reactivity and imagery, while individuals with anxiety and social anxiety symptoms would show higher olfactory awareness, reactivity and imagery. In line with our hypothesis, general anxiety symptoms were found to be a significant predictor of higher odor awareness, importance of odors and reactivity to odors. Contrary to our hypothesis, social anxiety symptoms were only a significant predictor of lower social odor awareness. On the other side, depressive symptoms were a significant predictor of higher social odor awareness and lower affective responses to odors. Neither depressive nor anxiety symptoms were significant predictors of olfactory imagery.

The present findings on general anxiety symptoms are in line with previous studies on panic disorders (Burón et al., 2015, 2018), in which patients reported higher olfactory sensitivity, reactivity, and awareness of odors compared to the control group. Moreover, these results are consistent with previous studies reporting that anxiety sensitizes sensory cortical systems to enhance the detection of environmental stimuli both in the visual and acoustic modalities (for a review see Robinson et al., 2013). This pattern is also in line with clinical features of anxiety, in which individuals maintain heightened vigilance, hyperarousal and action readiness to respond to a sudden danger (Aikins & Craske, 2001; Eysenck, 1992; Mathews, 1990).

Contrary to our hypotheses, results of regression analyses showed that individuals with social anxiety symptoms reported being less attentive specifically toward social odors, which are crucial in interpersonal relationships. Our finding is at odds with the tendency of individuals with social anxiety to continually monitor the environment for signs of potential negative evaluations by others, and with studies on objective measures of olfactory processing, in which social anxious individuals have been associated with enhanced startle reactivity (Pause et al., 2009) and faster processing of social odor anxiety signals compared to healthy controls (Pause et al., 2010). A possible explanation of the observed conflicting findings of this study could arise from the fact that with self-report questionnaires we focused specifically on the cognitive/behavioral domain of social anxiety, whereas studies analyzing the physiological responses toward social odors focused on the physical domain (Rapee & Heimberg, 1997). Several models (e.g., Hartman, 1983; Hope et al., 1990; Rapee & Heimberg, 1997; Wells et al., 1995) propose that, at a cognitive level, social anxiety is associated with increased self-focus attention, rather than external attention to social cues. For instance, Mellings and Alden (2000) reported that socially anxious individuals focused their attention more on themselves than on their partner during social interaction. This is consistent with studies reporting an attentional avoidance from threatening social stimuli (Chen et al., 2002; Mansell et al., 1999) in individuals with social anxiety. The presence of this dysfunctional behaviour and attentional biases could partly explain the self-report reduced attention toward social odors in individuals with social anxiety symptoms found in the present study. An additional explanation for the unexpected result could lie in the easiest accessibility of online studies compared to in person ones. Indeed, individuals with social anxiety tend to avoid or delay seeking face-to-face interactions, often due to anxiety about travelling and meeting strangers in person (Kim, 2005; Wells et al., 1995). Hence, it is possible that individuals who agreed to participate in online studies are often left out from lab investigations.

The results of our study showed that enhanced depressive symptoms predicted lower affective interest to odors, which is related to the attention that individuals pay to odors, to olfactory memory and to the degree to which pleasant and unpleasant odors are liked or disliked based on their association with liked and disliked persons (Wrzesniewski et al., 1999). However, no relation has been found between depressive symptoms and olfactory reactivity, imagery, and awareness toward common odors. Again, this is in contrast to reports showing diminished olfactory functioning in multiple aspects of olfaction, including threshold, discrimination and identification in individuals with depressive symptoms (e.g., Croy, Symmank, et al., 2014; Croy & Hummel, 2016; Kohli et al., 2016; Negoias et al., 2010; Sivam et al., 2016; Taalman et al., 2017). Our non-significant results on meta-cognitive abilities to common odors could suggest that the present sample of individuals with non-clinically relevant depressed mood was not sufficient to detect such effects. This view is put forward by meta-analytic evidence of olfactory impairment in depression only found in individuals with clinical depression (Kohli et al., 2016; Taalman et al., 2017). Nevertheless, individuals with depressive symptoms seem to be characterized by a reduced response to odors that may be a sign of subsequent impairment of their olfactory abilities. Furthermore, we found that higher depressive symptoms led to higher levels of awareness of social odors. To date, no studies have investigated body odors' processing in individuals with depressive symptoms, as well as attention toward them, and this is surprising given the role this particular type of odors have in social communication. For example, it has been proposed that maladaptive social patterns, and in particular the fear of rejection (termed as rejection sensitivity), are risk factors for the development of depression (Coyne, 1976; Slavich et al., 2010). Using different attentional tasks, studies found hypervigilance to both rejection and neutral faces (Ehrlich et al., 2015) and increased attention to depression-relevant information after experiencing interpersonal rejection (Kraines et al., 2018), but also deployment of attention especially in the context of social threat stimuli (Berenson et al., 2009).

Given that olfaction guides the behaviour with the aim to approach reward and to detect and avoid threats (Gottfried et al., 2002), approach and avoidance tendencies were also assessed. Interestingly, the data showed that individuals with higher behavioral activation tendencies reported paying more attention to common and social odors, giving more importance to odors, and presenting higher olfactory imagery and higher reactivity to odors, all compared to individuals with lower behavioral activation tendencies. On the other side, the BIS scale was not related to olfactory meta-cognitive abilities but interacted with depression and anxiety in modulating individuals' responses to odors. Indeed, the BIS system is evolved in order to guide behaviour to signal the presence of food or threat and it's strongly related to anxiety-related symptomatology (Markarian et al., 2013) and depression (Kasch et al., 2002). However, future studies are needed to better disentangle the role of the approach and avoidance systems in olfaction, especially in psychopathological conditions.

In addition, in our study alexithymia was a predictor for lower levels of importance given to odors and lower reactivity to odors. These findings are in line with previous studies showing deficits in emotional processing (e.g., Donges & Suslow, 2017; Martínez-Velázquez et al., 2017; Pollatos & Gramann, 2011; Starita et al., 2016), even when presented through olfactory modalities (Cecchetto et al., 2017), and with studies showing alterations in experiencing salient stimuli (e.g., Goerlich et al., 2017; Grynberg et al., 2012) in individuals with alexithymia. Furthermore, we found that alexithymia modulates the effects of social anxiety symptoms on the levels of awareness toward common odors. This evidence supports the idea that alexithymia is significantly implicated in terms of impact on the outcome of mental disorders (Besharat, 2010; Pinna et al., 2020): alexithymia may act as a vulnerability factor, possibly by enhancing stress responses (de Timary et al., 2008; Franz et al., 1999; Pollatos et al., 2011).

Finally, in line with previous literature (e.g., Croy et al., 2010; Ferdenzi et al., 2008; Havlicek et al., 2008; Seo et al., 2011), women appeared to be more attentive and reactive to odors, to show a higher interest in the sense of smell, and to report a higher awareness toward social odors than men. Indeed, it is documented that women present higher olfactory abilities (Doty & Cameron, 2009), intensified neural processing of social odors (Pause et al., 2010), as well as higher odor awareness (Ferdenzi et al., 2008), higher interest in the sense of smell (Seo et al., 2011), and higher importance of olfaction (Croy et al., 2010; Havlicek et al., 2008). Likewise, attention and imagery of odors have been found to increase with age. Even if the olfactory performance decreases with age, meta-cognitive abilities related to odors seem to stay stable throughout life (Croy et al., 2010). Furthermore, increased olfactory awareness related to ageing has already been found (Demattè et al., 2011; Sorokowska et al., 2018), and can be explained by the observation that older people had experienced greater exposure to odors, which made them more aware of the odors in the environment (Demattè et al., 2011).

Although the present study involved healthy participants with different degrees of depressive or anxiety symptoms, these results could be seen in light of potential clinical implications. As the olfactory meta-cognitive abilities are related to the actual olfactory performance, they could be used to easily and in advance assess potential olfactory impairment being a useful target in the clinical setting. Indeed, in this exceptional historical time, online surveys are becoming more prevalent and validated questionnaires are a crucial tool for researchers and clinicians to investigate different facets of olfaction in clinical populations. Moreover, the COVID-19 pandemic shed light on the importance of the sense of smell in everyday life and, especially, how it is related to the attainment and maintenance of wellbeing, key aspects in the prevention and promotion of mental health (Boesveldt & Parma, 2021; Parma et al., 2020).

In interpreting our results, some limitations need to be acknowledged. First, we relied on social networks and a snowballing procedure to recruit participants. Although is a widely used and accepted methodology (Baltar & Brunet, 2012) it could have introduced some bias in our sample, moreover the prevalence of the female gender and the relatively young age of the participants limits the generalisation of the findings. Second, the majority of participants included in the study did not present clinical symptoms of depression or anxiety as assessed by self-reported questionnaires. However, the use of continuous measures allowed to avoid the loss of information and statistical power associated with dichotomization (Altman & Royston, 2006).

Taken together, the present study represents a first attempt to better understand the complex relationship between olfactory meta-cognitive abilities and depressive and anxiety symptomatologies. These results highlight the different role of olfaction in psychopathological disorders: anxiety symptoms seem to be associated with higher levels of common odor awareness, while social anxiety symptoms are associated with lower social odor awareness, and depressive symptoms with higher awareness of social odors. Hence, the assessment of meta-cognitive abilities may represent a useful tool in the assessment of depressive, anxiety and social anxiety symptoms. Future studies are needed to unravel the different role of common and social odors in depressive and anxiety symptoms, as well as their importance in full-blown psychiatric conditions.

CHAPTER 5

Is odor awareness a moderator in the relationship between affective disorders and olfactory abilities? [6]

5.1. Abstract

Olfactory disorders and affective symptoms are tightly related. However, the factors underlying this association are not yet understood. One candidate factor is the "odor awareness": the degree of attention individuals pays to the odors. However, the association between odor awareness and olfactory abilities in individuals with affective symptoms has not been clarified yet.

The present study examined whether odor awareness may moderate (a) the relation between olfactory dysfunctions and depressive, anxiety and social anxiety symptoms; (b) the relation between the perceptual ratings of the odors and depressive, anxiety and social anxiety symptoms in a sample of healthy individuals (n = 214). Self-report measures of depression and anxiety were collected, whereas the Sniffin' Stick test was employed to measure olfactory abilities.

Linear regression analysis revealed that individuals with higher depressive symptoms presented lower olfactory abilities and odor awareness was a significant moderator of the association between depressive symptoms and olfactory abilities. Anxiety and social anxiety symptoms were not related to any of the olfactory abilities considered, and this relationship did

[6] The results of the present chapter have been submitted for publication (and under review at the present moment) to the *Journal of Affective Disorders:* Dal Bò, E., Gentili, C., Natali, L., & Cecchetto, C. Low odor awareness predicts reduced olfactory abilities in individuals with depressive symptoms, but not with anxiety symptoms.

not change according to odor awareness. The familiarity rating of the odor was significantly predicted by odor awareness. These results were confirmed by the Bayesian statistics.

In a healthy population, only the presence of depressive symptoms is related to a reduced olfactory performance. Odor awareness may be implicated in the development and maintenance of olfactory dysfunction; hence it could be used as a useful target for specific treatments in clinical setting.

5.2. Introduction

Olfaction has received less attention compared to the other senses; however, the COVID-19 pandemic has shed light on the crucial role this sense has in human life. Besides the pandemic, moreover, olfactory dysfunctions are more common than expected, with an estimated prevalence of approximately 22% in the general population (Desiato et al., 2020). Indeed, the loss of the sense of smell leads to disturbances in crucial domains, mainly in nutrition, food enjoyment, protection from harmful (e.g., rotten) food and gas leaks or smoke (Croy, Nordin, et al., 2014; R. J. Stevenson, 2010), as well as in social relationships and working life, leading to a general reduction in well-being (Boesveldt & Parma, 2021; Croy, Nordin, et al., 2014; Mai et al., 2022). Interestingly, olfaction is also closely related to emotion and mood. Indeed, several mental disorders are associated with altered olfactory abilities (Croy & Hummel, 2017; Rochet et al., 2018; Soudry et al., 2011).

Among mental disorders, the most common are depressive and anxiety disorders, affecting 4.4% and 3.6% of the global population in 2015, respectively (World Health Organization, 2017). Individuals with depressive symptoms are characterized by diminished olfactory functioning in multiple aspects of olfaction, including threshold, discrimination and identification as shown in several studies (e.g., Athanassi et al., 2021; Croy et al., 2014b; Croy and Hummel, 2016; Kazour et al., 2020; Pabel et al., 2018; Rochet et al., 2018; Sabiniewicz et al., 2022), and meta-analyses (Kim & Bae, 2022; Kohli et al., 2016; Taalman et al., 2017). Furthermore, there is a mutual relationship between olfactory dysfunction and depression, as it has been reported that one-third of patients with olfactory loss present signs of depressive mood (Chen et al., 2021; Croy, Nordin, et al., 2014). A central feature of odor perception is its hedonic component, however, the relationship between depressive symptoms and the hedonic processing of odorants is not fully understood yet (for a review see Athanassi et al., 2021). Despite most of the studies have reported that depressed patients perceive unpleasant odors as more unpleasant and pleasant odor as less pleasant (e.g., Atanasova et al., 2010; Kazour et al., 2020) than healthy controls, other studies failed to observe this difference (Swiecicki et al., 2009), or even they found an opposite pattern (Lombion-Pouthier et al., 2006; Pause et al., 2001).

Regarding anxiety and social anxiety disorders, to date very few studies have investigated olfactory functions in this population, reporting conflicting results. In a group of patients with different anxiety disorders it has been found an impairment in olfactory discrimination, but not in identification and threshold, along with higher intensity and hedonic ratings compared to healthy controls (Clepce et al., 2012), whereas in a group of healthy subjects both state and trait anxiety ratings were significantly associated with reduced odor detection and identification (Takahashi et al., 2015). On the other side, studies focusing specifically on panic disorder reported lower olfactory detection thresholds (i.e., higher sensitivity; Burón et al., 2018, 2015), but intact olfactory identification performance (Kopala & Good, 1996).

In addition to the objective measure of olfaction, the degree of attention individuals pays to the odors in the environment, also called "odor awareness" (Smeets et al., 2008), has been suggested as one of the factors involved in olfactory dysfunction. Indeed, Croy and Hummel (2017) have proposed that at least two mechanisms participate in explaining the link between olfaction and depression. A stable, trait, mechanism is the presence of structural alterations in the olfactory bulb that make people vulnerable to depression. A second, state, mechanism active during depressive episodes is the reduction of olfactory attention which leads to a decreased olfactory receptor turnover rate. Indeed, animal studies reported that depressed rats exhibited a thinner olfactory epithelium as well as a reduction of olfactory receptor neurons (Li et al., 2015) which may be linked to olfactory attention. Despite the proposed theory, very few studies investigated odor awareness in affective disorders. These studies reported higher odor awareness in individuals with general anxiety and with panic disorder (Burón et al., 2015, 2018; Dal Bò et al., 2022), however, no relation has been found with depressive symptoms (Dal Bò et al., 2022).

Moreover, to our knowledge, the association between odor awareness and olfactory abilities in individuals with affective disorders has not been investigated yet. This is particularly surprising since a deeper understanding of the development and course of olfactory dysfunctions as well as the possible initial mechanisms that cause it may represent potential clinical targets in the prevention and treatment of depressive and anxiety symptoms.

Therefore, the aim of the present study was twofold: first, to test the hypothesis that odor awareness would represent a moderator underlying the relationship between depressive, anxiety and social anxiety symptoms and olfactory abilities and, second, to explore the association between odor awareness and hedonic perception of the odors, and in general odor rating, in individuals with depressive, anxiety and social anxiety symptoms.

5.3. Methods

Participants

A total of 214 female university students (mean age = 22.5, SD = 2.3) took part in this study. The enrolled sample was medically healthy and free from psychotropic medication, as assessed with an ad-hoc anamnestic interview. Exclusion criteria were being pregnant, having a cardiovascular, neurological, or psychiatric disease, diagnosis of COVID-19 (Parma et al., 2020) during the three months before the experiment, drug and nicotine consumption, olfactory dysfunction, previous head trauma leading to unconsciousness, chronic rhinitis or other conditions that may affect the ability to perceive odors, being younger than 18 years.

Data were collected during the screening session of a larger protocol held at the University of Padova between November 2019 and April 2022. The present study was conducted with the adequate understanding and written consent of the participants in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee, University of Padua (prot. no. 3667).

Procedure

Participants were recruited through an online survey on the Qualtrics XM platform. After signing the informed consent, participants answered questions regarding demographic information, health status, drug and nicotine consumption, olfactory dysfunction, and then completed the following questionnaires: Beck Depression Inventory-II (BDI-II; Beck et al., 1996; Italian version by Ghisi et al., 2006), Beck Anxiety Inventory (BAI; Steer and Beck, 1997; Italian version by Sica and Ghisi, 2007), Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987), and Odor Awareness Scale (OAS; Smeets et al., 2008). Subsequently, participants which met the inclusion criteria were called to the lab, where they completed the Sniffin' Sticks test and the perceptual ratings of the identification subtest's odorants. The entire procedure lasted approximately 60 min.

Self-report questionnaires

Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996 Italian version by Ghisi et al., 2006). The BDI-II is a reliable and valid self-report questionnaire that is used to assess the severity of current depressive symptoms in the past two weeks. Specifically, the BDI-II is composed of 21 items, each based on a four-point Likert scale and scores range from 0 to 63, with the higher scores indicating greater depressive symptoms.

Anxiety symptoms were assessed using the Beck Anxiety Inventory (BAI; Steer and Beck, 1997; Italian version by Sica and Ghisi, 2007). The BAI is a self-report questionnaire composed of 21 anxiety symptoms. Respondents have to rate how much each of these symptoms bothered them in the past week, from 0 ("not at all") to 3 ("severely, I could barely stand it") and the score ranges from 0 to 63, with the higher scores indicating greater anxiety symptoms.

Social anxiety was investigated using the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987). The LSAS is a 24-item questionnaire rating on a 4-point scale the fear and avoidance experienced in a range of social and performance situations. Scores range from 0 to 144, with higher scores indicating greater social anxiety symptoms.

To assess the person's tendency to pay attention to the odors in the environment, the Odor Awareness Scale (OAS; Smeets et al., 2008) was presented. The OAS is a 34-item questionnaire that covers topics such as food and drink, civilization, nature, and man. The OAS total score is calculated by the addition of the items (ranging from 32 to 158), with higher scores indicating higher odor awareness.

Olfactory assessment and odor rating

Olfactory function was assessed using the Sniffin' Sticks test, a validated and widely used paradigm (Burghart GmbH, see Hummel et al., 1997). This test allows to study the olfactory function in terms of three distinct olfactory abilities: odor identification, threshold and discrimination. The Sniffin' Sticks are felt-tips pens filled with an odorant solution, presented to the participant for approximately 3 s with a 2 cm distance in front of both nostrils. Olfactory identification was assessed with 16 common odors (Hummel et al., 1997). Participants were asked to identify the odor from a list of four verbal and visual descriptors. The number of correct answers was summated as identification score. Olfactory discrimination was assessed using a three alternative force choice (3AFC) task across 16 trials. For each trial, three pens were presented to the blindfolded participants in random order, two containing the same odor and the third containing the target odor. Finally, n-butanol diluted in propylene glycol with 16 available dilution steps was used to assess the olfactory threshold. Blindfolded participants were presented with a 3AFC task with two pens containing an odorless solvent (propylene glycol) whereas one was filled with n-butanol in a certain concentration. The participants' task was to detect the pen containing the odor. A staircase procedure was used to measure the odor threshold: if the odor had not been detected, the concentration was increased, if the odor was detected twice in a row, the concentration was decreased. The odor threshold was defined as the mean of the last four of seven staircase reversals. Each sub-test was scored between 1 and 16. A total TDI (Threshold Discrimination Identification) score below 16.5 is considered to be within the anosmic range, between 16.5 and 30 within the hyposmic range, whereas above 30 is in the normosmic range (Hummel et al., 2007).

Specifically for the present study, during the identification test, participants, after having answered the identification question, were asked to rate each odor for intensity, pleasantness, and familiarity. Ratings were collected on a 10-point computerized Visual Analogue Scale (VAS), ranging from "not at all" to "very much".

Since February 2020, due to the SARS-CoV-2 pandemic and to avoid the spread of the disease, the procedure slightly changed, and a single-use smell test system was adopted. Each odor was presented on a single-use paper strip, which was then handed over to the participant. The participant smelled the paper and answered the question. The paper strip was then discarded, and the procedure was repeated for the next stick (Besser et al., 2020; Mueller et al., 2006; Wirkner et al., 2021). Moreover, to reduce the time the experimenter and participant spent together in the laboratory, a shorter version of the threshold test was used, which involved the ascending methods of limits (Besser et al., 2020).

Statistical analyses

To investigate whether the depressive, anxiety and social anxiety symptoms are related to altered olfactory function, and if this link was moderated by the level of attention to the odors, four stepwise linear regression models were conducted, one for each olfactory function measure (TDI, threshold, discrimination, identification), using the lm function (*stats* package; R Core Team, 2017).

The initial model for each dependent variable was:

~ (BDI-II + BAI + LSAS) × (OAS)

Odor ratings (intensity, pleasantness, and familiarity) were analyzed to evaluate whether the depressive, anxiety and social anxiety symptoms may modulate the perceptual qualities of odors, and if this effect was moderated by the level of attention to the odors. The odorants used for the perceptual rating were classified into three main categories (pleasant, neutral and unpleasant) based on the results of the database Hedos-F (Clepce et al., 2014; Markovic et al., 2007; Thuerauf et al., 2009): unpleasant odorants are turpentine, garlic, and fish; neutral odorants are shoe leather, liquorice, coffee, and clove; pleasant odorants are orange, cinnamon, peppermint, banana, lemon, apple, pineapple, rose, and anise.

Three Linear Mixed Models (LMM) were performed with the main effects of BDI-II and BAI and their interactions with the OAS scores, using the lmer function (*stats* package; R Core Team, 2017). In addition, we explored the interaction between each of these predictors with a categorical variable, called *odor category* indicating whether the odor rated was pleasant, neutral or unpleasant. The participant's ID and the individual TDI score were included as random factors:

~ (BDI-II + BAI + LSAS) × OAS × odor category + (1 | ID) + (1 | TDI)

Simple slope analysis was conducted to interpret the interactions using the *interactions* package (Long, 2019). All continuous variables were centered and scaled, and collinearity was tested by calculating the Variance Inflation Factors (VIF) with the vif function of the *car* package (Fox et al., 2019). All factors showed low collinearity with values below 3.5. For all regression models, to ensure that each predictor improved the models' fit, models were simplified using the step function (*stats* package; R Core Team, 2017), which relies on the AIC criterion (Bolker et al., 2009). Factors that did not significantly improve the models' fit were removed. AIC values of the initial and final models were calculated using the anova function (*stats* package, R Core Team, 2017).

All analyses were repeated with Bayesian statistics, performed with JASP software (JASP, 2018; Wagenmakers et al., 2018). Bayes factors (BF) were interpreted following standard recommendations (Jarosz & Wiley, 2014; Jeffreys, 1998): BF between 1 and 3 implies indecisive to anecdotal evidence, 3–10 substantial, and 10–30 strong evidence. Separate Bayesian linear regression were performed for each continuous variable and included as covariate OAS and BDI-II, OAS and BAI or OAS and LSAS scores. For the odor ratings, separate analyses were also performed for neutral, pleasant and unpleasant odors.

5.4. Results

Descriptive statistics

The final sample consisted of 214 participants (see Table 5.1 for sample characteristics). Of these, 37 performed the "Sniffin' Sticks" test with the classical procedure, 177 with single-use paper strips. No significant differences were found between these two types of testing for TDI score [$t(212) = -1.59$, $p = 0.11$], identification score [$t(212) = -1.1$, $p = 0.27$], discrimination score [$t(212) = -0.03$, $p = 0.97$], or threshold score [$t(212) = -1.52$, $p = 0.13$], thus it was not included as a control variable in the multivariate models. The lack of differences between the two types of testing was also confirmed by Bayesian statistics showing all $BF_{10} < 1$.

Table 5.1. Characteristics of the sample.

Sample (N)	214
Age (years)	22.5 (2.3)
Education (years)	15.7 (2.7)
BDI-II	11.3 (8.4)
BAI	12.6 (9.0)
LSAS	48.0 (23.2)
OAS	115.7 (14.4)

TDI	34.3 (3.9)
Threshold	7.3 (2.9)
% normosmic	89%
Discrimination	13.1 (1.6)
Identification	13.8 (1.4)

Notes: Data are M (SD) of continuous variables. BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory; LSAS = Liebowitz Social Anxiety Scale; OAS = Odor Awareness Scale; TDI = Sniffin' Sticks Threshold Discrimination Identification total score.

Basic olfactory abilities

The model for the TDI score included the main effects of the BDI-II and the OAS and their interaction.

TDI ~ BDI-II + OAS + BDI-II × OAS

The TDI score was significantly predicted by the BDI-II [F(1, 210) = 7.35, p = 0.007], showing that participants with higher depressive symptoms presented lower olfactory abilities, and by the OAS [F(1, 210) = 6.37, p = 0.012], indicating that higher attention to the odors predicted higher olfactory abilities. Moreover, a significant interaction between depressive symptoms and OAS scores emerged [F(1, 210) = 6.36, p = 0.012]. Simple slope analysis revealed that the effect of depressive symptoms in predicting olfactory abilities was only significant for OAS scores 1 SD below or equal to the mean (p < 0.001 and p = 0.01 respectively, Fig. 5.1A).

The model for the threshold subtest score included the main effects of the BDI-II and the OAS and their interaction.

Threshold ~ BDI-II + LSAS + OAS + BDI-II × OAS

A significant interaction between depressive symptoms and OAS scores emerged [F(1, 209) = 5.76, p = 0.017]. Simple slope analysis revealed that higher depressive symptoms predicted lower olfactory threshold in individuals with low (- 1 SD) odor awareness (simple slope = -0.30, t = -2.73, p = 0.01) but not average (p = 0.09) and high (+1 SD, p = 0.67) odor awareness (Fig. 5.1B).

The model for the discrimination subtest score included the main effects of the LSAS and the OAS and their interaction.

Discrimination ~ LSAS + OAS + LSAS × OAS

However, for the discrimination subtest, no significant results emerged from the model.

Finally, the model for the identification subtest score included only the main effects of the OAS.

Identification ~ OAS

The identification score was significantly predicted by the OAS score [$F(1, 212) = 4.28$, $p = 0.04$], showing that individuals with higher odor awareness presented higher identification scores.

The Bayesian Linear regressions showed that the TDI score changed in function of the interaction BDI-II × OAS ($B_{10} = 4.19$). In addition, there is anecdotal evidence for the interaction LSAS × OAS ($B_{10} = 2.25$) in predicting TDI score and anecdotal evidence for the LSAS ($B_{10} = 1.66$) in predicting the threshold subscale. For the other subtests, the Bayes Factor supported H0 both for BDI-II, LSAS and BAI ($B_{10} < 1$).

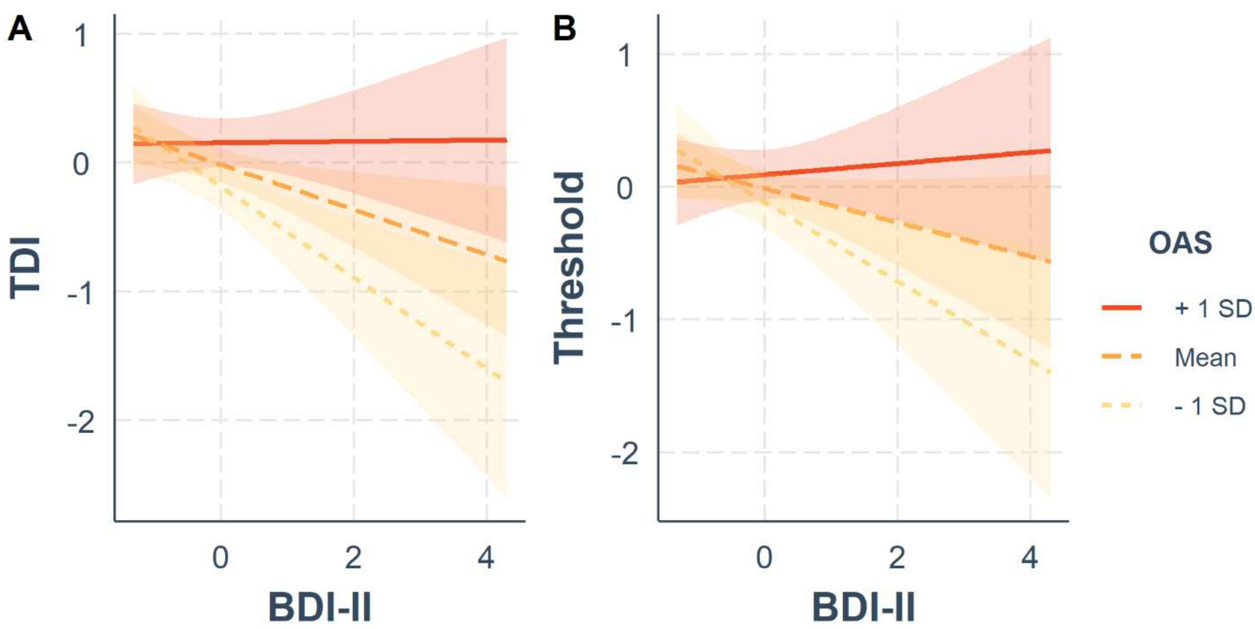

Fig. 5.1. (A) Interaction effects of depressive symptoms and odor awareness on TDI score. (B) Interaction effects of depressive symptoms and odor awareness on threshold score. *Notes*. Ninety-five % confidence bands for mean, +1 SD, - 1 SD values of odor awareness are presented in different colors.

Perceptual ratings of the odors

The model for Pleasantness rating included the main effects of the BDI-II, the OAS and their interaction, the main effect of the odor category, and participants' ID as a random factor.

Pleasantness ~ BDI-II + OAS + odor category + (1 | ID) + BDI-II × OAS

The final model investigating the pleasantness rating revealed a significant main effect of the category of the odors [$\chi(2) = 1533.58$, $p < 0.001$]. Specifically, unpleasant odors were rated as less pleasant than pleasant and neutral odors ($p < 0.001$), whereas pleasant odors were rated as more pleasant than neutral ones ($p < .001$). Moreover, a significant interaction between the BDI-II score and OAS score [$\chi(1) = 5.29$, $p = 0.021$] emerged. In particular, simple slope analysis revealed that higher depressive symptoms predicted higher pleasantness ratings in individuals with low (-1 SD) odor awareness ($p = 0.05$) but not average ($p = 0.56$) and high (+1 SD, $p = 0.18$) odor awareness (Fig. 5.2).

The model for Intensity rating was the following:

Intensity ~ BAI + OAS + odor category + (1 | ID) + BAI × OAS + BAI × odor category + OAS × odor category + BAI × OAS × odor category

The intensity rating was significantly predicted by the category of the odors [$\chi(2) = 421.26$, $p < 0.001$]: Tuckey post-hoc analysis revealed that unpleasant odors were rated as more intense than pleasant and neutral odors ($p < 0.001$), whereas pleasant odors were rated as more intense than neutral ones ($p < .001$). The model also revealed a significant interaction between OAS and the category of the odors [$\chi(2) = 7.78$, $p = 0.020$]. Enhanced attention to the odors predicted higher intensity ratings only for the unpleasant ($p < 0.001$) and pleasant odors ($p = 0.03$), but not for the neutral ones ($p = 0.61$). In addition, the intensity rating was significantly predicted by the triple interaction between the BAI score, the OAS score and the category of the odors [$\chi(2) = 6.18$, $p = 0.045$]. However, no significant results were found in the post-hoc tests.

The model for Familiarity rating included the main effects of the BDI-II, the OAS and their interaction, the main effect of the odor category, and participants' ID as a random factor.

Familiarity ~ BDI-II + OAS + odor category + (1 | ID) + BDI-II × OAS

The familiarity rating was significantly predicted by the OAS [$\chi(1) = 7.04$, $p = 0.008$], indicating that higher attention to the odors predicted higher familiarity ratings, and by the category of the odors [$\chi(2) = 149.46$, $p < 0.001$]. Specifically, Tuckey post-hoc analysis showed that pleasant odors were rated as more familiar than unpleasant and neutral odors ($p < 0.001$), whereas unpleasant odors were rated as more familiar than neutral ones ($p < .001$). Finally, the model was also predicted by an interaction between BDI-II and OAS [$\chi(1) = 4.06$, $p = 0.044$]. Subsequent simple slope analysis showed that low, medium or high levels of odor awareness did not affect the relation between familiarity rating and depressive symptoms (all ps > 0.14).

The Bayesian Linear regressions of intensity ratings for unpleasant odors support the hypothesis of the modulation by the interaction between OAS and BDI-II ($B_{10} = 7.56$) and between OAS and BAI ($B_{10} = 7.76$). Moreover, Bayesian Linear regression of intensity for unpleasant odors and familiarity ratings for both pleasant and unpleasant odors support the hypothesis of the modulation by OAS score (intensity unpleasant odors: $B_{10} = 38.41$; familiarity pleasant odors: $B_{10} = 3.70$; familiarity unpleasant odors: $B_{10} = 4.38$). All the other results showed $B_{10} < 1$.

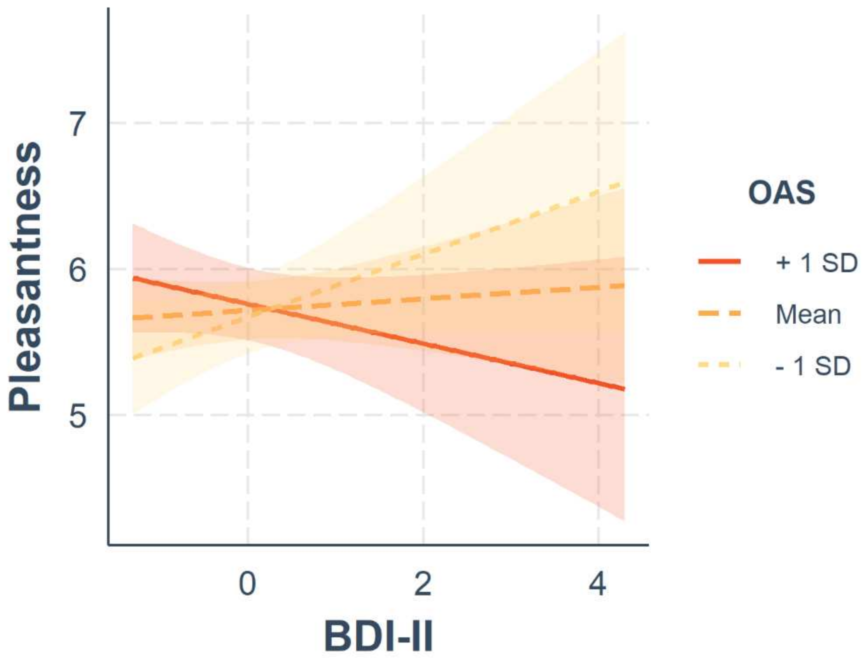

Fig. 5.2. Interaction effects of depressive symptoms and odor awareness on pleasantness ratings. *Notes*. Ninety-five % confidence bands for mean, +1 SD, - 1 SD values of odor awareness are presented in different colors.

5.5. Discussion

The attention that individuals pay to the odors in the environment, i.e., *odor awareness*, has been proposed to be one of the factors leading to olfactory disturbances. With this study, our first aim was to explore if the degree of odor awareness moderates the relationship between depressive and anxiety symptoms and olfactory abilities. Our data show that, first, individuals with higher depressive symptoms present lower olfactory abilities. Second, odor awareness is a significant moderator of the association between depressive symptoms and olfactory abilities (specifically for olfactory threshold). Conversely, anxiety and social anxiety symptoms are not related to any of the olfactory abilities taken into account, and this relationship did not change according to the degree of odor awareness.

The present findings, confirmed by the Bayesian framework, support the hypothesis that attention is a central mechanism in explaining the presence of reduced olfactory functions in depression. Specifically, the reduced attention toward odors in the environment may affect the peripheral function of olfaction, as measured by the olfactory threshold test (Croy & Hummel, 2017). Our result is partially consistent with previous literature: we found a reduced olfactory sensitivity, in line with previous study on patients with depression (e.g., Kazour et al., 2020; Lombion-Pouthier et al., 2006; Negoias et al., 2010; Pabel et al., 2018; Pause et al., 2001; confirmed also by systematic reviews Athanassi et al., 2021; Taalman et al., 2017) and in healthy individuals with depressive symptoms (Pollatos et al., 2007), however, we found no relation between depressive symptoms and higher olfactory functions, namely odor identification and discrimination (e.g., Hardy et al., 2012; Lombion-Pouthier et al., 2006; Naudin et al., 2012; Swiecicki et al., 2009, but see Kazour et al., 2020; Pabel et al., 2018). These mixed findings can be explained mainly by the tests used and by the fact that previous studies examined individuals that presented clinical depression as well as an older age than the present sample.

Contrary to our hypothesis, we did not find any relationship between anxiety symptoms and olfactory abilities. Our hypotheses were based on previous studies reporting impaired olfactory functions (e.g., Clepce et al., 2012; Takahashi et al., 2015), but also increased odor awareness (Burón et al., 2015, 2018; Dal Bò et al., 2022), in anxiety. However, there is still a wide discrepancy within the literature, indicating the need for further studies to better understand the role of olfactory functions in anxiety disorders.

The second aim of the present study was to explore the association between odor awareness and the perceptual ratings of odors in individuals with affective disorders. Given that one of the key aspects of depression is anhedonia, we could expect a reduced hedonic evaluation of the odors in individuals with depressive symptoms. Our results partially confirmed our hypothesis. Even though no association has been found between depressive symptoms and the category of the odors (pleasant, neutral and unpleasant), a significant relationship between depressive symptoms and pleasantness rating emerges, mediated by the attention that individuals pay to the odors: in individuals with low odor awareness, higher depressive symptoms led to higher pleasantness rating, whereas the opposite relation emerged for individuals with higher odor awareness. A possible explanation of the present finding could be found in the cognitive theories of depression, stating that a key characteristic of depressive disorders is the presence of a preferential processing bias for mood-congruent information (Clark & Beck, 2010). This bias potentiates like-valenced or matching emotions, leading to enhanced emotional responses to negative stimuli (Rottenberg et al., 2005), but also to rate the odors presented in this study as more unpleasant. However, this result should be interpreted with caution since this finding is not confirmed by Bayesian statistics.

Notably, both LMM and Bayesian analyses showed that odor awareness is a significant predictor of the familiarity ratings of the odor: the higher the attention that individuals pay to the odors, the higher the odor familiarity. This result highlights how this metacognitive ability affects not only the level of objective olfactory perception (Nováková et al., 2014; Smeets et al., 2008), but also the perceptual ratings of the odors. Odor familiarity is an important characteristic in odor perception, representing prior knowledge of the odor without the semantic association that is characteristic of odor identification (Larsson et al., 2006; J. P. Lehrner et al., 1999). Hence, it is possible that individuals that pay more attention to the odors in the environment become also more familiar with them.

Our results also provide some insights to develop future treatments. Considering that odor awareness proved to have a key role in determining the presence of olfactory dysfunctions in individuals with depressive symptoms, it could be used as a useful target in the clinical setting. Accordingly, there is evidence showing that daily olfactory training improves not only the olfactory function but also the depressive symptoms and the general wellbeing in individuals experiencing subclinical depression (Birte-Antina et al., 2018, but see Pabel et al., 2020; Pieniak et al., 2022). New trainings are emerging, mainly focusing on odor-based cognitive interventions (for example including a smell memory game; Olofsson et al., 2020). However, future treatments should be aimed to strengthen not only the cognitive, but also the emotional functions. In addition, they should specifically take into account the characteristics of individuals with depressive symptoms, to increase the compliance and the motivation to follow the treatment.

The current findings ought to be interpreted in light of some methodological limitations. First, all participants included in the present study were females, thus making it impossible to generalize the current results to a male population. However, only women were included to avoid gender-related effects, considering that it is documented that women present higher olfactory abilities (Doty & Cameron, 2009), higher odor awareness (Ferdenzi et al., 2008), higher interest in the sense of smell (Seo et al., 2011), and higher importance of olfaction (Croy et al., 2010; Havlicek et al., 2008) than men. Second, the study was not pre-registered since it was part of the screening procedure within an extensive research project. However, hypotheses were based on the review of the literature.

To conclude, while with the present study it is not possible to state if the reduced olfactory abilities are the cause or the consequence of the development of depressive symptoms, the evidence that odor awareness is a mediator of this relationship is an important step forward in the understanding of the disorder and in the development of useful treatments. Moreover, the current study has several implications for vulnerability to and early identification of depression, identifying olfactory dysfunction and odor awareness as potential risk factors in the development of clinical depression. Indeed, the concomitant evaluation of depressive and anxiety symptoms has allowed us to better disentangle the different roles of these two disorders in olfaction. With the present findings we provide evidence that in a healthy population, only the presence of depressive symptoms is related to reduced olfactory performance, whereas anxiety symptoms are not. In addition, odor awareness may be involved in the development and maintenance of olfactory dysfunction.

CHAPTER 6

Emotion perception through the nose: how affective disorders modulate the perception of olfactory emotional cues[7]

6.1. Abstract

Human body odors have been shown to be an effective modality of social communication. Importantly, individuals exposed to emotional body odors report a partial reproduction of the affective state of the sender. This phenomenon is particularly relevant in conditions in which social interactions are impaired, as in depression and social anxiety. A high-density EEG study was conducted to investigate how body odors collected in a happiness and a fearful condition modulate the subjective perceptual experience and the neural processing of neutral faces in individuals with symptoms of depression (DEP), with symptoms of social anxiety (SAD), and healthy participants as controls (CONT) (for each group N = 22). Time-frequency analysis was performed to simultaneously investigate affective disposition and cognitive processing of neutral faces presented in the context of emotional body odors. Cluster-based statistics revealed a reduced beta desynchronization for the emotional body odor conditions (both happiness and fear) compared to the clean air condition in the CONT group. Moreover, a reduction in delta and theta power for the clean air condition in DEP group relative to CONT group emerged. On the other side, SAD individuals presented an increased delta power for the fear body odor condition, compared to the CONT group. Regarding the subjective ratings, the fear body odor reduced the pleasantness of the faces in the CONT group and increased

[7] A manuscript related to the experiment and the results described in the present chapter is in preparation for the submission

the subjective arousal in the DEP group. The present study provides novel insight into the complex role of happiness and fear body odors as powerful social signals, especially in social anxiety and depression. In the DEP group, only in the clean air condition, an altered affective disposition, as well as cognitive processing, of the neutral faces have been observed, but not when they were presented with the emotional body odors. With respect to the SAD group, a higher motivational disposition toward the neutral faces presented in the context of the fear odor emerged, highlighting a hyperactivation of the defensive motivational system. Hence, given the strong relevance of body odors in both depression and social anxiety, future studies should investigate their potentially beneficial role as contextual social cues in therapeutic intervention.

6.2. Introduction

Social relationships are intricately tied to health and well-being. Good quality social relationships are essential for happiness and life satisfaction as they can represent powerful rewards (e.g., social support, companionship, and intimacy) or potential threats (e.g., rejection, conflict, and exploitation; Gable & Gosnell, 2013). It has been theorized that social behavior is regulated by the motivation to approach rewards, i.e. approach social motives (e.g., hope for affiliation), and the motivation to avoid threats, i.e. avoid social motives (e.g., fear of rejection) (Gable & Gosnell, 2013). It is reported that stronger social approach motivation is related to more satisfaction toward social life and less loneliness, while stronger social avoidance motivation is associated with less satisfaction, more loneliness and insecurity (Gable, 2006). In turn, social isolation and loneliness are associated with poor psychological health and with the development of psychopathological symptoms such as depression, anxiety and substance abuse (Cacioppo & Patrick, 2008; House et al., 1988; Whisman, 2001).

Depression and social anxiety are among the most common mental disorders and are both characterized by impaired social functioning. Social anxiety is characterized by increased activity of the defensive motivational system (Davidson, 2000; Nusslock et al., 2015) which causes these individuals to perceive intense fear and avoidance of social situations (Hofmann & Bögels, 2006; Rapee & Spence, 2004). Individuals with social anxiety show abnormal processing of social threat information, with the presence of biases in attending to, interpreting and remembering social cues (Hirsch & Clark, 2004). In particular, avoidance behaviors play a crucial role in the maintenance of the disorder since they do not allow the extinction of fear of social situations (Stangier et al., 2006; Wells et al., 1995). Conversely, depressive disorders are characterized by anhedonia, apathy and psychomotor retardation, which seem to be associated with hypoactivation of the appetitive motivational system (Henriques & Davidson, 1990; Stewart et al., 2010), resulting in reduced motivation to respond in social interactions, altered empathic responses and the inability to find effective solutions for interpersonal problems (Kupferberg et al., 2016). In addition, individuals with depression are characterized by altered cognitive processes that play a prominent role in the development and maintenance of the disorder (Clark & Beck, 2010). In particular, negative self-referential schemata facilitate the processing of negative information (Beck & Bredemeier, 2016; LeMoult & Gotlib, 2019), generating a rigid pattern of negative appraisal of unpleasant stimuli (Disner et al., 2011; Kircanski et al., 2012), but also a reduced processing of pleasant content (Dell'Acqua, Dal Bò, et al., 2022; Messerotti Benvenuti et al., 2020; Messerotti Benvenuti et al., 2019; Moretta et al., 2021; Winer & Salem, 2016). Social impairment is so pervasive that both social anxiety disorder and depression are considered among the 5 most impairing psychiatric disorders (Alonso et al., 2004).

In the study of social motivation, researchers have focused predominantly on the acoustic and visual aspects of human social interaction. Only recently, they have directed their attention to another relevant aspect, which is olfaction. Notably, humans transfer socially relevant information (such as age, health status, and personal predispositions) and emotional states via body odors (also referred to as chemosignals) (Disner et al., 2011; Parma et al., 2017; Pause, 2012, 2017). Compared to other modalities, the transmission of social information through body odors has several advantages related to the intrinsic nature of the signal (Wyatt, 2003). For example, molecules can easily move across timely and physical barriers allowing the signal to be transmitted over long distances and to persist even after the sender is no longer in the place. Moreover, olfactory communication, which is totally effortless for the sender and it requires very low energy for the receiver, can transmit different types of signals but, at the same time, can be extremely detailed (Parma et al., 2017; Pause, 2012, 2017). Most importantly, the decoding of such social information succeeds even when the body odor is not consciously perceived, as when they are masked by fragranced products (Cecchetto et al., 2020; Cecchetto, Lancini, Bueti, et al., 2019; Cecchetto, Lancini, Rumiati, et al., 2019). Previous studies have shown that individuals exposed to body odors collected during strong emotional events report a partial reproduction of the affective, perceptual and behavioral state of the sender, in a phenomenon called "emotional contagion" (Hatfield et al., 1993).

The ability of body odors to convey emotional information is particularly relevant in all conditions in which social interaction and emotional processing are impaired, as in affective disorders. Given the exceptional advantages of emotional communication through human chemosignals, the investigation of positive and negative emotional body odors could shed light into the complex interplay between the two motivational systems in the development and course of affective disorders. However, to date, only a few studies have investigated the perception of body odors in affective disorders and all of them have focused on social anxiety and on fear or anxiety body odors. Social anxious individuals reported enhanced startle reactivity (Pause et al., 2009) and faster processing of anxiety chemosensory signals compared to healthy controls (Pause et al., 2010) and this effect is similar to those obtained with threatening visual stimuli (i.e., Kolassa & Miltner, 2006; Mühlberger et al., 2009). When visual (fearful faces) and olfactory (chemosensory anxiety signals) stimuli were presented together, high social anxious individuals showed reduced motivated attentional allocation (LPP) and larger startle responses for the facial expressions than healthy controls (Adolph et al., 2013). To our knowledge, there are no studies on positive emotional body odors or on individuals with depression.

The current study was designed to investigate social motivation toward neutral facial expressions presented in the context of negative (fear) and positive (happiness) emotional body odors in individuals with symptoms of depression and with symptoms of social anxiety. Therefore, neutral faces were presented to 66 women [22 women with symptoms of social anxiety (SAD), 22 with symptoms of depression (DEP), 22 without symptoms of depression or social anxiety (CON)] during the contextual delivery of happiness body odor or fear body odor or clean air, used as control. Cortical dynamics were measured through electroencephalography (EEG). Specifically, in the present study, a time-frequency analysis of EEG activity within specific frequency bands while participants are exposed to relevant (neutral faces with happiness or fear body odors) vs. neutral (neutral faces with clean air) content was adopted. This method is particularly advantageous since the time-frequency analysis can give a unique inside into emotional stimulus processing allowing the extrapolation of information that is not available using event-related potentials (ERPs) analysis. In addition, this approach permits the simultaneous examination of affective disposition and cognitive processing, two synchronous mechanisms that are rarely jointly studied (e.g., Herrmann et al., 2014). Delta (1-3 Hz) and alpha (8-12 Hz) frequency bands are thought to reflect affective disposition, while theta band (4-7 Hz) the cognitive processing of salient stimuli. Finally, the functional role of beta band (13-30 Hz) is not yet fully understood but is supposed to convey information regarding both the affective and the cognitive processing of the stimuli.

Finally, emotional reactions to the neutral faces presented in the context of emotional body odors were also collected directly through self-report measures of arousal and valence by means of the self-assessment manikin (SAM; Bradley & Lang, 1994).

6.3. Materials and methods

Participants

Participants were enrolled among the students at the University of Padova through advertisements on social media. In order to be included in the study, participants were pre-screened with online questionnaires to exclude the presence of: chronic rhinitis or other conditions that may affect the ability to perceive odors, smoking, pregnancy or breastfeeding, presence of other mental disorders (including substance abuse disorders) apart from Major Depression, Chronic Depression, Minor Depression, or Dysphoria and Social Anxiety Disorder, presence of any severe somatic or neurological conditions, use of psychotropic drugs at the moment of the recruitment (including antidepressants, antipsychotics, anxiolytics and mood stabilizers), presently undergoing psychological therapy, presence of severe psychotic symptoms (i.e. hallucinations and/or delusions), presence of suicidal thoughts, incapability to understand and to give informed consent for the experiment, being younger than 18 years or older than 35 years, being left-handed, no previous diagnosis of COVID-19. Moreover, participants were recruited if they could be included in one of the three experimental groups: a group with depressive symptoms (DEP), a group with social anxiety symptoms (SAD) and a healthy control group (CON). Inclusion criteria were a score over or equal to 50 on the Liebowitz Social Anxiety Scale in its self-report formulation (LSAS-SR) for the SAD group, a score over or equal to 12 on the Beck Depression Inventory II (BDI-II) for the DEP group, and a score below 12 on the BDI-II and a LSAS score below 40 for the CON group. A confirmation of the presence or absence of the disorder during a face-to-face interview through the Structured Clinical Interview for DSM-5 (SCID-5-CV) was also required for participants. Finally, in order to be included in the study, participants were screened for normative olfactory function with the Sniffin' Sticks test.

A total of 79 participants were tested in the EEG study (27 CON, 22 DEP, 30 SAD), however, the data of 13 participants were removed from analyses due to technical problems. The final sample included 66 participants (22 CON, 22 DEP, 22 SAD). With respect to demographic variables, the three groups included in the analyses (CONT, DEP, SAD) did not differ in terms of age ($p = .58$; CONT group: Mean (M) = 23.09, standard deviation (SD) = 2.00; DEP group: M = 22.73, SD = 2.59; SAD group: M = 22.41, SD = 2.32).

Sniffin' Sticks test

Olfactory function was assessed with the computer-testing version of the standardized clinically approved "Sniffin' Sticks" test (Burghart Instruments, Wedel, Germany; Hummel et al., 1997). The task and each subscale are explained in detail in Chapter 5 of the present thesis. Only participants obtaining a TDI score in the normosmic range (above or equal to 30.5) were included in the study.

Body odor collection and preparation

Emotional body odors were collected before the beginning of the experimental session from a different group of participants [called “body odor donors”, 32 healthy Caucasian participants (16 females) aged between 18 and 35 (mean = 21.64, SD = 3.63)] which were exposed to videos that induced emotional states of fear or happiness. Body odor samples were collected at the Instituto Superior de Psicologia Aplicada (Lisbon, Portugal). Body odor donors reported to be heterosexual, nonsmokers, to not have past or current psychological disorders and to not take medications. Body odors were collected through sterilized cotton pads attached to the armpit zone while donors were exposed to videos that induced emotional states of fear or happiness. The videos were composed of several short video clips (already used in previous studies to induce fear and happiness; de Groot et al., 2014a, 2014b; de Groot, Smeets, Rowson, et al., 2015) with a total average duration of 25 min. Fear and happiness body odor collections were separated by a week’s interval, with participants following a strict behavioral and dietary regimen every 2 days prior to each odor collection session to avoid sweat contamination (see de Groot et al., 2012 for a detailed list of restrictions).

Before and after each emotional state induction, donors rated to what extent they felt angry, fearful, happy, sad, disgusted, neutral, surprised, calm, and amused on separate 100-point Likert scales that ranged from 1, not at all, to 100, very much. After emotional state induction, pads were removed, frozen individually in amber vials at −80 °C, and then shipped in dry ice to the University of Padova (Italy), where they were stored again in a −80 °C freezer.

The rating of the emotional state performed before and after each emotional state induction confirmed that the emotional induction procedure worked as the body odor donors after the fear induction, compared to before, felt less calm [$t(60) = 8.27$, $p < .0001$], less neutral [$t(60) = 4.88$, $p < .0001$], less amused [$t(60) = 3.31$, $p = .0001$], less joyful [$t(60) = 4.95$, $p < .0001$], more surprised [$t(60) = -5.46$, $p < .0001$], more disgusted [$t(60) = -4.15$, $p < .0001$], angrier [$t(60) = -3.27$, $p =$

.00017], more fearful [t(60) = -3.37, p < .0001], while after the happiness induction, compared to before, they felt less neutral [t(60) = 2.38, p =.0.02], less fearful [t(60) = 2.52, p = .01], more surprised [t(60) = -2.16, p =.034], more joyful [t(60) = -3.25, p =.00018], more amused [t(60) = -5.45, p < .0001]. See Table 1B in Appendix B for mean and standard deviation of emotional state ratings.

As in previous studies (e.g., Cecchetto, Lancini, Rumiati, et al., 2019; de Groot, Smeets, Rowson, et al., 2015), in order to reduce the effects of interindividual variability in sweat production, body odor pads were prepared for presentation as follows: while still frozen, each pad obtained from the sweat donors' armpits was cut into eight equal parts. Using a randomization script, pad pieces from four sweat donors (two females, two males; two from the left and two from the right armpits) of the same emotional state – fear or happiness – were combined to create a super-donor.

Three odor conditions were presented during the experimental task: clean air, fear emotional body odor, happiness emotional body odor. Odors were delivered with a custom-built, continuous airflow, computer-controlled olfactometer with 3 lines: one providing baseline odorless air and the other two connected to the airtight jars containing the super-donor pads (fear and happiness). Airflow was kept constant between 50 and 70 ml/min. Odorous or odorless air was delivered directly to both nostrils with a nasal cannula.

Visual stimuli

126 neutral faces (63 females, 63 males) were selected from the Chicago face database (Ma et al., 2015) for the passive viewing task. The images were distributed over the 21 blocks constituting the task in order to match for physical facial features, age of the actors, attractiveness, femininity, masculinity, trustworthiness and for the seven levels of emotional expressiveness (ratings from Ma et al., 2015). Moreover, six faces were used for training purposes. All faces were presented on a white background.

Recordings

EEG was recorded continuously using a 256-channel Geodesics EGI System (Electrical Geodesics, Inc., Eugene, Oregon, USA) with a sponge-based Geodesic Sensor Net. The sensor net was aligned with respect to four anatomical landmarks: two pre-auricular points, the nasion and the inion. Electrode-to-skin impedances were kept below 50 kΩ and at equal levels across all electrodes. The sampling rate was 500 Hz and electrode Cz was used as the online reference.

Procedure

After the application of the EEG cap, participants were seated in a dimly lit, sound attenuated and electrically shielded room facing an LCD monitor placed approximately 0.7 m in front of them. Then, the olfactometer tube for odor delivery was fitted onto the participants. First, the baseline was recorded for 3 min. Second, ratings of odor pleasantness, intensity, and familiarity were recorded before and after the experimental task. During odor ratings, each odor was administered individually, in a four-second pulse. After each odor pulse, on-screen visual-analogue scales prompted participants to rate the pleasantness (from 0 very unpleasant to 100 very pleasant), intensity (0 no odor to 100 very intense odor) and familiarity (0 not familiar at all to 100 extremely familiar) of the odor. Third, participants were presented with 6 training trials and instructions were given. Finally, the task began.

The task was a passive viewing task in which participants were asked to simply look at the neutral faces appearing on the screen while breathing normally. Odors and images were presented in a randomized block design. The odor stimulation session consisted of 21 blocks (7 displaying happiness body odor, 7 displaying fear body odor, 7 displaying clean air). In each block, lasting on average 36 seconds, only one odor was displayed and 6 images were shown. Each picture was preceded by a 2-s grey interval with a white fixation cross placed centrally on the screen. Each image was displayed for 2 s. The ISI ranged from 1 to 3 s. Between each block, images were displayed again and after each image participants were asked to rate the valence and arousal of the emotions transmitted by the images using the 9-point Valence and Arousal scale of the Self-Assessment Manikin (SAM) (Bradley & Lang, 1994). During the rating, only clean air was presented. The experimental session lasted around 90 min in total. In Figure 7.1 an overview of the study design is presented.

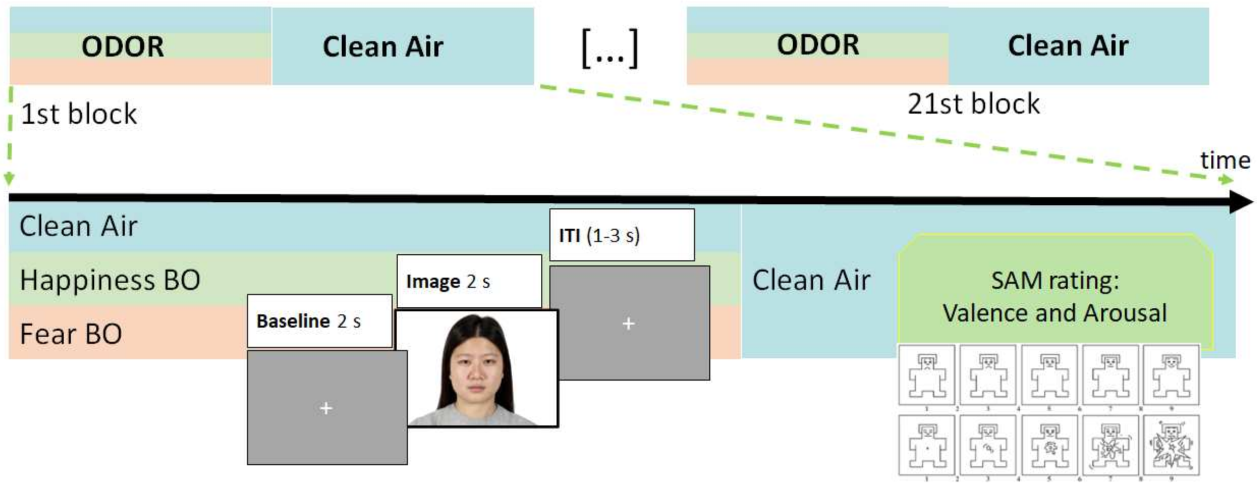

Fig. 7.1. Experimental protocol. For each block one among clean air, happiness body odor or fear body odor and 6 neutral faces were presented.

EEG analysis

Preprocessing. EEG signal was analyzed offline with EEGLAB and MATLAB custom scripts (MATLAB (2020). version 9.9 (R2020b). Natick, Massachusetts: The MathWorks Inc.). All signals were band-pass filtered between 0.1 Hz and 50 Hz and downsampled to 125 Hz. Then, bad channels were removed if flat for more than 5 s or if poorly correlated with the reconstruction obtained from their adjacent channels ($\rho < 0.8$) (Mullen et al., 2015). Removed channels were recovered through spherical spline interpolation. Pre-processed signals were then referenced to the numeric average of all channels. Afterward, EEG signals were segmented into epochs ranging from -1000 ms to 2000 ms around visual stimulus administration. After a visual inspection, the epochs contaminated by abrupt signal changes were discarded. Cleaned epochs were decomposed into sets of statistically independent components through independent component analysis (ICA) (Makeig et al., 1995). These components reflected both brain sources of activity as well as different types of artifacts such as muscular activity, ocular movements, and channel noise. Here, we exploited ICLabel to tag components as *brain*, *muscle*, *eye*, *heart*, *line noise*, *channel noise* and *other* (Pion-Tonachini et al., 2019). Accordingly, we reconstructed the EEG signal with the only contribution of *brain* components. Additionally, an expert performed a visual inspection for removing potentially misclassified components. Finally, for each epoch, we removed a subtractive baseline estimated in the 1000ms preceding the stimulus administration.

Time-frequency analysis. Time–frequency analysis was performed using a Morlet wavelet transformation on individual trials for each 1-Hz frequency bin between 1 and 25 Hz, using a mother wavelet at 1 Hz with 3-s time resolution (full width at half maximum; FWHM). Time-frequency decompositions were then averaged for each participant and odor condition, and the event-related spectral perturbation (ERSP) was computed as the change in power expressed in decibels (dB) relative to the baseline (− 900 to − 400 ms) in each frequency bin at each time point. Then, data were grand averaged across each group for each odor condition.

Statistical analysis

Ratings of the odors. Dependent variables were intensity, familiarity and pleasantness of the three odors. Separate linear mixed models (LMMs) were computed for each dependent variable, using the *lmer* function (*stats* package; R Core Team, 2017), with odors (clean air, happiness odor, fear odor), and Time (Before, After) and their interaction as fixed factors, and subjects' identity and images as random factors.

Self-report rating of the visual stimuli. Similarly, to analyze the self-report rating of valence and arousal of the neutral faces, separate LMMs with Group (SAD, DEP, CONT), Odor (clean air, happiness odor, fear odor), and their interaction as fixed factors, and subjects' identity and images as random factors were conducted.

EEG time-frequency analysis. A cluster-based permutation approach was adopted to control over type I error rate arising from multiple comparisons across electrodes and time points (Maris & Oostenveld, 2007), as implemented by the FieldTrip toolbox (Oostenveld et al., 2011). This approach has several advantages since it does not rely on the distribution of the data or the theoretical underlying distribution of test statistics under the null hypothesis (i.e., Gaussian) (Cohen, 2014). On the contrary, the data itself generates the theoretical underlying distribution of test statistics under the null hypothesis, by iteratively shuffling the condition labels over trials (i.e., within-subjects) or over subjects (i.e., between-subjects) and recomputing the statistics. The data are shuffled thousands of times until the distribution of the test statistic value observed under the null hypothesis is generated. If the test statistic associated with the non-shuffled data falls within the distribution of the null-hypothesis test statistic values, the null hypothesis cannot be rejected and this would indicate that the observed data could have been randomly generated (Cohen, 2014; Luck, 2014). Cluster-based correction assumes that a true effect should show a temporal and spatial extension, with neighbor sensors showing similar patterns (Cohen, 2014). With cluster-based correction, at each iteration of the null hypothesis distribution generation, a threshold is applied to the time-frequency map, such that the outcome is units of clusters instead of single pixels (i.e., electrodes) (Cohen, 2014). In the present study, the differences within odor conditions or between groups were shuffled pseudo-randomly 2000 times. To obtain a 'null' distribution of effect sizes, the maximal cluster-level statistics (i.e., the sum of values across contiguously significant electrodes and time points at the threshold level) were extracted for each shuffle. For each significant cluster in the (non-shuffled) data, the cluster-corrected p-value was computed as the statistics of the proportion of clusters in the null distribution that exceeded the one obtained for the cluster in question. The analysis was conducted with a − 100 to 1500 ms time window and clusters with a pcorr < .05 were considered statistically significant. This approach provides solid control over type I error rate arising from multiple comparisons across electrodes and time points (Maris & Oostenveld, 2007).

Cluster-based repeated measures ANOVAs were conducted to test within-group differences in event-related power changes between odor categories (clean air, happiness body odor, fear body odor). Two-tailed independent samples t-tests were conducted to test between-group (i.e., DEP versus CONT, SAD versus CONT) differences within each odor category. The cluster-based statistical tests were run on the event-related delta (1–3 Hz), theta (4–7 Hz), alpha (8–13 Hz) and beta (14-25 Hz) power over time-points in the − 100 to 1500 ms interval and a $p < .05$ criterion was employed to threshold the matrices.

6.4. Results

Fear and happiness body odors were not perceived as different odors

Before and after the EEG experimental task, participants were asked to rate the intensity, pleasantness, and familiarity of the three odor conditions (fear and happiness body odors, and clean air). Participants did not rate the three odor conditions as different in terms of pleasantness [all $\beta < 4.05$, $t < 1.61$, $p > 0.11$] and familiarity [all $\beta < 3.35$, $t < 1.33$, $p > 0.18$]. They rated the three odors as more intense after the experimental task compared to before [time effect: $\beta = 6.09$, $t = 2.90$, $p = 0.004$] but there was no difference among odors [all $\beta < 0.37$, $t < 0.18$, $p > 0.74$] or odor × time interaction [all $\beta < -1.69$, $t < -0.17$, $p > 0.57$; see Figure 7.2]. These results confirmed that the three odor conditions were not consciously perceived as different.

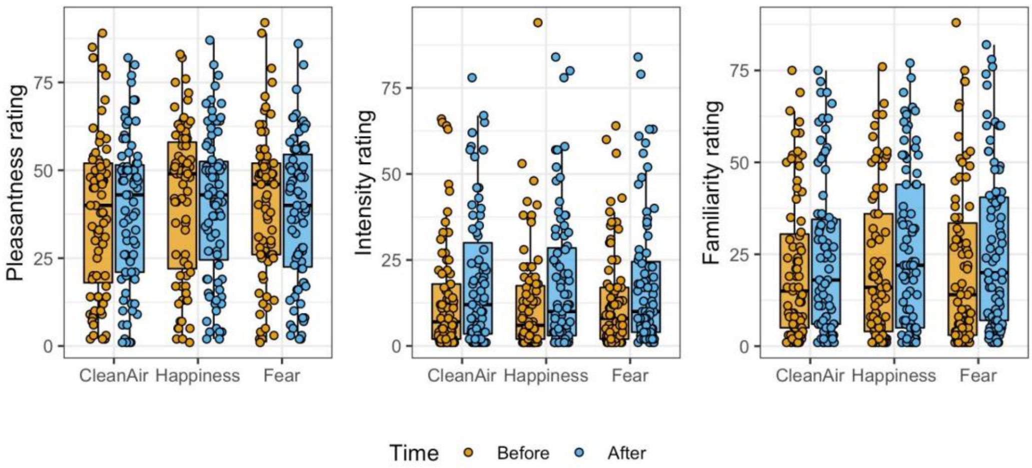

Fig. 7.2. Mean self-report rating of pleasantness, intensity and familiarity for the three odor conditions, collected before and after the experimental task. The plot shows the median (indicated by the horizontal band), the first through the third interquartile range (the vertical band) of the subjective rating in each group. Each dot represents one participant.

Self-report data of valence and arousal

Having established that the three odor conditions were perceived as similar, we tested how each odor condition affected emotional reactions to neutral facial images through self-report ratings of perceived valence and arousal.

For valence ratings, the analyses revealed that the CONT group rated the faces presented with the fear odor as less pleasant than clean air [$\beta = -0.11$, $t = -1.99$, $p = 0.047$] (Figure 7.3, panel a). No other significant effects were found.

For arousal ratings, results showed that, regardless of the odor condition, SAD and DEP groups rated the faces as more arousing than the CONT group [SAD: $\beta = 1.08$, $t = 2.77$, $p = 0.007$; DEP: $\beta = 0.83$, $t = 2.13$, $p = 0.04$]. Moreover, the analyses revealed that the DEP group rated the faces presented with the fear odor as more arousing than the faces presented with clean air [$\beta = 0.19$, $t = 2.83$, $p = 0.005$] but no significant differences were found between clean air and happiness odor [$\beta = 0.10$, $t = 1.57$, $p = 0.11$] or between happiness and fear odors [$\beta = -0.08$, $t = -1.29$, $p = 0.20$] (Figure 7.3, panel b). No other significant effects were found.

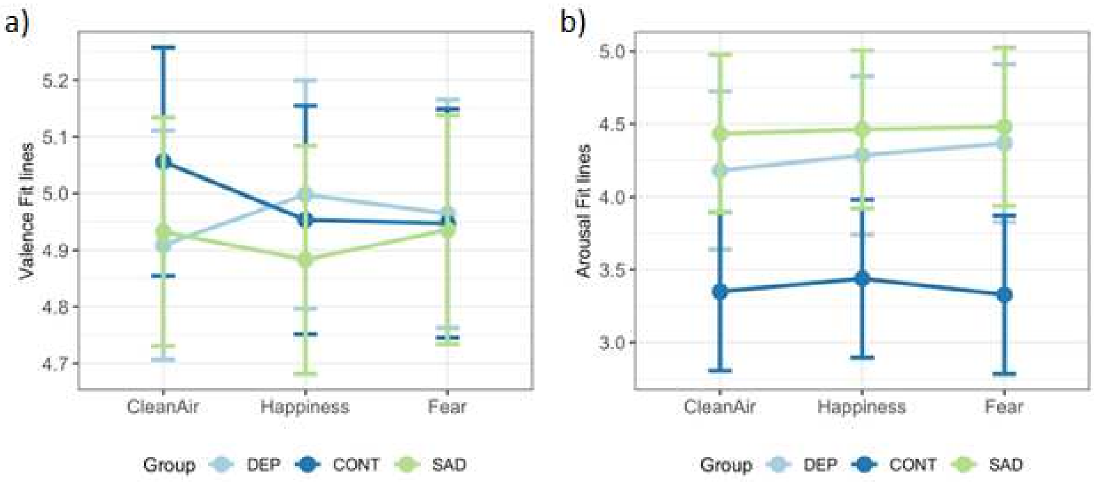

Fig. 7.3. (a) Interaction effects of group and odor on the valence rating. **(b)** Interaction effects of group and odor on the arousal rating.

Time-frequency data

Delta power.

Differences among odor categories in event-related delta power. The cluster-based analyses on event-related delta power did not reveal any statistically significant cluster in testing possible within-group differences.

Differences between CONT and DEP in event-related delta power for each odor category.

Cluster-based unpaired t-tests on event-related delta power revealed a significant positive cluster for the difference between DEP and CONT groups within the clean air condition (electrodes = E3 E4 E5 E6 E8 E13 E14 E15 E16 E17 E20 E21 E22 E23 E24 E26 E27 E28 E29 E30 E33 E34 E35 E36 E38 E39 E40 E41 E42 E43 E44 E47 E48 E49 E50 E51 E52 E55 E56 E57 E58 E59 E60 E62 E63 E64 E65 E66 E69 E70 E71 E72 E74 E75 E76 E84 E85 E86 E96 E97 E98 E99 E107 E108 E109 E116 E118 E125 E129 E130 E131 E138 E140 E141 E142 E143 E144 E150 E151 E152 E153 E154 E155 E160 E161 E162 E163 E164 E170 E171 E172 E173 E180 E181 E182 E183 E184 E185 E192 E193 E194

E195 E196 E197 E198 E205 E206 E207 E214 E215 E223 E224; cluster t-value max = 32,749.09, pcorr = .012, time window = -0.104 to 1.496 ms), as shown in panel a of Figure 7.4. Specifically, the DEP group showed reduced delta in response to neutral faces presented with clean air relative to the CONT group (see Figure 7.4, panels b, c). Unpaired t-test did not reveal any significant cluster for the difference between the groups within the fear and happiness odor conditions.

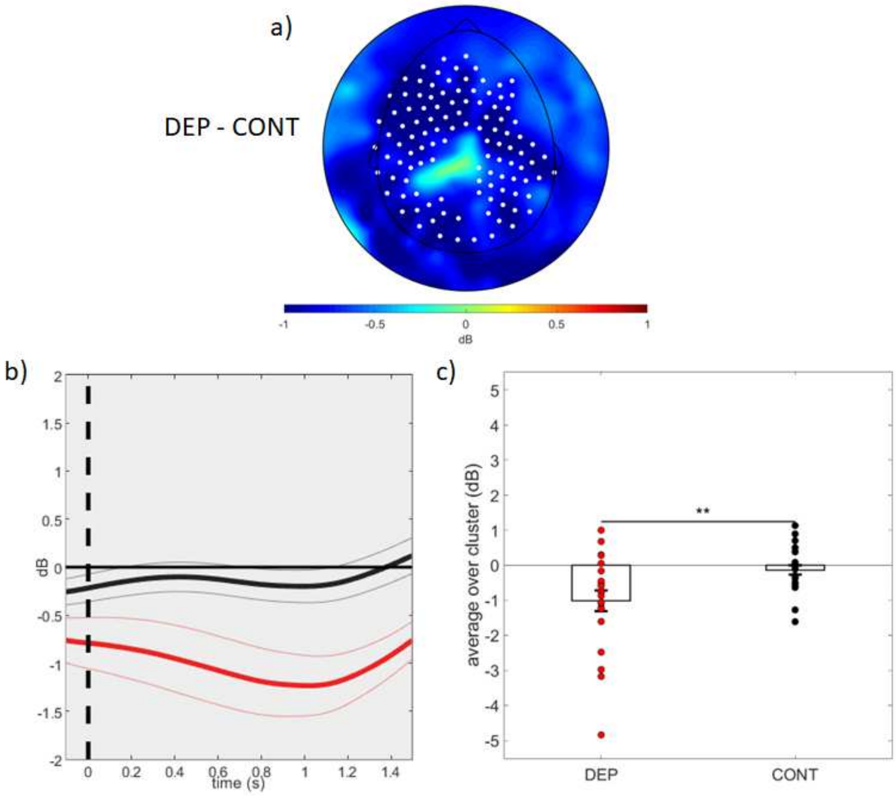

Fig. 7.4. (a) Topography of the mean difference between groups in event-related delta power (dB; DEP group minus CONT group) averaged over the significant time points (-0.104 to 1.496 ms time window) for the clean air condition. **(b)** Time course of grand-average event-related delta power averaged over the significant electrodes for the clean air condition in the CONT group (black line) and the DEP group (red line). Shaded areas represent ± standard error of the mean (SEM); the grey line represents the end of significant time windows. **(c)** Mean event-related delta power of each participant in the CONT group and the DEP group averaged over the significant electrodes and time points for the clean air condition. Each circle represents one participant; the frames represent the mean event-related delta power across all participants in the CONT group and the DEP group and the solid black lines represent ± SEM. **p < .01.

Differences between CONT and SAD in event-related delta power for each odor category.

Cluster-based unpaired t-tests on event-related delta power revealed a significant negative cluster for the difference between CONT and SAD groups within the fear odor condition (electrodes = E2 E4 E5 E6 E7 E8 E11 E12 E13 E14 E19 E20 E26 E77 E78 E79 E80 E81 E86 E87 E88 E89 E90 E97 E98 E99 E100 E107 E108 E109 E110 E116 E117 E132 E184 E185 E186 E194 E195 E196 E197 E198 E202 E203 E204 E205 E206 E207 E211 E212 E213 E214 E215 E221 E222 E223 E224; cluster t-value max = -14,824.23, pcorr = .026, time window = -0.104 to 1.496 ms), as shown in panel a of Figure 7.5. Specifically, the SAD group showed increased delta in response to neutral faces presented with the fear odor relative to the CONT group (see Figure 7.5, panels b, c). Unpaired t-test did not reveal any significant cluster for the difference between the groups within the clean air and happiness odor conditions.

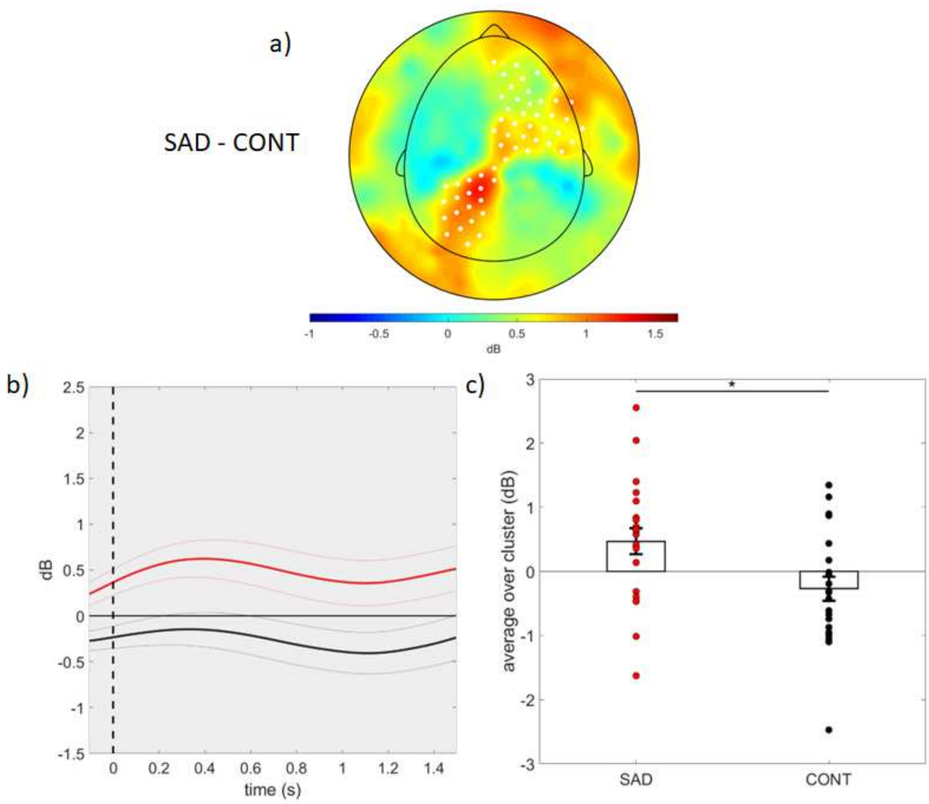

Fig. 7.5. (a) Topography of the mean difference between groups in event-related delta power (dB; SAD group minus CONT group) averaged over the significant time points (-0.104 to 1.496 ms time window) for the fear condition. **(b)** Time course of grand-average event-related delta power averaged over the significant electrodes for the fear condition in the CONT group (black line) and the SAD group (red line). Shaded areas represent ±

standard error of the mean (SEM); the grey line represents the end of significant time windows. **(c)** Mean event-related delta power of each participant in the CONT group and the SAD group averaged over the significant electrodes and time points for the fear condition. Each circle represents one participant; the frames represent the mean event-related delta power across all participants in the CONT group and the SAD group and the solid black lines represent ± SEM. *p < .05.

Theta power.

Differences among odor categories in event-related theta power. The cluster-based analyses on event-related theta power did not reveal any statistically significant cluster in testing possible within-group differences.

Differences between CONT and DEP in event-related theta power for each odor category.

Cluster-based unpaired t-tests on event-related theta power revealed a significant positive cluster for the difference between the DEP and CONT groups within the clean air condition (electrodes = E3 E4 E5 E6 E8 E12 E13 E14 E15 E16 E17 E21 E22 E23 E24 E27 E28 E29 E30 E33 E34 E35 E36 E38 E39 E40 E41 E42 E43 E47 E48 E49 E50 E51 E55 E56 E57 E58 E59 E62 E63 E64 E65 E69 E71 E74 E75 E76 E129 E130 E140 E141 E142 E151 E152 E153 E154 E160 E161 E162 E163 E164 E170 E171 E172 E173 E179 E180 E181 E182 E183 E184 E185 E192 E193 E197 E207 E215; cluster t-value max = 18,971.64, pcorr = .037, time window = -0.072 to 1.496 ms), as shown in panel a of Figure 7.6. Specifically, the DEP group showed reduced theta in response to neutral faces presented with clean air relative to the CONT group (see Figure 7.6, panels b, c). Unpaired t-test did not reveal any significant cluster for the difference between the groups within the fear and happiness odor conditions.

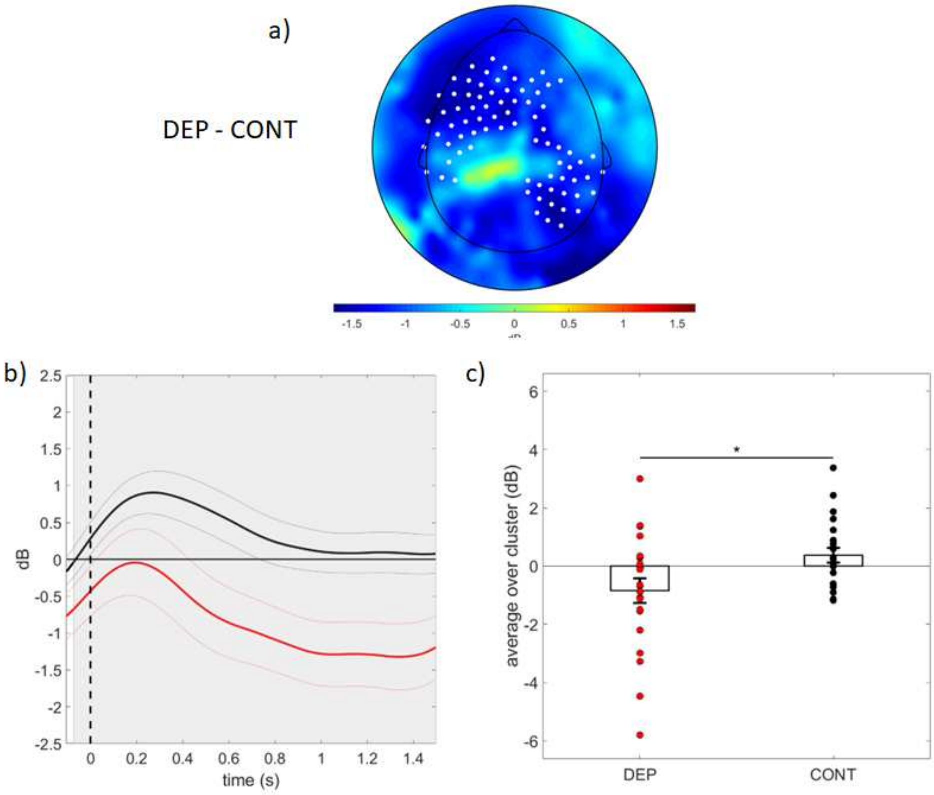

Fig. 7.6. (a) Topography of the mean difference between groups in event-related theta power (dB; DEP group minus CONT group) averaged over the significant time points (-0.072 to 1.496 ms time window) for the clean air condition. **(b)** Time course of grand-average event-related theta power averaged over the significant electrodes for the clean air condition in the CONT group (black line) and the DEP group (red line). Shaded areas represent ± standard error of the mean (SEM); the grey line represents the end of significant time windows. **(c)** Mean event-related theta power of each participant in the CONT group and the DEP group averaged over the significant electrodes and time points for the clean air condition. Each circle represents one participant; the frames represent the mean event-related theta power across all participants in the CONT group and the DEP group and the solid black lines represent ± SEM. *p < .05.

Differences between CONT and SAD in event-related theta power for each odor category.

Unpaired t-test conducted on event-related theta power did not reveal any significant cluster for the difference between the CONT and SAD groups within each odor condition.

Alpha power.

Differences among odor categories in event-related alpha power. The cluster-based analyses on event-related alpha power did not reveal any statistically significant cluster in testing possible within-group differences.

Differences between CONT and DEP in event-related alpha power for each odor category. Unpaired t-test conducted on event-related alpha power did not reveal any significant cluster for the difference between the CONT and DEP groups within each odor condition.

Differences between CONT and SAD in event-related alpha power for each odor category. Unpaired t-test conducted on event-related alpha power did not reveal any significant cluster for the difference between the CONT and SAD groups within each odor condition.

Beta power.

Differences among odor categories in event-related beta power. The cluster-based analysis on event-related beta power showed a significant positive fronto-central cluster (electrodes = E72 E75 E76 E84 E85 E86 E87 E88 E89 E96 E97 E98 E99 E100 E101 E107 E108 E109 E110 E116 E117 E118 E119 E125 E126 E127 E128 E129 E130 E138 E139 E140 E141 E142 E150 E151 E152 E153 E160 E161 E170) (cluster F-value max = = 9,221.11, pcorr = .026, time window = 0.584 to 0.904 ms) and a significant positive parieto-occipital cluster (electrodes = E2 E3 E4 E11 E12 E13 E14 E19 E20 E21 E22 E23 E27 E28 E29 E30 E33 E34 E35 E36 E38 E39 E40 E41 E42 E43 E47 E48 E49 E50 E55 E56 E194 E195 E196 E203 E204 E211 E212 E213 E214 E221 E222 E223 E224) (cluster F-value max = 8,010.43, pcorr = .040, time window = 0.520 to 0.768 ms) in the CONT group, as shown in panels a and d of Figure 7.7, respectively. The CONT group showed, in both clusters, reduced beta power in response to neutral faces presented with clean air compared to those presented with both fear or happiness body odors (all $ps < 0.01$; Figure 7.7 b,c,e,f).

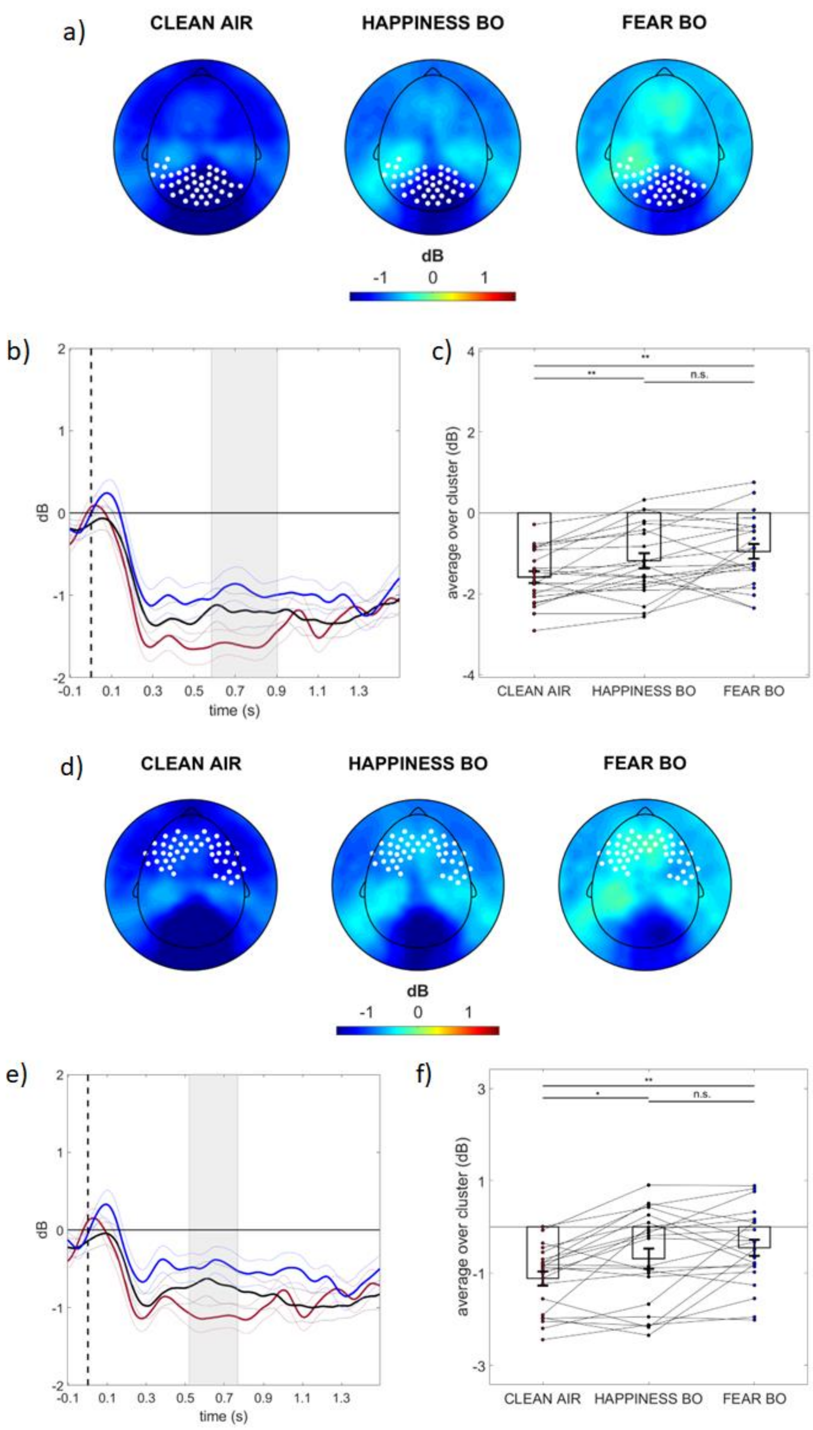

Fig. 7.7. (**a, d**) Topography of the mean event-related beta power (dB) of CONT group averaged over the significant time points (a, 0.584 to 0.904 ms time window; d, 0.520 to 0.768 ms time window) for clean air, happiness, and fear conditions. (**b, e**) Time course of grand-average event-related beta power of CONT group averaged over the significant electrodes for clean air (red line), happiness (grey line), and fear (light blue line) conditions. Shaded areas represent ± standard error of the mean (SEM) and the grey line represents the end of the significant time window. (**c, f**) Mean event-related beta power of each participant (in the CONT group)

averaged over the significant electrodes and time points for clean air, happiness, and fear conditions. Each circle represents one participant; colored frames represent the mean event-related beta power across all participants and the solid black lines represent ± SEM. *p < .05; **p < .01.

Differences between CONT and DEP in event-related beta power for each odor category.

Unpaired t-test conducted on event-related beta power did not reveal any significant cluster for the difference between the CONT and DEP groups within each odor condition.

Differences between CONT and SAD in event-related beta power for each odor category.

Unpaired t-test conducted on event-related beta power did not reveal any significant cluster for the difference between the CONT and SAD groups within each odor condition.

6.5. Discussion

The present study examined the subjective responses, affective disposition and cognitive processing of neutral facial expressions presented in the context of happiness and fear body odors in depression and social anxiety. A time-frequency approach has been adopted to examine event-related changes within the delta, theta, alpha, and beta bands in individuals with depressive symptoms or with social anxiety symptoms vs. healthy controls.

With respect to the subjective ratings, in the healthy control group, the neutral facial expressions were perceived as less pleasant when presented in the context of fear body odor compared to the clean air condition. This result is in line with previous studies reporting that exposure to fear or anxiety body odor affects the perception of visual stimuli, reducing the perceptual acuity for happy faces (Pause et al., 2004; Zernecke et al., 2011), increasing the attention toward fearful and angry facial expression (Adolph et al., 2013; Mujica-Parodi et al., 2009; Zhou & Chen, 2009) but also for neutral faces (Rubin et al., 2012). On the other side, in line with our results, happiness body odor did not modulate the perception of ambiguous stimuli (Zhou & Chen, 2009), possibly because it does not have direct vital consequences (Pratto & John, 1991). Both the group with social anxiety symptoms and the group with depressive symptoms evaluated the neutral facial expressions as more arousing compared to the control group, regardless of the odor condition. However, the group with depressive symptoms rated the faces presented with the fear body odor as more arousing compared to those presented with clean air, further confirming the ability of negative body odors in modulating the subjective ratings of neutral or ambiguous visual stimuli (e.g., Rubin et al., 2012).

From a neural point of view, in a healthy population, emotional body odors resulted to be a powerful social cue, being effective in modulating the affective and cognitive processing of neutral faces, as indexed by a reduced beta desynchronization during the presence of both happiness and fear body odors, compared to the clean air condition. This effect was strongest between ~ 500-900 ms post-stimulus as was seen in extended posterior as well as anterior sites. Notably, in both clusters (the anterior and the posterior), a significant difference between clean air and fear body odor, and between clean air and happiness body odor conditions, emerged. However, no difference between the two body odor conditions was reported. Beta oscillations have been observed in various different cortical and subcortical areas, such as the thalamic nuclei, the basal ganglia and the olfactory bulb. Despite their well-known role in motor processes (Pfurtscheller et al., 1996), growing evidence highlight their function in the processing of simple (Kveraga et al., 2011) but also complex (Smith et al., 2006) visual stimuli. In addition, beta activity has been related to various non-somatomotor tasks, such as visual perception (Kloosterman et al., 2015; Piantoni et al., 2010), language processing (Weiss & Mueller, 2012), working memory (Axmacher et al., 2008; Deiber et al., 2007), decision making (Wimmer et al., 2016; Wong et al., 2016) and reward processing (Marco-Pallarés et al., 2015). Starting from the studies in the motor domain, it has been shown that beta activity is mainly related to the maintenance of the current motor set, or "status quo" (Engel & Fries, 2010; Spitzer & Haegens, 2017): specifically, beta desynchronization appears during anticipation and stimulation, followed by a re-synchronization (Bauer et al., 2006; Spitzer et al., 2010; van Ede et al., 2010). In cognitive processes, the beta band has a similar role. According to the above-mentioned hypothesis, an increase in beta power is expected when the system is required to maintain the current cognitive set, while a decrease when a novel event occurs, disrupting the current status quo (Engel & Fries, 2010; Spitzer & Haengens, 2017). In a recent study investigating the processing of high arousing (i.e., erotic pictures) vs. low arousing (i.e., romantic pictures) stimuli, a higher beta desynchronization for the high arousing stimuli compared to the low arousing stimuli has been observed in both posterior and anterior clusters between 600-1000 ms post-stimulus, showing that beta power is not only related to cognitive processing, but its activity is content specific (Schubring & Schupp, 2019). In addition, also the processing of socially relevant stimuli seems to be modulated by beta oscillations. fMRI studies analyzing the convergence between beta oscillations and the blood oxygen level-dependent functional MRI (BOLD fMRI) signal during cognition reported a strong relationship between an increase in BOLD power and a decrease in beta activity during perceptual cognition and decision-making (Scheeringa et al., 2011; Stevenson et al., 2011; Winterer et al., 2007; Zumer et al., 2010) but also during the perception of emotional facial expressions (Jabbi et al., 2015), further confirming a possible role of beta band in the processing of emotional and social stimuli.

From a first look, the results of the present study, reporting a higher beta desynchronization for neutral faces presented with clean air, compared to those presented with emotional body odors, might seem contradictory to the above-mentioned literature. However, it is likely that the emotional body odors, which have been presented before the face, might have been processed preferentially, thus leaving fewer neural resources available to process the neutral faces, resulting in reduced beta desynchronization. This result is in line with a previous study in which neutral and emotional facial expressions were presented with body odors (collected in an anxious and in a sport condition) or with a clean pad (as control) (Adolph et al., 2013). Similarly, preferential processing of body odors compared to the visual stimuli has been reported, showing a reduction in late ERPs, indicative of reduced elaborative processing, when the faces were presented with the body odors, compared to the control condition (Adolph et al., 2013). The results of the present study showed, for the first time, that, from a neutral level, happiness and fear body odors act in a similar vein in modulating the neural processing of neutral social stimuli.

The group with depressive symptoms, compared to the control group, showed a pattern of decreased event-related delta power in response to the faces only in the clean air condition. Delta oscillations, across large cortical regions, are mainly involved in motivational processes. Indeed, the generation of delta rhythm is linked to the activity of brain areas involved in the brain reward system, such as the ventral tegmental area (VTA), the nucleus accumbens and the medial prefrontal cortex (Knyazev, 2007, 2012). Accordingly, previous studies reported an increase in event-related delta power in response to emotionally relevant stimuli (pleasant and unpleasant) compared to neutral ones (Güntekin & Başar, 2016; Klados et al., 2009; Knyazev, 2007, 2012; Zhang et al., 2013). However, in affective disorders, only a few studies, to date, investigated delta oscillation in response to emotional stimuli, reporting, both in a clinical and a subclinical depressive sample, reduction in delta power for pleasant stimuli compared to controls, as an index of a hypoactivation of the approach-related motivational system (Dell'Acqua, Brush, et al., 2022; Dell'Acqua, Dal Bò, et al., 2022). This finding is in line with a previous study reporting, in individuals with subclinical depression relative to the group without subclinical depression, a reduction in delta power not only for pleasant images but also for neutral cues (Dell'Acqua, Dal Bò, et al., 2022), possibly indicating a reduction in motivation that is extended to non-relevant stimuli and further confirming the hypothesis of a hypoactivation of the approach-related motivation system.

Furthermore, regarding cognitive processing, the group with depressive symptoms, compared to the control group, reported a reduction in theta power during the processing of the faces presented with clean air. The event-related theta frequency band, across spatially distributed cortical regions, has been linked to different cognitive processes, such as multimodal sensory processing, memory encoding and attention processing (Aftanas et al., 2004; Karakaş, 2020; Klimesch, 1999; Kowalczyk et al., 2013; Sauseng et al., 2010). In particular, it is believed to have a functional role in orientation and attentional processing of arousing stimuli: higher theta power in response to affective and arousing stimuli, compared to neutral ones, has been observed, reflecting its role in the integration of affective and cognitive aspects during attentional processing (Knyazev, 2007; Knyazev et al., 2009). It has already been shown that depression is characterized by a reduced ability in recognizing emotionally neutral faces, and this impairment is present also during symptom remission (Leppänen et al., 2004; for a review see Bourke et al., 2010). Similarly, when presented with schematic faces, depressed individuals tend to judge them as negative (Bouhuys et al., 1999; Hale, 1998), confirming the presence of a negative bias. Hence, our results are in line with previous literature, supporting the hypothesis that a key feature of depression is an incorrect interpretation of emotionally neutral social cues (Drevets, 2001), with a reduced affective disposition as well as impaired cognitive processing of ambiguous social stimuli. However, when presented in the context of emotional body odors, the observed differences between the group with depressive symptoms and the control group disappeared. Thus, the present data suggest that the social information conveyed through the body odor may help individuals with depressive symptoms in extracting the social meaning of the situation, leading to a correct evaluation of the neutral stimulus.

On the other side, the group with social anxiety symptoms, compared to the control group, presented a higher delta power in response to the faces presented in the context of the fear body odor. Previous studies have shown enhanced motivated attention, reflected by an increased amplitude in late ERPs (Schupp et al., 2004), as well as an increased amygdala activation, in response to fearful faces in socially anxious individuals (Phan et al., 2006; Straube et al., 2004). In addition, highly socially anxious individuals showed an increase in late ERPs components and larger withdrawal-related motor behavior to anxiety body odors presented alone (Pause et al., 2009), but also to faces presented in the context of anxiety body odor (Adolph et al., 2013). The present findings extend the existing literature showing that individuals with social anxiety present an increased motivation toward social stimuli presented with the fear body odor, but not a preferentially cognitive/subjective evaluation of them. In addition, the heightened affective disposition toward social stimuli presented in the context of negative body odor, in line with the general increased sensitivity toward threatening social signals, may contribute to the maintenance of the disorder.

It is important to point out that the present results cannot be explained by a perceptual difference between the odor conditions. In line with previous reports, the emotional body odors were rated as intense, pleasant and familiar as the clean air condition (e.g., Cecchetto, Lancini, Bueti, et al., 2019; Parma et al., 2017). Hence, the observed effects occurred independently of conscious processing of the odor stimulation, confirming their role in social communication even when they are subliminally perceived, as it occurs in everyday life.

In the interpretation of the current results, some limitations should be acknowledged. First, the relatively small sample size, the inclusion of only females and the young age of the participants limit the generalization of the findings. Second, in the present study, as a first approach to the question and to limit the design complexity, it has been decided to include only neutral facial expressions, not allowing the study of the complex interaction between emotional facial expressions and emotional body odors. Finally, future research could apply more ecological social situations closer to real context, for example using virtual reality paradigms.

Taken all together, the present study provides novel findings and constitutes a significant step forward in understanding the role of emotional body odors in a healthy population and in a population with affective disorders. For the first time, a comprehensive view of the subjective and neural responses to emotional body odors, both positive and negative, has been provided. In addition, given the strong relevance of body odors in both depression and social anxiety, future studies should investigate their potentially beneficial role as contextual social cues in therapeutic intervention.

CHAPTER 7

Does exposure to emotional body odors increase the effect of mindfulness treatment in individuals with social anxiety symptoms? A pilot study[8]

7.1. Abstract

Social anxiety is a mental disorder characterized by intense fear and avoidance of social situations. Mindfulness-based interventions are believed to alter emotional responding by modifying cognitive-affective processes that maintain social anxiety. The present study aimed to investigate if emotional body odors – social stimuli conveying social information as well as the emotional state of the sender – can increase the benefits of a mindfulness-based intervention in individuals with social anxiety symptoms (SAD). Forty-eight women with SAD were recruited and divided into one of three odor conditions (happiness or fear body odors or clear air). The study was conducted over two consecutive days. Each day, participants performed the mindfulness intervention while being exposed to one of the three odor conditions. Heart rate variability (HRV) and skin conductance level (SCL) were recorded during the intervention. At the beginning and at the end of each day, anxiety was measured with the STAI-Y1 scale. Results on anxiety level showed, on day 2, a significant interaction of odor and time: both participants in the happiness and fear conditions reported a significant reduction of anxiety after the training. Moreover, on day 2, HRV analysis revealed a main effect of

[8] A manuscript related to the experiment and the results described in the present chapter is in preparation for the submission

odor: HRV was lower during the intervention with fear body odor compared to clean air. No significant differences between the odor conditions have been found regarding SCL. These findings give potential insights into how body odors may be utilized to support positive outcomes of psychological therapy. However, it is still not clear whether the present results are modulated by the specific emotion each body odor is meant to convey or if these results are more related to general social information transmitted by the body odors that enhance the salience of the social context.

7.2. Introduction

Social anxiety is one of the most common and frequent anxiety disorders, characterized by fear of social situations in which the individual can act in a humiliating or embarrassing manner and can be judged by others (American Psychiatric Association, 2013). Frequently, social situations are avoided or faced with intense anxiety and fear (American Psychiatric Association, 2013). A recent report showed that the prevalence of social anxiety is increasing, with a global prevalence of 36% in 2020 (Jefferies & Ungar, 2020). Furthermore, the prevalence rate might be underestimated, since about 16% of respondents reported not presenting social anxiety, although they exceed the threshold for social anxiety (Jefferies & Ungar, 2020). In the view of cognitive-behavioral models, the dysfunctional beliefs and assumptions that characterize social anxiety (e.g., "If I make a mistake then other people will humiliate me", "I'm not as good as other people") lead to affective and behavioral responses (e.g., sweating, blushing, shaking; hypervigilance toward these somatic symptoms; increasing of self-focus attention) which, in turn, results in the maintenance of the disorder (Hofmann, 2007; Rapee & Heimberg, 1997; Wells et al., 1995). In this light, the treatments commonly used for social anxiety include a variety of cognitive and behavioral strategies, which have been shown to be effective in reducing symptoms (for a meta-analysis see Stewart & Chambless, 2009). Nevertheless, 40-50% of patients report not benefiting from the cognitive and behavioral interventions and continue to experience symptoms (Rodebaugh et al., 2004).

An intervention that is becoming popular in the treatment of anxiety disorders and takes its ground from ancient Hindu and Buddhist culture is mindfulness meditation. Mindfulness meditation has been defined as "the non-judgmental observation of the ongoing stream of internal and external stimuli as they arise" (Baer, 2003, p. 125) and has been proven to be moderately effective in reducing symptoms of depression, anxiety and general distress (Hofmann et al., 2010). Mindfulness training requires the individual to pay attention to whatever is happening at the moment, through exercises that are designed to increase their awareness of bodily sensations and non-judgmental observation of thoughts and feelings (Jaiswal et al., 2019). Two components constitute mindfulness training: self-regulation of attention, and being present at the moment with a curious, open and accepting attitude (Bishop et al., 2004). This practice has been repeatedly reported to decrease global psychological distress and improve overall mental and physical health (Keng et al., 2011). In addition, even brief mindfulness training (from 10 min to one hour) has been found to have a beneficial effect in affecting mood, anxiety level and cardiovascular variables (heart rate and blood pressure) (Edwards et al., 2018; Johnson et al., 2015; Zeidan et al., 2010). Specifically for social anxiety, the properties of mindfulness meditation (e.g., increasing self-focus attention) can be an effective response to the cognitive biases that typify this disorder. Confirming this, several studies on social anxiety patients reported a beneficial effect of mindfulness training in reducing anxiety symptoms and distress and in increasing positive thinking (Cassin & Rector, 2011; Vassilopoulos, 2008; Vassilopoulos & Watkins, 2009; for a review see Liu et al., 2021; Norton et al., 2015), in addition to reducing amygdala activity and increasing activity in regions implicated in attention deployment (Goldin & Gross, 2010).

In the present pilot study, the main aim was to test if the addition of a social stimulus to a mindfulness treatment can lead to better results in a group of individuals with social anxiety symptoms. In this context, an advantageous form of social communication is via body odors (i.e., the sweat chemicals produced by the apocrine glands): it is rather effortless for the sender and for the perceiver, does not require conscious processing, and is not limited by physical and time barriers (Dal Bò et al., 2020; Parma et al., 2017). In addition, once perceived, the chemicals produce in the receiver a partial reproduction of the affective, behavioral, perceptual and neural state of the sender, in a phenomenon called "emotional contagion" (Hatfield et al., 1993). Among the wide variety of information that can be transmitted by body odors (e.g., age, gender, relatedness, health status), emotional status is one of the less studied. Although the literature has mainly focused on the communication of negative states, there is evidence reporting a successful communication also of positive emotions: happiness body odor (i.e., body odor collected in a happiness-inducing situation) induced in the receiver a facial expression of happiness and a global processing style typical of happiness states (de Groot, Smeets, Rowson, et al., 2015), and increased creativity and reduced heart rate (Ortegón et al., 2022). However, so far, no studies investigated if the exposure to happiness body odor can be used as an add-on to mindfulness training, enhancing its beneficial effect in reducing anxiety symptoms. Hence, in the present study, individuals with social anxiety were presented with two consecutive sessions of mindfulness meditation and were divided into three groups: one group performed the training while exposed to body odor collected in a happiness-inducing situation, the second one while exposed to body odor collected in a fear-inducing situation, and the latter while exposed to clean air. The condition with the fear body odor was added to investigate the modulating effect of an opposite emotion already investigated in social anxiety: when exposed to negative body odors, individuals with social anxiety reported enhanced startle reactivity (Pause et al., 2009) and faster processing of chemosensory anxiety signals compared to healthy controls (Pause et al., 2010) and this effect is similar to those obtained with threatening visual stimuli (i.e., Kolassa & Miltner, 2006; Mühlberger et al., 2009). As the primary outcome, we hypothesized that individuals performing the mindfulness meditation with the happiness body odor presented a higher reduction in anxiety symptoms after the training compared to those that performed the training with both the fear body odor and the clean air.

At the physiological level, we hypothesized that the individuals performing the mindfulness training with the happiness body odor presented a higher heart rate variability (HRV), compared to those in the fear body odor and in the clean air condition. The HRV is measured by assessing the temporal variations between successive heartbeats, reflects the activity of the vagus nerve, and is an index of overall well-being and health (Task Force, 1996; Thayer & Lane, 2000). More specifically, HRV is modulated by a prefrontal-subcortical network (the central autonomic network, CAN; Benarroch, 1993; Mulcahy et al., 2019; Valenza et al., 2019), which controls the autonomic nervous system (ANS) activity (Thayer et al., 2012; Thayer & Lane, 2000, 2009). Furthermore, numerous structures involved in CAN control also cognitive functions, such as working memory, attention and emotion regulation, as well as mood and stress reactivity (Carnevali et al., 2018; Hansen et al., 2003; Mather & Thayer, 2018; Siennicka et al., 2019). In addition, to better understand the two subsystems regulating the activity of the ANS, a measure to study the activity of the sympathetic nervous system was employed. Specifically, skin conductance level was recorded to obtain a moment-by-moment measure of sympathetic arousal (Boucsein, 2012). We hypothesized that the skin conductance level (SCL) was lower in the group performing the training with the happiness body odor compared to those performing the training with the fear body odor or with clean air.

7.3. Methods

Participants

A total of 48 women from the University of Padova took part in the study. Only women were included since it has been shown that the processing of human body odor is influenced by gender (Krajnik et al., 2014; Martins et al., 2005). Additionally, social anxiety symptoms are more common among women than men and women present greater preference as compared to men for social and emotional stimuli (Lübke et al., 2012; Proverbio et al., 2008). By focusing on a homogenous sample, gender-related effects could be avoided and the power of the results would increase.

To be included in the study, participants had to obtain a score over or equal to 50 on the Liebowitz Social Anxiety Scale in its self-report formulation (LSAS-SR, Liebowitz, 1987), and a confirmation of the presence of the symptoms during a face-to-face interview through the Structured Clinical Interview for DSM-5 (SCID-5-CV, First et al., 2016, 2017). In addition, participants were pre-screened to exclude the presence of: chronic rhinitis or other conditions that may affect the ability to perceive odors, smoking, pregnancy or breastfeeding, presence of other mental disorders (including substance abuse disorders) apart from Social Anxiety Disorder, presence of any severe somatic or neurological conditions, use of psychotropic drugs at the moment of the recruitment (including antidepressants, antipsychotics, anxiolytics and mood stabilizers), presently undergoing psychological therapy, presence of severe psychotic symptoms (i.e. hallucinations and/or delusions), presence of suicidal thoughts, incapability to understand and to give informed consent for the experiment, being younger than 18 years or older than 35 years. Finally, their olfactory abilities were tested by means of a standardized olfactory test (the Sniffin' Sticks test): only participants with a score above or equal to 30.5 were enrolled in the study.

Participants were compensated €13 for their participation. The present study was conducted with the adequate understanding and written consent of the participants in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee, University of Padua (prot. no. 3667).

Screening procedure

Social anxiety symptoms were assessed using the Liebowitz Social Anxiety Scale (LSAS; (Liebowitz, 1987). The LSAS is a 24-item questionnaire rating on a 4-point scale the fear and avoidance experienced in a range of social and performance situations. Scores range from 0 to 144, with higher scores indicating greater social anxiety symptoms.

Only participants with normal olfactory abilities were recruited. Olfactory abilities were assessed with the computer-testing version of the standardized clinically approved "Sniffin' Sticks" test (Burghart Instruments, Wedel, Germany, Hummel et al., 1997). The task and each subscale are explained in detail in Chapter 5 of the present thesis. Participants that obtained a summated score (TDI) below 30.5 were not included in the study.

The mindfulness training

The mindfulness training was guided by two audio tracks on mindfulness exercises. The two practices comprised breathing, meditation and relaxation exercises, with a focus on bodily sensations elicited by the practices. The two practices ("The breath that frees" and "The thin breath") were presented using the app "Con tatto" (developer LifeSTech research team). Participants were simply asked to follow the guiding voice, direct all their attention to the present, feel their breathing and be mindful of their bodily sensations. In total, the mindfulness training lasted about 24 minutes.

To assess the anxiety level before and after the mindfulness training, the state subscale of the State-Trait Anxiety Inventory (STAI-Y1; Spielberger et al., 1983; Italian version by Spielberg et al., 2012) was employed. This scale has 20 items scored on a four-point Likert scale with greater scores reflecting higher levels of anxiety.

Body odor collection and preparation

Body odor samples were collected at the Instituto Superior de Psicologia Aplicada (Lisbon, Portugal). The procedure is explained in detail in Chapter 6 of the present thesis. Briefly, happiness and fear body odors were collected by means of sterilized cotton pads attached to the armpit area while healthy participants were asked to watch happiness- or fear-inducing video clips, respectively. Body odor samples were frozen at -80 °C, and then shipped in dry ice to the University of Padova (Italy), where they were stored again at -80 °C.

Since individual factors shape the production of body odor, the so-called super-donors were created. In brief, pad pieces from four sweat donors (two females, two males; two from the left and two from the right armpits) of the same emotional states – fear or happiness – were combined together and placed in new glass jars.

Odors were delivered with a custom-built, continuous airflow, computer-controlled olfactometer with 3 lines: one providing baseline odorless air and the other two connected to the airtight jars containing the super-donor pads (fear and happiness). Airflow was kept constant between 50 and 70 ml/min. Odorous or odorless air was delivered directly to both nostrils with a nasal cannula during the mindfulness training.

Procedure

Prior to each experimental session, participants were requested to avoid eating and drinking anything except water an hour before the appointment. During the screening procedure, participants were administered the social anxiety module (module F) of the SCID-5-CV to assess the presence of social anxiety symptoms and the Sniffin' Sticks test to assess their olfactory abilities. Then, if eligible, they were asked to come to the lab for the two experimental sessions on two consecutive days.

The study was a single-blind, between-subjects randomized trial design with one between-subjects factor (3 levels, odor type: happiness body odor, fear body odor or clean air). The study was conducted over two consecutive days.

On the first day of the study, all participants were asked to complete the State-Trait Anxiety Inventory, state version (STAI-Y1) to assess their anxiety level. After the sensors were positioned, the heart rate and the skin conductance were recorded at rest over a three-minute period for each participant. Next, participants were randomized to one of the three odor groups (happiness or fear body odor, or clean air). Then, all participants followed the mindfulness training while smelling the odor through the olfactometer. During the intervention, their heart rate and skin conductance were continuously recorded. After the intervention, participants completed once more the STAI-Y1 questionnaire.

The next day, all participants answered the same questionnaire (STAI-Y1) as they did at the beginning of the first day and completed the three-minute period of resting state while their heart rate and skin conductance were recorded. Following this, in order to evoke a social stress response and test the effect of the mindfulness training, a stress induction procedure was introduced on the second day. Specifically, participants were told that they would have to give a short presentation at the end of the study session about a prespecified topic in front of a small audience. The stress induction has been included on the second (and last) day of intervention to avoid possible drop-out. After the stress induction, they were administered again the STAI-Y1 questionnaire to evaluate the effectiveness of the stress induction procedure. Then, all participants followed the mindfulness training while smelling the same odor as they did the previous day, with their heart rate and skin conductance being measured again. When they were done, they completed the STAI-Y1 questionnaire. Finally, they were told they did not have to make a presentation. In Figure 7.1 an overview of the study design is presented.

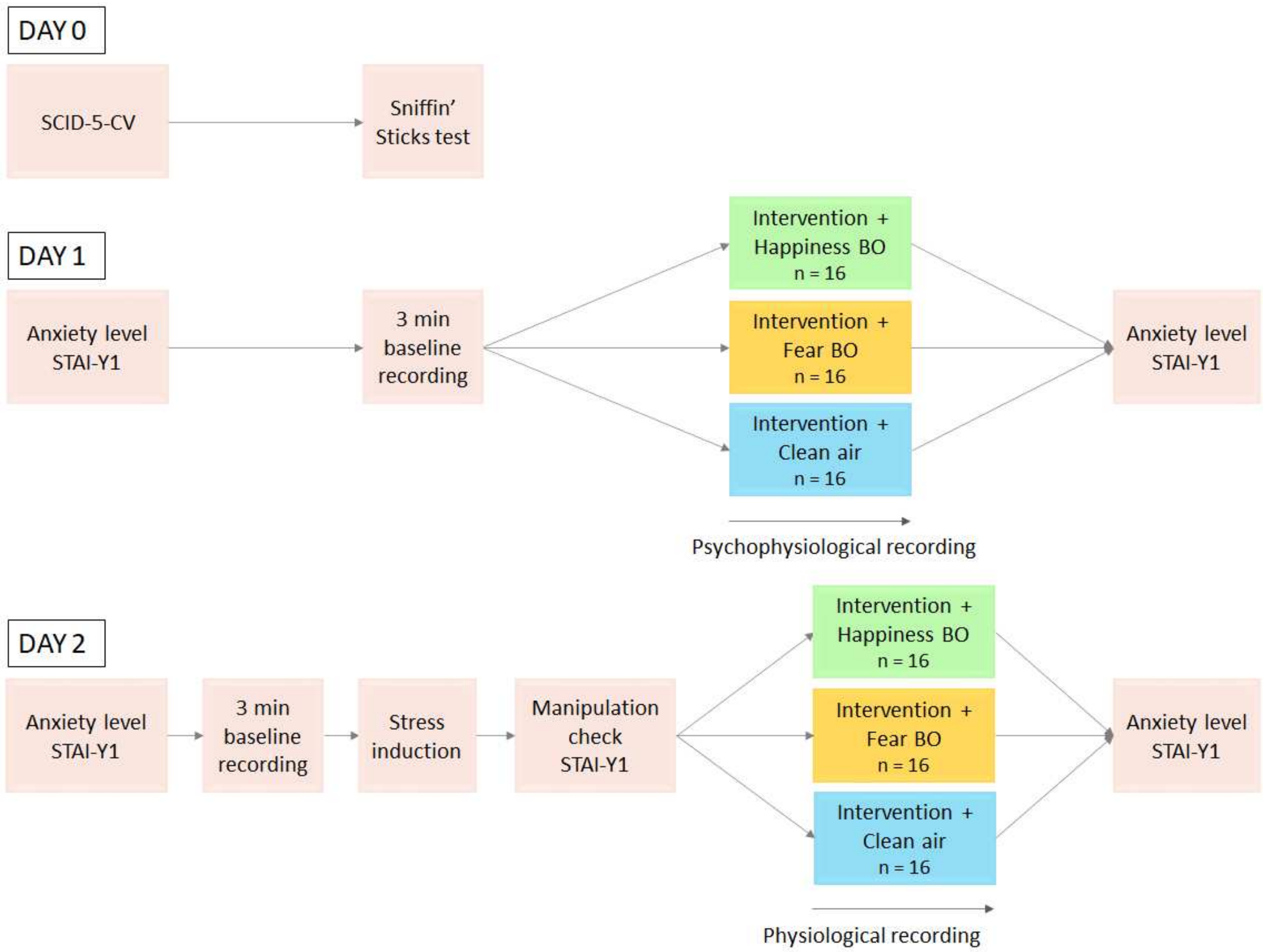

Fig. 7.1. Overview of the study design.

Physiological recording and analysis

Physiological measures were recorded in a standardized fashion using a wearable device (Shimmer3 GSR+ Unit, Shimmer 2018, Realtime Technologies Ltd, Dublin, Ireland). To obtain the heart rate (HR), the blood volume pulse (BVP) was recorded by means of an optical pulse sensor providing a photoplethysmogram (PPG) signal from the left ring finger with a sampling rate of 500 Hz. Since electrical and mechanical activities of the heart are coupled, photoplethysmography can be used to detect blood volume changes that reflect heart rate and, consequently, allow the determination of the inter-beat intervals.

In order to assess time- and frequency-domain HRV parameters, the PPG signal was analyzed offline using Kubios HRV Analysis Software 3.3.1 (Matlab, Kuopio, Finland). The PPG signal was recorded continuously during the three-minute resting state and during all the mindfulness training, which lasted about 24 minutes. To analyze the HRV changes during the entire procedure, HRV indices were computed every three minutes, obtaining 8 values. Among all time- and frequency-domain parameters of HRV, it was decided to calculate only the most frequently used HRV measures in the literature (e.g., Koch et al., 2019; Patron et al., 2012; Thayer et al., 2012) and the most appropriate measures for short-term recordings (Task Force, 1996). Specifically, the root mean square of successive difference of NN intervals (RMSSD), expressed in ms, was computed. The RMSSD reflects estimates of short-term variability of heart rate, is highly sensitive to the fluctuation of high frequency of HRV and is an index of vagal control on heart (Task Force, 1996). In the frequency domain, High Frequency (HF) power (0.15 to 0.40 Hz), an index of cardiac vagal tone, was obtained in ms^2 through autoregressive (AR) spectral analysis (Kamath et al., 1987; Task Force, 1996). Both time- and frequency-domain indices were logarithmically transformed before the statistical analyses to normalize their distribution.

Skin conductance (SC) was measured using two 8 mm snap-style finger Ag/AgCl electrodes placed on the left hand's distal phalanges of the index and middle fingers with a sampling rate of 500 Hz. The SC data were analyzed offline using the MATLAB Ledalab toolbox. The SC signal was downsampled to 125 Hz and a continuous deconvolution analysis was computed, optimizing the fit and reducing the error of the model (Benedek & Kaernbach, 2010). Then, the average skin conductance level (SCL) was calculated during the 3-min baseline and every 3 minutes during the mindfulness training.

HRV and SCL modifications during the mindfulness training were obtained by subtracting the HRV and the SCL values measured during the baseline period from the values obtained during the eight 3-min time windows obtained during the mindfulness. In order to analyze the pattern of HRV and SCL modification during the mindfulness in the three odor groups, to reduce the number of comparisons, only four time-points were selected for the statistical analysis (3-6 min, 9-12 min, 15-18 min, 21-24 min).

Statistical analysis

Separate analysis of variance (ANOVAs) with Odor (happiness BO, fear BO, clean air) as between-subject factor were conducted on age, education and LSAS score.

Then, a mixed ANOVA with Odor (happiness BO, fear BO, clean air) as a between-subject factor and Time (start, end of the training session) as a within-subject factor was conducted on self-report questionnaire score (STAI-Y1) for day 1. While for day 2 a mixed ANOVA with Odor (happiness BO, fear BO, clean air) as a between-subject factor and Time (start, after stress induction and end of the training session) as a within-subject factor was conducted on STAI-Y1 score.

HRV measures (lnRMSSD, lnHF), as well as SCL data, were analyzed with mixed ANOVAs, with Odor (happiness BO, fear BO, clean air) as a between-subject factor and Time (time during the mindfulness training: 3-6 min, 9-12 min, 15-18 min, 21-24 min) as a within-subject factor. The analyses were conducted separately for day 1 and day 2. Significant main effects ($p < 0.05$) were followed by Tukey HSD post-hoc tests in order to correct for multiple comparisons.

7.4. Results

Demographics and clinical characteristics

With respect to demographic variables, the mixed ANOVAs revealed no differences for age ($p = 0.67$) and education ($p = 0.22$) among the participants in the three odor groups. In addition, the three groups did not differ in their initial LSAS score ($p = 0.89$). Hence, these variables were not included as covariates in the following analysis. The descriptive statistics of self-report measures are reported in Table 7.1.

Table 7.1. Demographic and psychological characteristics of the three odor groups (happiness BO, fear BO and clean air).

Variable	Happiness BO (n = 16)	Fear BO (n = 16)	Clean air (n = 16)	p
Age (years)	22.7 (2.36)	22.0 (2.35)	22.4 (2.00)	0.67
Education (years)	16.4 (1.78)	15.3 (1.85)	15.3 (3.09)	0.22
LSAS	66.8 (13.02)	65.3 (10.92)	64.8 (8.73)	0.89

Notes. Data are reported M (SD)

The effect of the mindfulness treatment on self-report anxiety level

On day 1, the mixed ANOVA revealed a main effect of Time ($F_{(1,45)} = 32.85$, $p < 0.001$, $\eta^2_p = 0.42$), showing a reduction in the anxiety level after the mindfulness training regardless of the odor condition (Figure 7.1, Panel A).

On day 2, the mixed ANOVA revealed a main effect of Time ($F_{(2,84)} = 11.61$, $p < 0.001$, $\eta^2_p = 0.22$), and an interaction Time × Odor ($F_{(4,84)} = 2.98$, $p = 0.024$, $\eta^2_p = 0.12$). Both in the group performing the mindfulness training with the fear body odor and in the one performing the training with the happiness body odor the anxiety level was significantly lower after the mindfulness training compared to their anxiety level after the stress induction (happiness odor, $p = 0.006$; fear odor, $p < 0.001$). However, no reduction in anxiety level was observed in the group performing the training with clean air ($p = 1.00$) (Figure 7.1, Panel B).

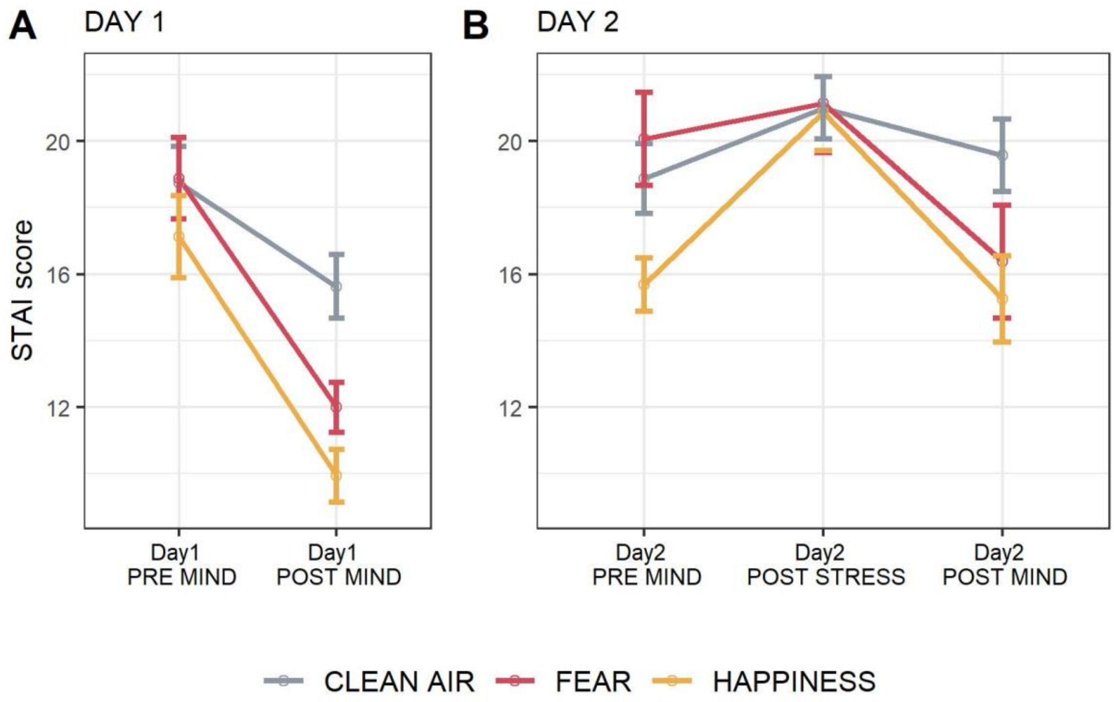

Fig. 7.1. Panel A. STAI-Y1 score on the first day of mindfulness training in the three odor group (clean air, fear body odor and happiness body odor) collected before the starting of the training (PRE MIND) and after the training (POST MIND). **Panel B.** STAI-Y1 score on the second day of mindfulness training in the three odor group (clean air, fear body odor and happiness body odor) collected before the starting of the training (PRE MIND), after the stress induction (POST STRESS) and after the training (POST MIND). Error bars represent ± standard deviation.

The effect of the mindfulness treatment on HRV

Regarding lnRMSSD, on day 1, the mixed ANOVA did not reveal any significant main effects or interaction (all ps > 0.57). On day 2, the mixed ANOVA yielded a main effect of Odor ($F_{(2,42)}$ = 4.23, p = 0.021, η^2_p = 0.17), and an interaction Time × Odor ($F_{(6,126)}$ = 2.20, p = 0.048, η^2_p = 0.095). For the interaction effect, no significant differences emerged from the Tuckey HSD post-hoc test (Figure 7.2, Panel B). However, for the Odor main effect, Tukey HSD post-hoc test revealed that the group in the fear body odor condition showed significantly lower lnRMSSD values than the group in the clean air condition (p = 0.016), whereas no difference emerged between the group in the fear odor condition and the happiness body odor condition (p = 0.239), as well as between the happiness body odor condition and the clean air condition (p = 0.427), as shown in Figure 7.2, Panel A.

Regarding the lnHF, on day 1, the mixed ANOVA did not reveal any significant main effects or interaction (all ps > 0.57). On day 2, the mixed ANOVA revealed a marginally significant main effect of Odor ($F_{(2,42)} = 3.11$, p = 0.055, $\eta^2_p = 0.13$), with tendentially lower lnHF values in the group in the fear body odor condition compared to the clean air condition (p = 0.066), but not in the group in the happiness condition vs. the clean air condition (p = 0.942) or in the group in the fear condition vs. the group in the happiness condition (p = 0.131) (Figure 7.3).

Fig. 7.2. Panel A. Mean lnRMSSD values in the three odor groups (clean air, fear body odor and happiness body odor) during the second day of mindfulness intervention. The plot shows the median (indicated by the horizontal band), the first through the third interquartile range (the vertical band) of the lnRMSSD in each group. Each dot represents one participant. Units are lnRMSSD values changes from 3 min baseline. **Panel B.** Mean lnRMSSD values change during the mindfulness training in the three odors group (clean air, fear body odor, happiness body odor). Units are lnRMSSD values changes from 3 min baseline. Error bars represent ± standard deviation.

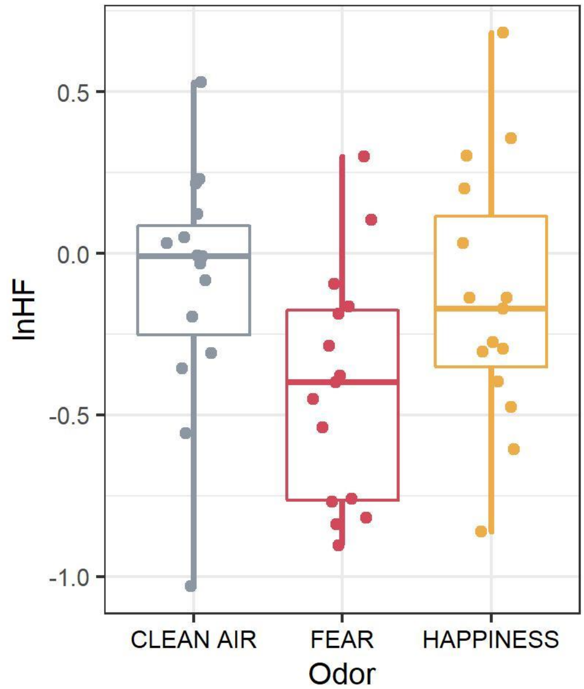

Fig. 7.3. Mean lnHF values in the three odor groups (clean air, fear body odor and happiness body odor) during the second day of mindfulness intervention. The plot shows the median (indicated by the horizontal band), the first through the third interquartile range (the vertical band) of the lnHF in each group. Each dot represents one participant. Units are lnHF values changes from 3 min baseline.

The effect of the mindfulness treatment on SCL

Regarding the SCL, on day 1, the mixed ANOVA revealed only a Time main effect ($F_{(3,123)} = 10.37$, $p < 0.001$, $\eta^2_p = 0.20$), with an SCL reduction over time. On day 2, similarly to day 1, the mixed ANOVA yielded only a Time main effect ($F_{(3,129)} = 8.58$, $p < 0.001$, $\eta^2_p = 0.17$). On both day 1 and day 2, no significant Odor main effect or Time × Odor interaction was noted (all ps > 0.38).

7.5. Discussion

The present study examined whether emotional body odors may be utilized to support positive outcomes of psychological treatment in individuals with social anxiety. To this aim, individuals with social anxiety symptoms performed a mindfulness intervention for two consecutive days while exposed to either happiness body odor, fear body odor, or clean air. Both subjective measures of anxiety and psychophysiological responses (HRV and SCL) were recorded.

Partially in line with our hypotheses, results showed that individuals with social anxiety symptoms benefited from the mindfulness training when exposed to emotional body odor: A significant reduction in anxiety symptoms was achieved with both the happiness and the fear body odor, but not with clean air. The reduction of the anxiety level after the mindfulness intervention in the presence of the happiness body odor is in line with previous studies demonstrating that exposure to positive body odor impacts the receiver's responses in a congruent way (Chen & Haviland-Jones, 2000; de Groot, Smeets, Rowson, et al., 2015; Ortegón et al., 2022). Similarly, participants reported a reduction in their anxiety level when performing the mindfulness training while exposed to the fear body odor. This result is in contrast with studies employing negative body odors (e.g., fearful, anxiety and sad body odors) that showed an increased anxiety level (Albrecht et al., 2011), general negative affect (de Groot et al., 2012, 2014a, 2014b; de Groot, Smeets, & Semin, 2015; de Groot, Smeets, Rowson, et al., 2015), as well as an increase vigilance (e.g., Chen et al., 2006; de Groot et al., 2012) and amygdala activity (Mujica-Parodi et al., 2009) in the perceivers. Hence, according to the "emotional contagion" hypothesis, we should have expected an increased self-reported anxiety level in the group performing the mindfulness training with the fear body odor. However, it should be taken into account that the odors were presented as context during a mindfulness intervention, while the previous studies refer to subjective, behavioral and physiological responses to the odor alone, or during lab-designed tasks (e.g., passive viewing of faces with matching emotions). In this context, a possible explanation could lie in the fact that body odors may be processed primarily as social stimuli rather than emotional stimuli, conveying the social presence of another individual, instead of conveying only the emotion they were supposed to communicate. The simple co-presence of others is contagious and heightens a positive experience (Devereux & Ginsburg, 2001; Golland et al., 2015), possibly further enhancing the positive outcome of a treatment, such as mindfulness meditation. In addition, from a neural level, it has been shown that the processing of social signals of human body odor requires the involvement of brain areas specialized in the processing of other socioemotional information (e.g., inferior frontal gyrus), as well as of brain networks involved in attention (e.g., middle frontal gyrus) and emotion regulation (e.g., cerebellum) (Dal Bò et al., 2020; Lübke et al., 2014; Lundström & Olsson, 2010; Pause, 2012). Interestingly, the same circuits seem to be involved during mindfulness meditation (Tang et al., 2015). Hence, the addition of a social stimulus presented as context during mindfulness training may have further activated the brain regions involved in the process of developing a mindfulness state. However, further studies are needed to explore these hypotheses.

In addition, contrary to our hypothesis, the happiness body odor did not affect the physiological responses taken into account. Only the fear body odor resulted in reducing the HRV during the training compared to clean air. Here, a reduced vagal tone is an index of an inadequate response to stressors in the environment that require a fight or flight response. In this context, the fear body odor contrasted with the effect of mindfulness training in reducing stress and improving self-regulatory capacity (Brown & Ryan, 2003; Keng et al., 2011). In the animal kingdom, the role of fear chemosignals is well known, acting as a warning signal, increasing vigilance and affecting the physiological responses of the receivers (Wyatt, 2003). In the same way, for humans, negative body odors are indicators of potential threats in the environment, able to induce, at a physiological level, adaptive responses to predispose the organism to handle dangerous situations. Consistent with our results, previous studies reported, in response to fear body odor, a decreased vagal tone (Fernandes et al., 2018), but also activation of the amygdala (Mujica-Parodi et al., 2009), and an increased startle response (Adolph et al., 2013; Lübke et al., 2017; Prehn et al., 2006), suggesting the adoption of escape behaviors and the activation of the defensive motivational system (Lang et al., 1990).

However, in the fear body odor group, the observed lower vagal tone was discrepant with the reduction in the anxiety level after the mindfulness training. Inconsistent results between subjective and physiological domains have been previously reported (Grossman et al., 2001; Wilhelm et al., 2001). A tentative explanation could lie in the fact that the physiological level is more automatic and a conscious access to the stimulus is not required. Hence, it is plausible that, from a physiological point of view, the emotion conveyed by the fear body odor was strong enough to modulate the vagal tone. On the other side, positive body odors, not having direct consequences for the survival of the species (Pratto & John, 1991), are less studied, more difficult to elicit in lab settings, and probably their physiological effect is less automatic or requires a longer exposure. Interestingly, at a subjective level, it seems plausible that both the happiness and the fear body odors have elicited a feeling of social presence, thus increasing the effect of the mindfulness intervention and reducing the participants' anxiety level.

In interpreting our results, several limitations have to be acknowledged. First, we included only a relatively small sample size and all participants were females, thus reducing generalizability. However, only women were included to avoid gender-related effects, considering that it is documented that women present higher olfactory abilities (Doty & Cameron, 2009), higher odor awareness (Ferdenzi et al., 2008), higher interest in the sense of smell (Seo et al., 2011), and higher importance of olfaction (Croy et al., 2010; Havlicek et al., 2008) than men. Second, despite the promising findings obtained with short mindfulness intervention (Edwards et al., 2018; Johnson et al., 2015; Zeidan et al., 2010), more sessions would have provided more consistent results and, ideally, long-term benefits. Third, stress induction was introduced to evoke a social stress state during the second day of intervention, not allowing a comparison between the two days of intervention. Finally, the inclusion of a neutral body odor condition would have helped to disentangle the role of emotional body odor in modulating the subjective and physiological responses during a mindfulness intervention and, specifically, to investigate whether the effect found was due to the social context transmitted by the body odors rather than the specific emotion.

To conclude, this is the first study using emotional body odors as a catalyst for psychological treatment in a group of individuals with social anxiety. These results are promising, suggesting that body odors are a powerful tool in enhancing the positive outcome of a short mindfulness training. However, it is still not clear whether the present results are modulated by the specific emotion each body odor is meant to convey or if these results are more related to general social information transmitted by the body odors that enhance the salience of the social context.

CHAPTER 8

General conclusions

In the past few decades, a flourishing of studies emerged investigating the role of olfaction, and its dysfunction, in human life. When navigating our environment and facing everyday activities, we encounter a wide variety of odors that, mainly unconsciously, shape our cognition, behavioural, and emotional responses. The olfactory experience is a complex phenomenon, being modulated by the properties of odorants, their biological relevance, the characteristics of the olfactory systems, and the predisposition of the perceivers. These aspects become especially relevant when considering affective disorders, in which the social sphere is flawed as well as their cognitive and emotional competencies. Nevertheless, the majority of previous studies have investigated the role of olfaction mainly in healthy populations and, in the social domain, they focused almost exclusively on the transmission of negative emotions.

The experimental work of the present thesis was aimed to extend the knowledge on the role of olfaction in affective disorders, with a special focus on the multi-componential factors that shape the olfactory experience. With the goal of contributing to this question, five experiments were designed to investigate multi-level correspondence by assessing the objective olfactory abilities, subjective and cognitive evaluation, as well as psychophysiological measures in individuals with different degrees of anxiety, social anxiety and depressive symptoms. In addition, besides the adoption of common odors, a special look at emotional body odors has been provided.

As a first step, a meta-analysis of the studies conducted so far on body odors has been conducted, to unravel the neural correlates involved in the processing of olfactory social signals (**Chapter 3**). The results confirmed that body odors are processed outside the main olfactory pathways. Specifically, both neutral and emotional body odors activate the right inferior frontal gyrus (IFG), confirming that biologically relevant odors are processed already in early stages as salient social stimuli. Moreover, the emotional body odors have a specific pattern of activation composed by the right middle frontal gyrus (MFG) and the left cerebellum, both areas involved in emotion regulation. With this first meta-analysis, I further confirmed the prominent role of human body odors in social communication (IFG for both neutral and emotional body odor) and in the communication of emotions (MFG and cerebellum for emotional body odor). In addition, from this review, another important aspect that emerged was the heterogeneity of methodologies and tasks used to collect and deliver the olfactory stimuli. If we want to develop our knowledge and shed light on this fascinating, but complex, field, a clear and common methodology has to be developed. Otherwise, at present, the comparison of results between studies is, at best, problematic.

Then, I focused my investigation on two of the most common and pervasive affective disorders: anxiety and depression. With the aim of building a multi-level analysis of olfactory experience, in **Chapter 4** the subjective and cognitive levels have been assessed. Subsequently, in **Chapter 5** a psychophysical approach was adopted and in **Chapters 6** and **7** psychophysiological and subjective methods and measures were used to investigate both affective dispositions and cognitive processing of emotional body odors. Finally, in **Chapter 7**, a clinical intervention has been proposed.

The results of each experiment have been discussed in detail in their corresponding chapter. Hence, in the following sections, I will focus on the main implications arising from the results of the studies in this thesis, as well as their limitations and questions that are still open.

8.1. Common odor perception and olfactory subjective experience

Given the strict relationship between olfaction and emotion, my experimental work started with two trivial questions: Are individuals with symptoms of anxiety and depression affected by olfactory dysfunction? How individual differences in olfactory perception may depend on initial differences in awareness of such odors? As reviewed in Chapter 1, cognitive factors play a key role in shaping the olfactory experience. However, surprisingly, no study, so far, investigated the association between odor awareness and olfactory abilities in individuals with affective disorders.

The results of Study 2 presented in Chapter 4 highlighted that general anxiety presented higher attention to common odors in the environment. This result is in line with previous studies on other anxiety disorders (e.g., panic disorder) in which individuals reported higher awareness to odors compared to healthy controls (Burón et al., 2015, 2018). In addition, this is consistent with the clinical features of the disorder, in which the individual is ready to respond to sudden dangers and, hence, maintains a constant state of vigilance, arousal and higher sensitivity to stimuli in the environment (Aikins & Craske, 2001; Eysenck, 1992; Mathews, 1990; Robinson et al., 2013). However, in anxiety disorder heightened odor awareness does not result in better olfactory abilities, as was found in Chapter 5.

From a meta-cognitive point of view, depressive symptoms came out with lower affective interest to odors, which is related to the attention that individuals pay to odors, to olfactory memory and to the degree to which pleasant and unpleasant odors are liked or disliked based on their association with liked and disliked persons (Wrzesniewski et al., 1999). However, no relation has been found between depressive symptoms and olfactory reactivity, imagery, and awareness toward common odors (Chapter 4). On the other side, from a psychophysical perspective, depressive symptoms resulted to be characterized by reduced olfactory abilities, and this relation was moderated by their attention to the odors: higher depressive symptoms lead to lower olfactory abilities only in individuals with low odor awareness (Chapter 5). According to the hypothesis put forward by Croy and Hummel (2017), the link between depression and olfaction can be explained by two mechanisms: structural alterations in the olfactory bulb and/or a reduction in the attention to the odors that leads to a reduction in the olfactory receptor turnover rates. The results reported in Chapter 5 support the hypothesis that attention is a central mechanism in explaining the presence of reduced olfactory functions in depression. From an anatomical point of view, the olfactory bulb is the first structure from which olfactory information spreads out to a number of structures, particularly to the amygdala (but also to the piriform cortex and the entorhinal cortex) (Freiherr, 2017). It is well known that the amygdala is involved in emotional processing and its functioning is impaired in depression (Davidson, 2001; Drevets et al., 2008). The aforementioned reduced olfactory input in depression, conceptualized here as reduced attention that individuals pay to the odors, may not only induce a reduction in receptor turnover rate, but also lead to changes in the functioning of the amygdala that, in turn, reduces the ability to encode olfactory information as well as their response to emotional stimuli (Pause et al., 2001; Pollatos et al., 2007). This hypothesis may also explain the altered hedonic evaluation of the odors present in individuals with depressive symptoms, highlighting a preferential processing bias for mood-congruent information. Also in this case, odor awareness resulted to be a significant moderator of this relation: in individuals with low odor awareness, higher depressive symptoms led to higher pleasantness rating, whereas the opposite relation emerged for individuals with higher odor awareness (Chapter 5).

With the results of the studies reported in this section, for the first time, it has been shown that even healthy individuals with depressive symptoms present reduced olfactory abilities and this is especially true for those that do not pay attention to the odors in the environment. Moreover, the evidence that odor awareness is a mediator of this relationship is an important step forward in the understanding of the disorder and in the development of useful treatments. From a clinical perspective, the current data suggest that reduced olfactory abilities may represent a correlate of vulnerability to depression. Hence, the employment of standardized tests, as well as the screening for odor awareness, may serve as an index of risk for clinical depression, being valuable tools for the early recognition of vulnerable individuals. In this context, a few insights for treatments can be proposed. Already existing olfactory trainings have been shown to improve not only the olfactory function, but also the depressive symptoms and general well-being (Birte-Antina et al., 2018, but see Pabel et al., 2020; Pieniak et al., 2022). One example of olfactory training (OT) requires the systematic sniffing of a set of odorants for 12-20 weeks (Hummel et al., 2009). This training resulted to modulate both structural and functional changes in the human brain. From a structural point of view, after the OT, the olfactory bulb, the orbitofrontal cortex, the hippocampus, the thalamus and the cerebellum volume increased (Gellrich et al., 2018; Han et al., 2021; Mahmut et al., 2020; Negoias et al., 2017). In addition, after the OT, a greater number of functional connections emerged in the olfactory, somatosensory and integrative networks (Kollndorfer et al., 2015). Its beneficial effects extend also to the emotional domain, showing improvement in mood and a decrease in anxiety after exposure to odors (Field et al., 2005; Kiecolt-Glaser et al., 2008; Lehrner et al., 2005), however, a recent report showed no beneficial effects of the OT in clinical depression (Pabel et al., 2020). It has to be pointed out that the OT is efficient when the training is prolonged and consistent: stable effects emerge when the OT lasts about 32 weeks (Pieniak et al., 2022). It is likely that individuals with depression present difficulties in following the procedure, leading to high drop-out rates. All in all, this training could be beneficial in the early stage of the disorder, or in healthy individuals at risk of developing depressive disorders. Furthermore, as it has been done in the cognitive domain, with training focusing specifically on odor-based cognitive interventions (Olofsson et al., 2020), personalized and emotion-based treatment should be developed.

Moreover, with the studies reported in the present work, we cannot state if the observed olfactory dysfunction is the cause or the consequence of the development of depressive symptoms. Future studies should include individuals at risk of depression (e.g., healthy individuals with familiarity for depression), individuals in remission from the disorder, as well as individuals with full-blown clinical depression, to provide a complete overview of olfactory abilities during the illness course. This approach could also allow the investigation of the underlying factors as well as the initial mechanisms that cause the disorder in a more comprehensive manner.

8.2. Emotional body odors: from a diagnostic to a therapeutic tool

With the aim of building a multi-level analysis of olfactory experience, in Chapter 4 the subjective and cognitive levels have been assessed. As reviewed in Chapter 2, human body odors are essential in our relationships given their ability to convey socially relevant messages. This wide range of information is mainly transmitted without the conscious allocation of attention toward the odors. Nevertheless, humans are able to correctly identify and distinguish familiar from unfamiliar odors, as well as neutral from emotional odors (e.g., Chen & Haviland-Jones, 2000; Lundström & Olsson, 2010). However, despite these premises, no specific tool was available to study the attention individuals pay to body odor. Hence, the Social Odor Scale (SOS) has been designed, developed and validated, both in Italian and German (Study 1 in Chapter 4). As described in Chapter 4, the results indicated that SOS is a valid and reliable instrument to assess awareness toward social odors in everyday life. In addition, its three subscales allow the investigation of the awareness toward the three main types of social odors that we encounter, which are the familiar, romantic partner, and stranger body odors. Subsequently, the SOS scale, along with questionnaires that investigate the attention individuals pay to common odors, the importance they attribute to the sense of smell and their olfactory imagery abilities, was administered to individuals with different degrees of anxiety, social anxiety and depression. The results revealed that both depression and social anxiety resulted to be related to social odor awareness, however, they act in an opposite way. Depression seems to be characterized by an increased social odor awareness, while social anxiety by a decrease of attention to social odors. As expected, the social impairment present in depression and social anxiety is reflected in their meta-cognitive ability only toward olfactory stimuli able to convey socially relevant information.

Finally, Chapter 6 and Chapter 7 focused on the use of emotional body odors (both happiness and fear body odor) to investigate the processing of these odors using a psychophysiological approach (Chapter 6) as well as their potential role in a mindfulness treatment (Chapter 7). The time-frequency approach employed in Chapter 6 allowed the simultaneous investigation of both affective dispositions and cognitive processing of neutral faces presented in the context of fear and happiness body odor vs. clean air condition, to further explore the assumed hyperreactivity toward social emotional stimuli in social anxiety and the hyporeactivity in depression. In general, body odors confirmed their role as powerful emotional cues, especially in healthy individuals. In line with previous studies, individuals with social anxiety symptoms resulted to be particularly sensitive to fear social signals, as stated by an increased delta power in response to the fear body odor. Regarding the group with depressive symptoms, the pattern is more composite. While individuals with depressive symptoms, at a subjective level, evaluated the neutral faces as more arousing when presented with the fear odor, at a neural level, both the fear and the happiness body odors seemed to help these individuals to extract the social meaning of the situation. Indeed, when presented without the body odors, individuals with depressive symptoms reported a reduced affective disposition as well as reduced cognitive processing of the neutral facial expressions, in line with previous findings supporting the hypothesis of a hypoactivation of the appetitive motivational system in clinical and subclinical depression (e.g., Dell’Acqua, Brush, et al., 2022; Dell’Acqua, Dal Bò, et al., 2022; Messerotti Benvenuti et al., 2020; Messerotti Benvenuti et al., 2019; Moretta et al., 2021). However, when the neutral faces were presented with both the fear and happiness body odors, no differences emerged in the processing of the visual stimuli between the healthy control group and the group with depressive symptoms.

To our knowledge, these are the first studies analyzing the role of body odors in individuals with depressive symptoms. This preliminary evidence suggests a specific multilevel sensitivity toward body odors in depression. Results showed that individuals with depressive symptoms exhibited higher attention to social odors (Study 2 in Chapter 4), higher arousal subjective ratings of neutral stimuli presented in the context of fear body odor, and a facilitation effect of both positive and negative body odors in the correct processing of social stimuli (Chapter 6). Given these promising results, a future step should be the integration of body odors in the treatment of depressive symptomatology, to promote social pro-activeness and stimulate their drive for social activity.

Regarding social anxiety, taken together, results from the present studies are in line with the general assumption that social anxiety is accompanied by a processing bias toward social information (Hirsch & Clark, 2004). At a psychophysiological level, the bias is reflected in an enhance affective disposition and hyperreactivity to neutral faces presented in the context of fear body odor, while, at a subjective/cognitive level, by a reduced social odor awareness. The presence of a dissociation between physiological, subjective and cognitive levels is far from being uncommon in psychological research. From a cognitive level, when forced to face social situations, socially anxious individuals are more focused on themselves rather than on external social cues (Mellings & Alden, 2000). In addition, the avoidance behaviour they adopt rarely exposes them to the smell of other people, possibly making them less aware of the social odors in their surroundings.

Given the consistently observed role of body odors as social cues, in Chapter 7 an attempt to use emotional body odors as a catalyst during a mindfulness treatment has been provided. Given the preliminary nature of this study, the focus was put only on individuals with social anxiety. This decision has been made for several reasons. First of all, more evidence was available on the higher sensitivity of socially anxious individuals to body odors (e.g., Adolph et al., 2013; Pause et al., 2009), and second, they proved to particularly benefit from a mindfulness intervention (e.g., Vassilpoulos, 2008; Vassilpoulos & Watkins, 2009; Cassin & Rector, 2011). In this experiment, both subjective (anxiety level) and physiological (HRV and SCL) measures have been collected. From a subjective point of view, both participants performing the training with the happiness and with the fear body odor reported a significant reduction of anxiety after the training. From the psychophysiological level, similarly to the results reported in Chapters 4 and 6, an opposite pattern emerged. Despite the positive effect of the fear body odor – in combination with the mindfulness training – in reducing the anxiety level, from a psychophysiological point of view, it resulted in a reduced HRV compared to the clean air condition. The HRV reduction in response to the fear odor was expected and was in line with previous evidence reporting a decreased vagal tone (Ferreira et al., 2018), but also activation of the amygdala (Mujica-Parodi et al., 2009), and an increased startle response (Adolph et al., 2013; Lübke et al., 2017; Prehn et al., 2006) following the fear body odor presentation. On the other side, happiness body odor did not modulate the psychophysiological measures recorded in Chapter 7, but also the subjective responses in Chapter 6.

According to the emotional contagion hypothesis (Hatfield et al., 1993), differential responses to body odors conveying positive or negative emotions should be expected, with the fear odor inducing the adoption of escape behaviors and the activation of the defensive motivational system, while the positive odor leading to positive emotions and approach behaviors. However, from the results of the studies reported in Chapters 6 and 7, the emotional contagion hypothesis is not fully supported. Several factors could have contributed to these partially unexpected findings. First of all, studies on negative emotions have been predominant in the field of social communication, with only a few studies investigating the communication of positive emotions. Starting from the evidence in the animal kingdom, the role of fear chemosignals is well known (Wyatt, 2003). The communication of possible dangers in the environment is essential and needs to be automatic, effortless and efficient. On the other side, the communication of positive emotions has no direct vital function (Pratto & John 1991). Hence, it is possible that their communication is less automatic or requires a longer exposure. In addition, positive emotions are more difficult to elicit in laboratory settings. Nevertheless, positive emotions have a crucial part in health and cognition, with happier people having more fulfilling relationships, better work performance, creativity, altruism, better health and longer life (Lyubomirsky et al., 2005).

Furthermore, emotional body odors, in addition to the communication of information regarding the emotional state of the sender, transmit also – and probably, primarily – the simple social presence of another individual. The mere feeling of presence of others is contagious and enhances a positive experience (Devereux & Ginsburg, 2001; Gervais & Wilson, 2019), leading to preferential processing of emotional body odors in healthy individuals (Chapter 6), and a better outcome of psychological treatment (Chapter 7). However, the evolutionary significance of the fear body odor results in differential subjective (Chapter 6) and psychophysiological (Chapter 7) responses, especially in socially anxious individuals, which further confirm to be especially sensitive to threatening social cues. To overcome this issue, future studies should include a neutral body odor condition to investigate whether the effects found in the present work were due to the social context transmitted by the body odors or by the specific emotion each odor was meant to convey.

To our knowledge, the present work is the first to investigate the processing of emotional, and in particular positive, body odors in affective disorders. On the basis of the present results, it can be speculated that not only fear, but also happiness, is transmitted chemosensorily between humans. Nevertheless, it is needless to say that more studies are warranted to untangle how specific emotions are transmitted by means of body odors, and to what extent their processing is altered in affective disorders. The adoption of a multi-level approach is advantageous in order to provide deeper insight into the factors that can play a role in the development and maintenance of the symptoms that make up social anxiety and depressive disorders.

8.4. Limitations and future directions

The results of the present work should be interpreted in light of several limitations that have been partially discussed in each experimental chapter and in the previous sections.

First, the participants included in the studies presented in Chapters 5, 6 and 7 were all females. The choice of focusing only one gender allowed us to avoid gender-related effects, since women and men differ in their olfactory abilities and attitudes toward odors: in general, women present higher olfactory abilities (Doty & Cameron, 2009), higher odor awareness (Ferdenzi et al., 2008), higher interest in the sense of smell (Seo et al., 2011), and higher importance of olfaction (Croy et al., 2010;

Havlicek et al., 2008) than men. Additionally, depressive and anxiety symptoms are more common among women than men and women present greater preference as compared to men for social emotional stimuli (Lübke et al., 2012; Proverbio et al., 2008). For similar reasons, to minimize variability due to olfactory decline related to ageing (Oleszkiewicz et al., 2019), only a young population has been selected (between 18-45 years for Chapter 4, and between 18-35 years for Chapter 6 and 7). If these choices made it possible to prevent age- and gender-related effects and to increase the power of the results, the generalization of the present findings is limited. Hence, future studies should include both genders as well as a wider age range.

Second, this dissertation focused on subclinical forms of affective disorders in a healthy young population. If this approach allowed us to better understand the initial mechanisms related to the altered olfactory abilities that might be used as a possible future marker of vulnerabilities, without confounding factor related to medications or the chronicity of the disorder, it does not fully speak to the factors linked to the development of clinical disorders. Only a longitudinal assessment will be able to fully establish whether the current findings represent vulnerability factors linked to the development of clinical mental disorders, and if the olfactory dysfunction is the cause of the consequence of them.

Moreover, Chapter 6 and 7 focused on body odors' processing including only two representative odors related to approach-related and avoidance-related emotions (i.e., happiness and fear body odors, respectively). As detailed in Chapter 2, 3, 6 and 7, the literature on emotional body odors is still at its beginning, and the mechanisms underlying the chemosensory communication in humans are mainly unknown. The results observed in Chapter 6 and 7 did not fully support the emotional contagion hypothesis, hence future studies are needed to untangle this complex phenomenon, that is chemosensory communication. Some suggestions, for future studies, should be to include a neutral body odor condition, to investigate the specific role emotional body odors plays in comparison to the simple social presence conveyed by a neutral condition. Connected to this point, one aspect to be taken into consideration is the collection of body odors. As reviewed in Chapter 3, researchers should make an effort to create a clear and unified methodology in the collection of body odors. In the studies presented in Chapter 6 and 7, emotional body odors were collected while participants were viewing emotional video clips. While this procedure has proven effective for the transmission of negative emotion, it can be possible that it was not strong enough to modulate the body odor related to the positive emotion condition (although subjectively the participants reported to be happier after the emotional induction).

Finally, in Chapter 7 an effort has been made to use emotional body odors as catalyst in a psychological treatment. However, it has been performed only in individuals with social anxiety symptoms. Given the promising results obtained in the reduction of anxiety symptoms (Chapter 7), and the beneficial effect body odors seem to have in the individuals with depressive symptoms in extracting the social meaning of the situation (Chapter 6), future studies should investigate more the possible role of body odors in the treatment of depression. For example, including approach-related body odors (i.e., body odor collected in a happiness-inducing situation) during interventions specifically aimed at increasing motivation for action, as the behavioral activation treatment (Jacobson et al., 2001). In addition, it could be interesting to explore the possible beneficial effect of body odors collected in other emotionally inducing situations. One example could be the collection of positive social olfactory stimuli during mindfulness meditation. The adoption of such odors can represent a reassuring signal that prime approach-related behavioral drives, increasing feelings of trust and social activities.

8.3. Epilogue

In the study of emotions and their role in the development of affective disorders, olfaction has always been neglected. In the present thesis, I wanted to put emphasis on how much we, as humans, rely on the sense of smell in our everyday life, whether we deliberately realize it or not. I have attempted to adopt a comprehensive approach, ranging from the study of subjective, and cognitive to psychophysical and psychophysiological aspects, adopting both common and social (i.e., biologically relevant) odors. This methodology led me to uncover which aspects are preserved, and which ones are impaired, in individuals with subclinical symptoms of depression and anxiety. With this work, new knowledge arose on the possible mechanisms underlying the reduced olfactory abilities in subclinical depression, as well as the possible future role of body odors in the treatment of affective disorders. A step forward has been made in the psychophysiological characterization of affective disorders and in the development of diagnostic and olfactory-based intervention protocols.

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Appendix A: Supplemental results of Chapter 4

Table 1A. Initial factor loading of the 24 items version in Study 1.

Item n°	Factor 1	Factor 2	Factor 3	Factor 4	Uniqueness
1. I smell my clothes to see if I should wash them or not	0.385	0.077	-0.156	0.196	0.787
2. I smell my clothes before I put them on	0.385	0.239	-0.032	0.225	0.662
3. I think about how other people perceive my body odor	0.180	0.116	0.057	0.470	0.685
4. I like my body odor without deodorant or perfume	0.246	0.161	-0.026	-0.186	0.850
5. I think about how members of the opposite sex perceive my odor	0.199	0.022	-0.073	0.656	0.548
6. I have a tendency of bringing often my hands close to my face when I'm in an unfamiliar situation	0.122	0.225	-0.194	-0.030	0.899
7. I can recognize people by their odor	0.022	0.690	0.083	-0.048	0.479
8. I prefer that other people hide their body odor with deodorant or perfume	-0.188	-0.219	0.284	0.388	0.663
9. The odor of a person is important to understand whether I like that person or not	0.267	0.328	0.209	0.227	0.564
10. I can relax when I smell someone I care about	0.150	0.591	-0.042	-0.049	0.566
11. I have well imprinted in my mind the odor of certain people	0.020	0.616	0.119	0.048	0.542
12. Smells can make me remember people I haven't seen in a long time	-0.068	0.770	-0.060	-0.000	0.470
13. I can be attracted to someone for their body odor	0.583	0.229	-0.005	0.235	0.428
14. I prefer my sexual partner to hide their body odor with deodorant or perfume	-0.336	-0.080	0.051	0.616	0.469
15. I like the way my partner's armpits smell	0.557	-0.025	0.009	-0.320	0.589
16. I can be sexually aroused by someone's natural body odor	0.790	-0.111	0.082	-0.003	0.427
17. My partner's smell or scent can inhibit my sexual behavior	-0.086	0.084	0.127	0.387	0.792
18. In a public place (e.g. the movie theater), I look for another place to sit if a person has an unpleasant odor	0.145	0.062	0.499	0.116	0.649
19. I don't take public transport because of	0.205	-0.109	0.443	0.045	0.770

the odor of other people					
20. When I enter in a crowded room, I ask if it is possible to open the windows	0.110	-0.088	0.437	0.073	0.793
21. The smell or scent of other people can be repulsive or sickening	0.020	0.270	0.344	0.049	0.739
22. When I'm close to strangers I notice if their shirt has a strong smell	-0.037	0.420	0.482	0.035	0.484
23. I get quickly annoyed by the odor of strangers	-0.025	0.018	0.700	-0.098	0.527
24. I can be aroused by my sexual partner's natural body odor	0.687	0.150	0.012	-0.063	0.408

Table 2A. Final Italian version of the SOS.

Indichi quanto è d'accordo o disaccordo con ciascuna delle seguenti affermazioni, segnando una casella corrispondente. Scelga l'opzione centrale soltanto se davvero non è nella possibilità di valutare il suo comportamento.	Non sono per niente d'accordo	Non sono molto d'accordo	Non sono né d'accordo e né in disaccordo	Sono abbastanza d'accordo	Sono completamente d'accordo
1. Riesco a riconoscere le persone dal loro odore					
2. Riesco a rilassarmi quando sento l'odore di qualcuno per cui provo affetto					
3. Ho bene impresso nella mia mente l'odore di certe persone					
4. Gli odori possono suscitare in me il ricordo di persone che non vedo da tempo					
5. Posso essere attratto da qualcuno per il suo odore corporeo					
6. Mi piace il modo in cui le ascelle del mio partner odorano					
7. Posso essere eccitato sessualmente dall'odore naturale del corpo di qualcuno					

8. Posso essere attratto dall'odore naturale del mio partner sessuale					
9. In luogo pubblico (es. al cinema) se una persona ha un odore sgradevole cerco un altro posto a sedere					
10. Non prendo mezzi pubblici a causa dell'odore degli altri					
11. Quando entro in una stanza affollata, mi informo se è possibile arieggiare aprendo le finestre					
12. Sono infastidito velocemente dall'odore degli estranei					

Table 3A. Final German version of the SOS.

Geben Sie an, in welchem Maße Ihre persönliche Art zu reagieren damit übereinstimmt, was in der Aussage steht. Die Mitte der Skala gebrauchen Sie nur, wenn Sie die beschriebene Reaktion überhaupt nicht beurteilen können.	Ich bin überhaupt nicht einverstan den	Ich bin nicht sehr einverstan den	Ich bin weder einverstan den noch dagegen	Ich bin ziemlich einverstan den	Ich bin völlig einverstan den
1. Ich kann Personen nach ihrem Geruch unterscheiden					
2. Ich kann mich entspannen beim Duft einer Person, für die ich positive Gefühle habe					
3. Der Geruch gewisser Personen bleibt mir gut in Erinnerung					
4. Gerüche können mich an Personen erinnern, die ich lange nicht gesehen habe					
5. Ich kann mich zu jemand hingezogen fühlen wegen seines Körpergeruchs					

6. Ich mag es, wie die Achseln meines Partners riechen

7. Der natürliche Körpergeruch von jemand kann mich sexuell erregen

8. Ich kann mich vom natürlichen Geruch meines Sexualpartners angezogen fühlen

9. Wenn eine Person an einem öffentlichen Ort (z.B. im Kino) unangenehm riecht, suche ich mir einen anderen Sitzplatz

10. Ich benütze keine öffentlichen Verkehrsmittel wegen des Geruchs der anderen

11. Wenn ich in einen überfüllten Raum komme, frage ich, ob man die Fenster öffnen und lüften kann

12. Der Geruch von Fremden geht mir schnell auf die Nerven

Table 4A. Final English version of the SOS. This version has not been validated.

Indicate how much you agree or disagree with each of the following statements by ticking a corresponding box. Choose the central option only if you are really unable to evaluate your behavior.	I totally disagree	I mostly disagree	I neither agree nor disagree	I mostly agree	I totally agree
1. I can recognize people by their odor					
2. I can relax when I smell someone I care about					
3. I have well imprinted in my mind the odor of some people					
4. Odors can evoke in me the memory of people I have not seen for a long time					
5. I can be attracted to someone for their body odor					
6. I like the way my partner's armpits smell					
7. I can be sexually aroused by someone's natural body odor					
8. I can be aroused by my sexual partner's natural body odor					
9. In a public place (e.g. the movie theater), I look for another place to sit if a person has an unpleasant odor					
10. I don't take public transport because of the odor of other people					
11. When I enter in a crowded room, I ask if it is possible to open the windows					
12. I get quickly annoyed by the odor of strangers					

Fig. 1A. Main effects of (A) approach tendencies, (B) alexithymia and (C) age on odour awareness. Black dots represent data distribution, red line is the fit of the main effect.

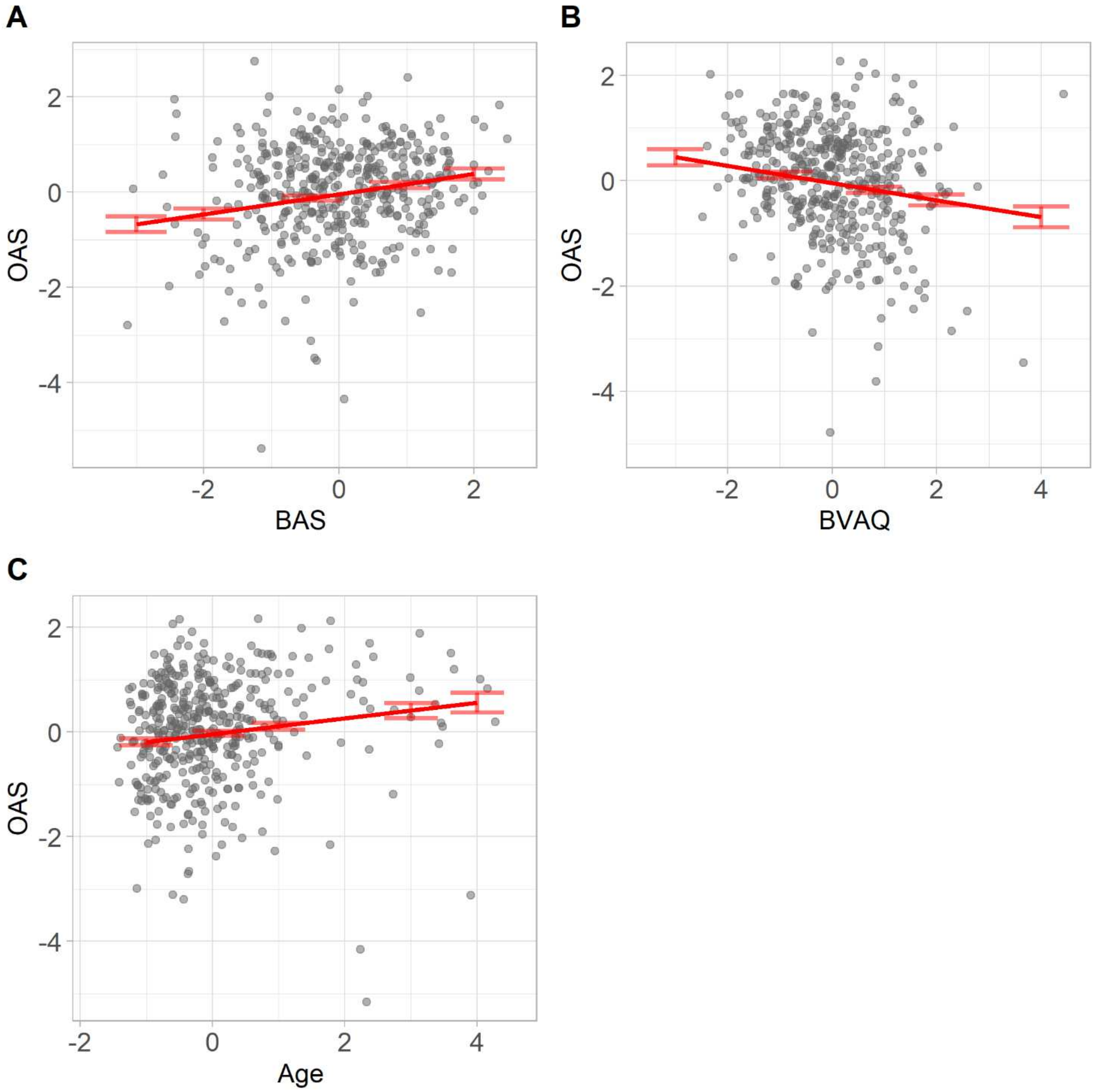


Figure 2A. Main effects of (A) approach tendencies and (B) alexithymia on affective importance of odours. Black dots represent data distribution, red line is the fit of the main effect.

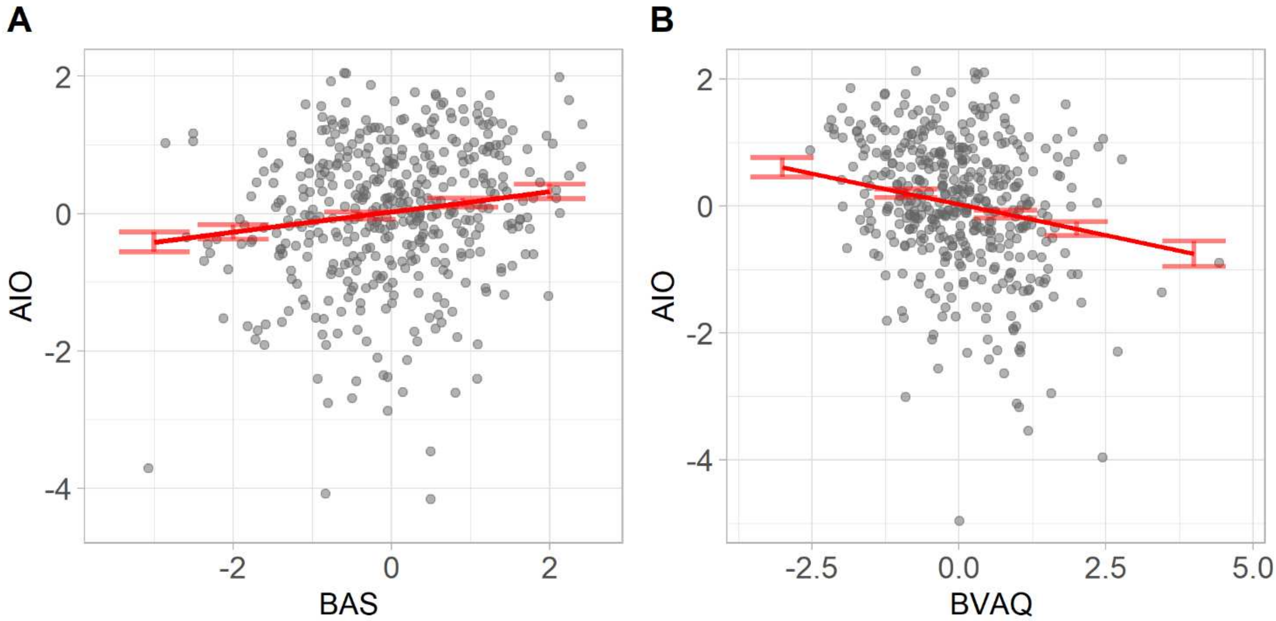


Figure 3A. Main effects of (A) approach tendencies and (B) age on olfactory imagery. Black dots represent data distribution, red line is the fit of the main effect.

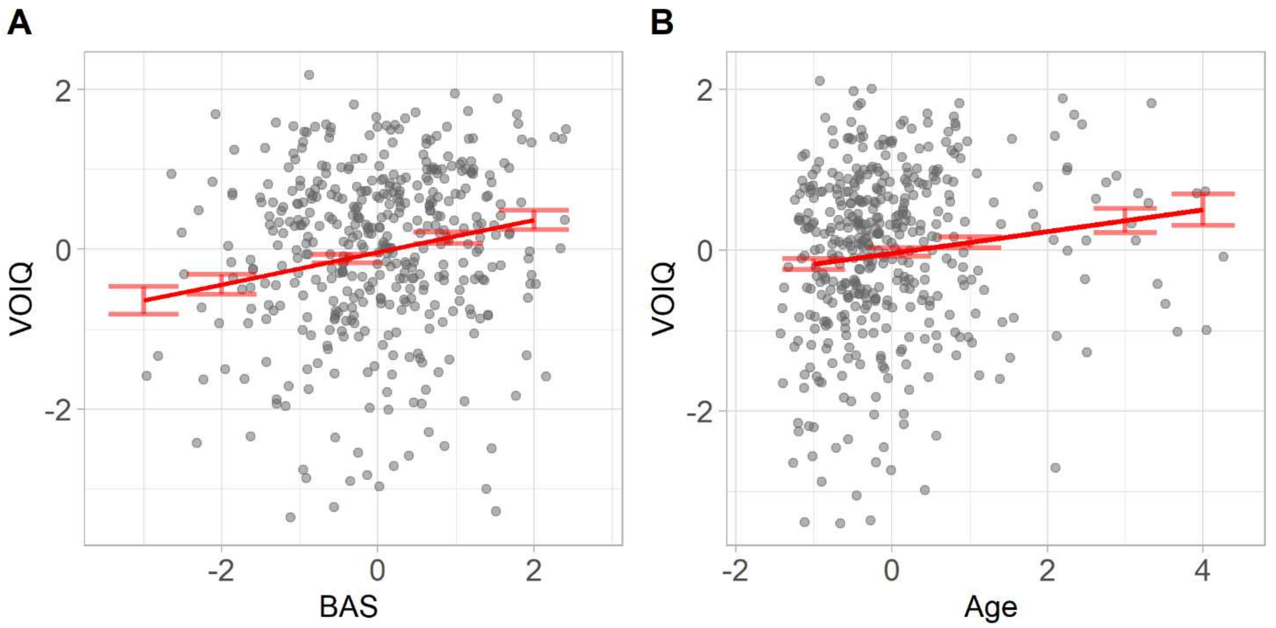
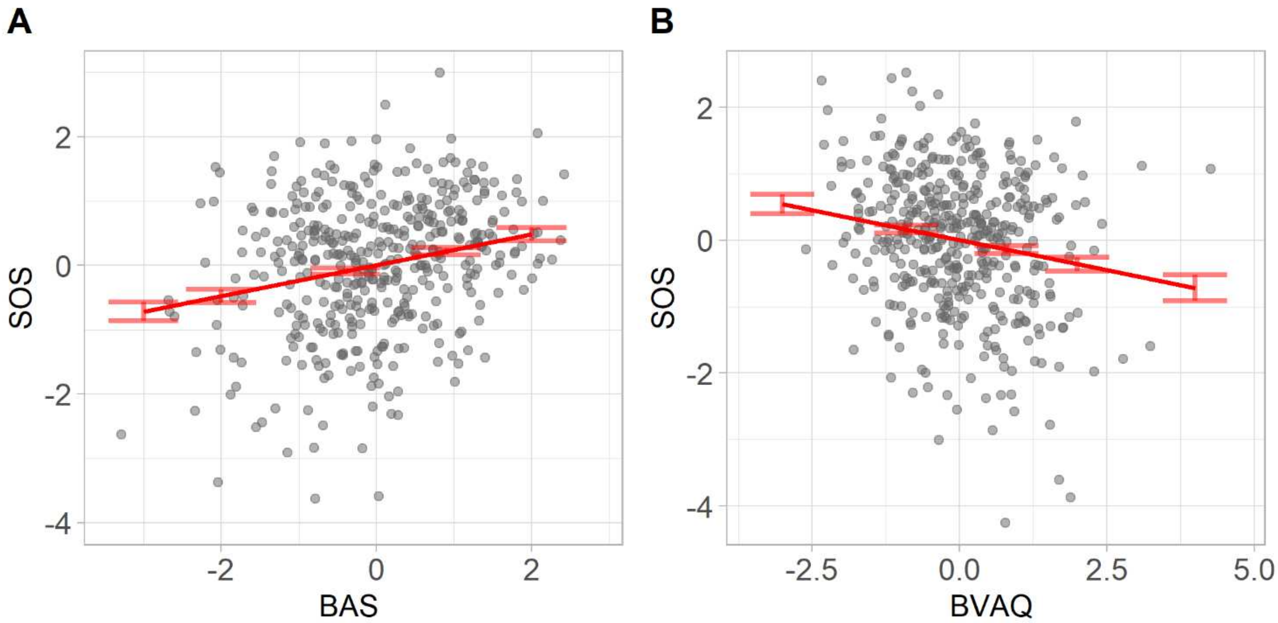


Figure 4A. Main effects of (A) approach tendencies and (B) alexithymia on social odour awareness. Black dots represent data distribution, red line is the fit of the main effect.



Appendix B: Supplemental results of Chapter 6

Table 1B. Mean and standard deviation of emotional state ratings of the senders before and after the emotional induction.

	Happiness induction			Fear induction		
Emotional state	**Pre**	**Post**	**sign**	**Pre**	**Post**	**sign**
Fear	8.16 (13.48)	1.64 (4.98)	*	8.81 (15.38)	54.06 (30.53)	*
Anger	1.64 (3.38)	1.19 (2.81)		2.03 (3.33)	11.93 (16.51)	*
Disgust	0.67 (1.87)	0.93 (2.51)		0.68 (1.70)	13.26 (16.79)	*
Surprised	9.90 (18.79)	21.26 (22.47)	*	8.74 (12.97)	36.64 (25.29)	*
Joy	42.10 (21.65)	58.71 (18.43)	*	44.77 (24.03)	16.58 (20.59)	*
Sadness	6.22 (11.12)	3.55 (7.65)		7.35 (11.89)	9.55 (13.97)	
Funny	26.97 (21.65)	56.02 (20.30)	*	33.87 (24.88)	14.84 (20.16)	*
Neutral	47.22 (24.99)	32.68 (23.03)	*	44.68 (28.17)	15.12 (18.43)	*
Calm	54.22 (23.90)	49.97 (29.59)		56.29 (24.75)	13.35 (14.92)	*