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## Interindividual variability in olfactory experience: an interdisciplinary approach

Marylou Mantel

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**Marylou Mantel**

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# **Variabilité interindividuelle dans l'expérience olfactive : une approche interdisciplinaire**

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## **ABSTRACT**

Odor perception is an essential function in humans, allowing for hazard prevention, food detection and social communication. However, this sense is often underestimated, especially regarding the ability to identify and describe odors through language. In this PhD, we aimed to better understand the subjective experience of smell, its diversity, and its neural correlates. To this end, we first introduced olfaction with its specificities and the importance of hedonics in odor perception. Then, we investigated interindividual variability in olfaction through a series of studies and showed that olfactory perception comprises both a shared and a diverse component depending on the odorants, with little effect of common factors of variation like age or sex. Also, we showed that the relation between chemical structure, receptors and perception of odors is influenced by the degree of interindividual variability, a finding important for the ongoing stimulus-percept issue in olfactory research. Through this bibliographic and experimental work, we show that there is a lack of reflection on the way we measure perception, and that its subjective nature has been under considered in contemporary research. We thus discuss the place of subjectivity in science and several methodologies that were proposed to better integrate first-person reports in experimental protocols. From these approaches, we set up a new study collecting unbiased subjective reports of odors, to construct a descriptive model of olfactory experience. We found that contrary to common belief, people can talk about odors, using references to diverse categories, including associated memories, qualitative description, source, impact, use and difficulty. With data mining, we were also able to get a fine-grained characterization a few perceptual profiles for the odors. Next, we considered the ongoing debate around the neural basis of consciousness, and the proposed methodologies to relate first-person data with cerebral activity measurements. Another study thus attempted to relate the subjective experience of odors with the evoked brain activity. The results open new ways to construct imaging protocols with a better inclusion of first-person accounts. In conclusion, we argue that subjective data has an important place in experimental research that it must be rigorously collected to fully understand human perception. We also emphasize the importance of integrating different disciplinary approaches to get a global picture of our objects of study.

## **RESUME**

La perception olfactive est une fonction essentielle chez l'humain, qui permet la prévention des dangers, la détection de nourriture et la communication sociale. Cependant, ce sens est souvent sous-estimé, en particulier au niveau des capacités d'identification et de description des odeurs par le langage. Dans cette thèse, nous avons cherché à mieux comprendre l'expérience subjective des odeurs, sa diversité et ses corrélats neuronaux. Pour cela, nous avons tout d'abord présenté le sens olfactif avec ses spécificités et l'importance de la valence hédonique dans la perception des odeurs. Ensuite, nous avons étudié la variabilité interindividuelle en olfaction et nous avons montré que la perception olfactive comprend à la fois une composante universelle et une composante variable selon les odeurs, avec peu d'effet de facteurs de variation bien connus en olfaction comme l'âge et le sexe. Nous avons également montré que la relation entre la structure chimique, les récepteurs et la perception des odeurs est influencée par le degré de variabilité interindividuelle, un résultat important pour le problème du stimulus-percept en recherche sur l'odorat. A travers ce travail bibliographique et expérimental, nous avons montré un manque de réflexion sur la manière de mesurer la perception, dont la nature subjective a été sous-étudiée dans la recherche scientifique contemporaine. Nous avons donc ensuite discuté la place de la subjectivité en science, ainsi que plusieurs méthodologies proposées pour mieux intégrer les données en première personnes dans les protocoles expérimentaux. A partir de ces approches, nous avons mis en place une nouvelle expérience qui nous a permis de recueillir des discours subjectifs non biaisés sur les odeurs et de construire un modèle descriptif de l'expérience olfactive. Nous avons trouvé que, contrairement aux idées reçues, les individus sont capables de parler des odeurs et utilisent des références à différentes catégories, comme des souvenirs, descriptions qualitatives, sources, impacts, fonctions et difficulté. Avec des algorithmes de data mining, nous avons également pu caractériser de grands profils perceptifs pour les odeurs. Dans un deuxième temps, nous avons évoqué le débat encore en cours sur les bases neurales de la conscience, et les méthodes proposées pour relier données subjectivité et données d'imagerie cérébrale. Une seconde expérience a donc cherché à relier l'expérience subjective des odeurs avec l'activité cérébrale évoquée. Les résultats ouvrent la voie pour de nouveaux protocoles expérimentaux incluant des données en première personne plus précises. Nous concluons que les données subjectives ont une place importante dans la recherche expérimentale et qu'elles doivent être recueillies rigoureusement pour mieux comprendre la perception chez l'humain. Nous insistons également sur l'importance d'intégrer plusieurs approches disciplinaires pour avoir une image globale de nos objets d'étude.

## Remerciements / Acknowledgments

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Speaking of **Thomas Hummel**, I must thank you too: from our first meeting in 2017, you have been so kind and welcoming, and I appreciated our scientific discussions. You even allowed me to torture your med students in my experiments (for the record, all of it was done under the convention of Helsinki, so don't worry) and I am forever grateful for that. I met fantastic people in your lab including **Ben, Caroline, Akshita, Yun Peng, Antje...** and especially **Annegrêt** who helped me greatly during my experiments. Also thank you to **Cornelia** for having us at your table, this night was fantastic. Now that we are back in France, I'll switch to French so that all people mentioned here can understand this.

Tout d'abord, je tiens à remercier mes deux directeurs de thèse, qui ont chacun à leur façon su m'accompagner tout au long de ce long voyage, à travers la construction du projet de thèse, les discussions enflammées, les relectures d'articles, et encore beaucoup d'autres. **Jean-Michel**, vous m'avez permis d'intégrer une formation qui m'a ouvert beaucoup de perspective sur ma discipline et vos cours m'ont donné l'inspiration pour cette thèse. Merci donc de m'avoir suivi tout au long de mon master, puis de ma thèse, sur un terrain assez inconnu pour nous tous. Débattre avec un neuroscientifique et un philosophe pendant des heures est une expérience à vivre et devrait être de moins en moins incongrue au sein des sciences cognitives.

Quant à **Moustafa**... que dire ? J'ai longtemps réfléchi à la manière de te remercier pour ces cinq ans à travailler ensemble, et je crois que je n'aurai jamais les mots pour l'exprimer complètement (un comble quand on travaille sur les descriptions verbales). Dès le début, tu as eu confiance en mes capacités et tu m'as accueillie dans ton laboratoire malgré mon profil atypique. Quand j'ai dû abandonner seulement un mois après mes débuts, tu m'as attendue quand tu aurais pu passer à autre chose. C'est en grande partie grâce à cette confiance que j'ai pu me reconstruire et reprendre là où tout semblait terminé. Le directeur de thèse idéal n'existe probablement pas mais si c'est le cas, il s'appelle sûrement Moustafa. Je n'aurais pas pu rêver mieux comme accompagnement pour mon doctorat mais aussi pour le monde mystérieux de l'après-thèse. Tu as répondu à toutes mes questions, toujours avec patience et respect, à la fois en tant que tuteur et en tant que collègue. Et au niveau de nos interactions, je n'aurais jamais pu terminer sans ta compréhension et compassion pour les moments plus difficiles et nos rires partagés lors des meilleurs. Au jour où j'écris ces lignes, cela ne fait que deux semaines que

j'ai quitté le laboratoire mais tu me manques déjà, tout en sachant que tu m'as permis d'avoir tous les outils en main pour continuer ma carrière en toute autonomie. Je pourrais en dire beaucoup plus, mais je crains que les émotions prennent le dessus alors je vais m'arrêter ici. Je peux simplement ajouter que s'il y a cinq ans, j'avais su que je terminerai une thèse, je n'y aurai jamais cru tant la situation était sombre. Merci encore d'avoir été ma lumière sur le chemin.

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Parmi toutes ces belles personnes, il y en a deux que je voudrais spécialement remercier car elles ont été à mes côtés tous les jours de ce long parcours. Nous avons crié, ragé et pleuré ensemble, mais nous avons surtout eu la chance de s'être trouvées et d'avoir passé de si bons moments. **Lucile**, ma Lulu, on sait tous que tu es une NeuroPopienne dans ton cœur, tu fais partie de la team rappelle-toi. Nous avons partagé un appartement, les chats les plus adorables du monde et les déboires de la thèse, nous en partagerons aussi les réussites quand le temps sera venu. **Kenza**, يا كنزة انت صديقتي و اختي, notre grande sœur de thèse, merci d'avoir été là et de nous avoir rassurées, après avoir vécu toi-même cette aventure. Mes biscuits je vous aime et je veux continuer à faire des brunchs avec vous.

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## List of Articles

In this manuscript, we will refer to several articles, that are presented in a table below for clarity, in their order of appearance. There are two types of articles there:

- *Main articles*, in which I had a major contribution and was either the first author or the first co-author. Among them, there were three review articles, one opinion article and five experimental studies, which were referred as Studies 1 to 5 in the manuscript, in their order of appearance.
- *Annexes*, in which my contribution was minor (e.g., data organization, draft redaction and revision...). Although they were experimental studies as well, they were not referred as Studies.

### *Main articles*

N°	Type	Title	Author rank	Status	Journal
1	Review	Individual Differences as a Key Factor to Uncover the Neural Underpinnings of Hedonic and Social Functions of Human Olfaction: Current Findings from PET and fMRI Studies and Future Considerations	First	Published	Brain Topography (2019) 32:977–986 <a href="#">Link to article</a>
2	Book Chapter	Senses and emotion: a complex relationship	First	Published	Emotion Measurement 2 <sup>nd</sup> Edition (2021) <a href="#">Link to book</a>
3	Review	On the contribution of the senses to food emotional experience	Co-First	Published	Food Quality and Preference (2021) 104120 <a href="#">Link to article</a>
4	Research Article (Study 1)	Olfactory perception and factors of variation in a large population	First	In preparation	
5	Research Article (Study 2)	An experimental investigation comparing a surface plasmon resonance imaging-based artificial nose with natural olfaction	Co-First	Published	Sensors and Actuators B: Chemical (2020) 128342 <a href="#">Link to article</a>
6	Research Article (Study 3)	Using a bio-inspired surface resonance plasmon electronic nose for fundamental research on human olfaction	First	Second revision	

7	Opinion Article	Accounting for Subjectivity in Experimental Research on Human Olfaction	First	Published	Chemical Senses (2021) 46, bjaa082 <a href="#">Link to article</a>
8	Research Article (Study 4)	Language descriptions of smells are richer than thought	First	In revision	
9	Research Article (Study 5)	Neural correlates of olfactory subjective experience	First	In preparation	

### *Annexes*

A.1	Research Article	Smell and taste changes are early indicators of the COVID-19 pandemic and political decision effectiveness	Second	Published	Nature Communications (2020) 11, 52 <a href="#">Link to article</a>
A.2	Research Article	Recovery From COVID-19-Related Olfactory Disorders and Quality of Life: Insights From an Observational Online Study	Eighth	Published	Chemical Senses (2021) 46, bjab028 <a href="#">Link to article</a>
A.3	Research Article	The prevalence of olfactory deficits and their effects on eating behavior from childhood to old age: A large-scale study in the French population	Third	Published	Food Quality and Preference (2021) 93, 104273 <a href="#">Link to article</a>
A.4	Research Article	Chemical features mining provides new descriptive structure-odor relationships	Second	Published	PLoS Computational Biology 15(4): e1006945. <a href="#">Link to article</a>

# INTRODUCTION

**“Smell is the muted sense, the one without words”**

**Diane Ackerman**

Odors are everywhere, whether they come from the bakery we pass by every morning going to work, the freshly cut grass in our favorite park, the perfume of our partner, or even the stink of the milk we forgot in our fridge. And yet, Western societies historically considered smell as minor, progressively lost as vision replaced it as our major sense during evolution. Viewed as a relic of our “animal” past, olfaction was often negatively associated with sexuality and dirtiness, thus unworthy of a civilized enlightened man<sup>1</sup>. With the rise of hygienics in the early 20th century, an odorless society became the ideal to achieve<sup>2</sup>.

However, if you ask someone who completely lost their sense of smell, a condition called *anosmia*, they will probably do not agree with this impoverished vision of olfaction. Beyond its precious function as a detector of potential threats to our organism, such as spoiled food or smoke, smell is indeed essential for our well-being and quality of life. Think about the times when you were so sick that you could not taste your favorite food anymore and it made you miserable. Or about the reassuring odor of your mother when she kissed you good night as a child. Or even about the smell of your freshly brewed morning coffee. Imagine losing all of this: would life have the same flavor to you? In fact, we know that anosmia is associated with a significant drop in perceived quality of life and to elevated rates of anxiety and depression<sup>3,4</sup>. For the elderly, the loss of smell is even related to higher mortality independently of other risk factors<sup>5</sup>.

In addition, recent work suggests that humans are far from having a bad sense of smell<sup>6</sup>. We have nothing to be ashamed about regarding our capacities to detect and discriminate odors compared to other species. Chemical communication occurs in humans as well, we are just usually not aware of it<sup>7</sup>. Also, cross-cultural studies show smell does indeed have words if we go beyond the Western scope<sup>8</sup>. In fact, the apparent poorness of smell is more of a historical and cultural conception than a grounded reality.

In other words, it is not that olfaction is not a part of our lives, but rather that we are not aware of it, at least until we lose it. We do not typically pay attention to our odor environment, except if something is suddenly smelling very bad or very strongly. It is also very difficult to talk about odors. Think about how you would describe the odor of coffee to someone who never smelled it. What words would you use? If you speak English or most Western languages, you will not have that many options. You could say that is pleasant, or not. You could also compare it to something else: “it is like the smell of chocolate”. However, you would have very few terms to describe its olfactory features. You would not have access to the equivalent of shape, color, or texture to describe this odor of coffee. This absence of olfactory lexicon is well known, as well as the inability to accurately name odors for most individuals<sup>9</sup>. It is part of the reasoning that the human sense of smell is overall poor compared to other sensory modalities for which we do not have any trouble talking about.

Another element that is often blamed is the subjectivity and ineffability of smell perception. What you perceive when you inhale a rose is the product of your biology combined with your previous experiences, learning and overall system of thought. It is thus considered as purely

subjective and impossible to share with another person. In contrary, vision is based on a shared reality composed of shapes, colors... all of which is easily depictable to someone speaking the same language as you. In experimental research, the issue of the subjectivity of olfaction is reflected by the important diversity in people's emotional responses, perceptual assessments and even cerebral responses for the same odor compared to visual, auditory, or even tactile stimuli.

Apropos of experimental research, how do we study olfaction today? In line with other areas of modern psychology, researchers focused on the behavior and on quantitative measures of olfactory perception, to construct an objective, rigorous and reproducible science of the human mind. This includes investigation of approach/avoidance behaviors, psychophysical recordings of individuals' reactions to odorants, and quantitative assessment of key perceptual dimensions such as intensity, pleasantness, or familiarity. Inspired by sensory analysis and experts in oenology or perfumery, atlases constituted of semantic descriptors are also widely used within the olfactory community. They include specific terms such as "woody", "green" or "ethereal", routinely used by experts to describe the subtle notes of substances they are working with. When asking novices about odors, instead of free description, a hard task for both the subject and the experimenter who must then analyze them, they are usually presented with quantitative scales or all-that-apply choices of descriptors. As we will show in the next chapters, this is not an accurate and unbiased measure of olfactory perception and there is a lack of methodologies including detailed subjective reports as a source of data.

In this thesis, we argue that considering and characterizing the subjectivity of odor perception and including it into experimental research will allow for a better understanding of the content of olfactory experience and its diversity in individuals, both at the perceptual and brain level. We hypothesize that olfactory language can be rich even in cultures with a priori poor smell lexicon if the right questions are asked. This requires the development of an alternative measure of perception, that is more centered around the actual experience of the individuals rather than quantitative ratings on a few dimensions. In this thesis, we will embark in a journey across the olfactory territory, to progressively draw a portrait of what is it like to smell an odor and how this is associated with brain activity.

In Chapter 1, we will introduce the reader to what is known about olfaction today. In a first section, we will depict its complicated history in Western civilization, which led to an impoverished view of our olfactory abilities. Then, we will expose the main biological functions of smell in humans, as well as its relationship with emotion and quality of life. We will also review the main factors contributing to the diversity of olfactory experiences among individuals. In the last section, we will discuss olfactory language and especially cross-cultural investigations. We will also refer to three review articles written during my PhD highlighting the predominant role of hedonics in odor processing.

In Chapter 2, we will focus more of the universality and diversity aspects of smell. We will begin with a study that allowed us to draw a portrait of olfactory perception in a large population, with both the shared aspects between the individuals and the weight of main factors of variation. Then, we will present another experimental study comparing the responses of humans with those of an artificial system, to show that while some odorants elicit similar reactions from an electronic nose and from individuals, others are very different, further supporting the hypothesis that smell perception comprises both universal aspects for certain

odorants, and diversity for others. These experiments show the complexity of perception and that its measurement is lacking to encompass the whole experience of the individuals.

In Chapter 3, we will enter the core of this PhD by discussing the place of subjective experience in experimental research. We will present its history and the recent attempts to include fine-grained subjective reports into psychology and neuroscience protocols. We will especially focus on the different methodologies that have been proposed and their applicability to the domain of olfactory research. Then, we will present a new protocol for the acquisition of olfactory perceptual data, as well as an experimental study in which it was implemented. This study allowed us to construct a descriptive model of olfactory experience that will be discussed and compared with standard measurements. We will also consider the benefits of a descriptive artificial intelligence approach, namely data mining, for the fine-grained characterization of subgroups of individuals with similar experience.

In Chapter 4, we will present the principles of neurophenomenology, an approach combining subjective reports and objective measurements of cerebral activity. We will propose a protocol for its application within the field of olfactory research and present the results of an experimental study conducted with functional neuroimaging. We will show that verbalizations can explain part of the variability in brain activity evoked by odors, complementary to standard quantitative ratings. This supports the integration of subjective reports into the interpretation of neuroimaging data.

In conclusion, we will discuss the results described in the different chapters of the manuscript and argue that they are in favor of a more rigorous inclusion of subjectivity in experimental research on olfaction, to better understand the observed variability in both perception and brain activity. Future studies should investigate how the model of subjective experience of odors that was developed here behaves according to other factors of variation and different populations of individuals. An individual-centered approach can also be of interest in various domains of application, especially the development of products adapted to consumers, the enrichment of sensory analysis methodologies, and personalized approaches to better understand olfactory disorders.

# Chapter 1

## INTRODUCTION TO THE SENSE OF SMELL

- To like or not to like, that is the question -

### 1. THE REHABILITATION OF SMELL

#### 1.1. SOCIO-HISTORICAL PERSPECTIVE

When we think of the Middle Ages, we often imagine dirty, smelly towns, invaded by animals and waste. People were not washing regularly and did their business in the streets. Nice picture, right? It would not be a nice smell neither. In his book about the entanglement of smell and the development of civilization<sup>1</sup>, Robert Muchembeld gives us a fine-grained description of the place of odors within the medieval and Renaissance eras. In the medieval cities, there was important olfactory pollution, due to human and animal feces and urine, professional activities, and the lack of sewers. People were used to the stink, but it did not prevent them to complain about it to the authorities. Villages were smelly, but not as much as cities which were closed and stuffed, and rich individuals often owned a countryside house to retreat when the odor became unbearable.

Despite its unpleasant smell, human waste was important for agriculture and medicine, especially urine which was used for diagnosis of various diseases<sup>10</sup>. In Antiquity, the physicist Galen thought that disease was caused by a disturbance in the air and announced by putrefaction odors. Centuries later, French surgeon Ambroise Paré recommended to fight the bad odor of diseases, considered as the devil's breath, with even worse smells. For example, the remedy for plague included smelling odors of urine or feces to cover the disease. To protect oneself, one could also use fumigations, fires and perfumes<sup>11</sup>. People would wear pomanders, small balls containing various odorous elements, near their orifices to avoid the bad smell to enter their bodies. Fumigations were also a means to communicate with the divine, through incense and fires supposed to transform offerings into spiritual food for the gods<sup>11</sup>.

Human odors were not as diabolized in the medieval era compared to today and were even erotized in some cases. There were many tales and writings depicting and making fun of them, whether they were aimed at the common peasant or at the nobility. During the Renaissance, the nose was so much associated to sexuality than poet Rabelais compared the size of the nose to the phallus. The prominent philosophy of the time urged to seek physical pleasure with a rejection of the erotic, obscene and scatological taboos. Christian censorship tried to combat trivial writings, but scatological tales were still very popular throughout the 16<sup>th</sup> century.

Note that female odors were considered as stronger than men due to cultural and social factors. Menstruations were even more feared and viewed as a manifestation of the devil. To combat this bad odor, women could use perfumed remedies. Artists showed this strong odor with the representation of animals near women, as it is shown in Crispin Van de Passe engraving about smell (*Figure 1*). In addition, although poets were indulgent with young women as they

were supposed to represent life and purity and smell like fresh flowers, they attributed the odor of death to old women.



**Figure 1. Smell. Engraving by Crispjin de Passe the elder (c. 1590-1637).**

*The engraving represents a young woman holding flowers.  
Next to her, a man is holding his nose because of her bad smell.*

Later, with the convenient claim of protecting oneself with odors, the next centuries were characterized by the development of perfumes. In the 17<sup>th</sup> and 18<sup>th</sup> centuries, the preferred components were musky, animal smells that were especially present in leather gloves and bags. Amber and civet were very popular as well. However, at the end of the 18<sup>th</sup>, with the improvement of the quality of life and sanitization, animal perfumes were less of fashion and floral, light smells were introduced by perfumers and glove-makers, as it became a fulltime job<sup>12</sup>. Also, the cities smelled different: beyond the feces and urine, new products filled the air, such as tobacco or coffee, even though they were also sources of complaints from the inhabitants<sup>2</sup>.

Despite the olfactory richness of the Medieval and Renaissance worlds, we have very few historiographies of smells. As Jenner points out<sup>2</sup>, there is a gradual erasure of the odors in the historical documents, and a growing concern about deodorization, both physically and metaphorically. This can be related to the rise in hygiene throughout the 19<sup>th</sup> century, with regular baths and soap resulting in less smelly individuals. Hygienists even declared a war against odors, with limewashed walls in houses, hospitals, and prisons, as well as disinfection of the streets by removing waste and various cadavers. Chloride solutions were especially used

as they were reputed to be very effective to annihilate putrefaction smells<sup>13</sup>. In addition, the development of germ theory led to the separation of the sense of smell from diseases, leading to a decreased fear of odors.

Odors still had cultural significance in the 19<sup>th</sup> and 20<sup>th</sup>. They were a marker of social status, as the upper class became more concerned with their body odors in order to be separated from smelly workers<sup>14</sup>. As George Orwell famously said, “the lower classes smell” after all<sup>15</sup>. In addition to class, racism was also at play in discussions about smell, since the outgroups were reputed to be stinky and smelly because of their animal and barbaric nature, in contrast to the ingroup<sup>10,16</sup>. Other races were foul-smelling but even within the same society, people living in the countryside were also considered bad smelling, with a different olfactory profile depending on geographical regions.

Today, it is usually accepted that smells do not bear as much importance as they used to, due to a decline in social significance. Nonetheless, we will see in the next sections of this chapter that this does not mean that odors are not an important part of our quality of life and emotional well-being. Also, such cultural disinterest of smells is not universal. In Western countries, odors are essential for certain professions, such as perfumers, oenologists, coffee experts and cooks. In fact, the progressive erasure of odors mainly regards body odors, animal, and musky smells, and not the scents of the perfumes that were increasingly used in the population and still very prevalent today. In other societies, especially in hunter-gatherer communities, odors are also still a considerable part of cultural practices.

## 1.2. PHILOSOPHICAL PERSPECTIVE

The social history of odors echoes the traditional philosophical views about smell perception within the Western civilization<sup>2</sup>. As Le Guérer points out, many philosophers belittled olfaction or completely ignored it in their work, including Aristotle, Descartes, Kant and Schopenhauer<sup>17</sup>. The rationale for such disdain is twofold: on the one hand, smell was considered as in the bottom of the hierarchy of the senses, dominated by the noble senses of vision and audition. Indeed, smell was associated to sensuality and animality, and was thus incompatible with rational thinking and subtle esthetics. On the other hand, there was – and there still is, a very scarce vocabulary for odors, which is an issue for the abstraction and theorization of olfactory perception. Smell was therefore considered as a pure subjective sense, inherently ineffable and incapable of mental representation, let alone shared representations between individuals. As we will explore further this issue of compatibility in Chapter 3, we will see that such view of the sense of smell is not quite compatible with latest scientific findings and contemporary thinking. In fact, the separation between objectivity and subjectivity comes from an era in which the biology of the brain was not yet understood, as Ann-Sophie Barwich reminds us<sup>18</sup>.

However, we must mention that not all philosophers viewed smell perception as inferior. Indeed, Nietzsche thought the animal dimension of olfaction was on the contrary a very important tool for knowledge, especially in terms of moral judgements and intuition. He even considered smell as the sixth sense of intuitive awareness<sup>17</sup>. Although Freud rejected olfactory perception in his work, as an archaic, childish and primal sense, contemporary thinkers such as

Ferenczi thought on the contrary that smell could be a means for accessing repressed feelings and thus an important tool for psychoanalysis<sup>17</sup>.

In sum, despite variations in authors' approaches, the main idea emerging from philosophical theories is, as Le Gu er highlights it, the notion that smell is a "flair", an intuitive sense that is not necessarily used for rational thinking. However, modern understandings of smell challenge this view, and more generally the very concepts of perception, subjectivity, objectivity, and intentionality, as we will further explore in Chapter 3.

### 1.3. EXPERIMENTAL PERSPECTIVE

During the Greek antiquity, odors were considered as waves or distinct entities depending on the writers. For Aristotle, there was a distinction between odors which were in their essence positive or negative, with the same reaction for everyone at any time, and other smells which could be different depending on the contexts. Later, Galen intertwined his theory of the four humors with smells, arguing that odors consistent with one's humor would be experienced as pleasant, while the others would be unpleasant. Progress in the comprehension of the biology of olfaction was made in the 20<sup>th</sup> century, in part with the invention of the olfactometer in 1895 by Zwaardemaker. Indeed, it allowed for a more systematic diffusion and measure of smells. For example, Gamble tested the Weber's law to measure the just noticeable difference between odors, one of the first attempts to apply principles of psychophysics to olfaction. In 1920, Dyson was the first scientist to propose that smells were molecular in nature, but it was not before 1991 that future Nobel prizes Linda Buck and Richard Axel discovered the family of genes coding for the olfactory receptors in the nasal epithelium, allowing for a fine-grained investigation of the biology behind olfaction.

In addition, many attempts were made to find primary odors, or at least primary categories of odors, to better understand the complexity of the olfactory space. In the 18<sup>th</sup> century for example, Carl Linnaeus ambioned to classify elements of the natural world, including odors. For him, they fell into 9 categories, namely ethereal, aromatic, balsamic, musky, alliaceous, burnt, caprylic, fetid and repulsive. In the 20<sup>th</sup> century, Henning proposed his own classification, with only 6 categories: rotten, flowery, fruity, spicy, burnt, and resinous. Also, Amoore<sup>19,20</sup> came with a number of primary odors (ethereal, camphoraceous, musky, floral, minty, pungent and putrid) based on his research on specific anosmia. However, such simple models were quickly invalidated as many odorants did not fit easily into them, and as the more recent discovery of the combinatory activity of olfactory receptors discards the idea of the existence of such primary odors.

For the scientists of the beginning of the 20<sup>th</sup> century, the evolution theory was a good explanation for the putative lesser importance of smell compared with other sensory modalities. Chemosensation is the first sense to have emerged in the evolutionary process, and it is also the second to develop during fetal growth. With the progressive enlargement of the brain and the development of other senses such as vision, humans relied less on their sense of smell, which is reflected at the neural level. Indeed, in other species, like mice or dogs, the relative size of the olfactory bulb (the first central neural structure in the olfactory processing) is higher than in humans. Also, we have only around 400 functional olfactory genes<sup>21</sup> compared to 800 for

dogs and 1000 for mice<sup>22</sup>. In addition, humans lack a functional vomeronasal organ, a structure which is crucial for chemosensory communication in other species. This led Broca and other researchers to state that humans are a microsmatic species.

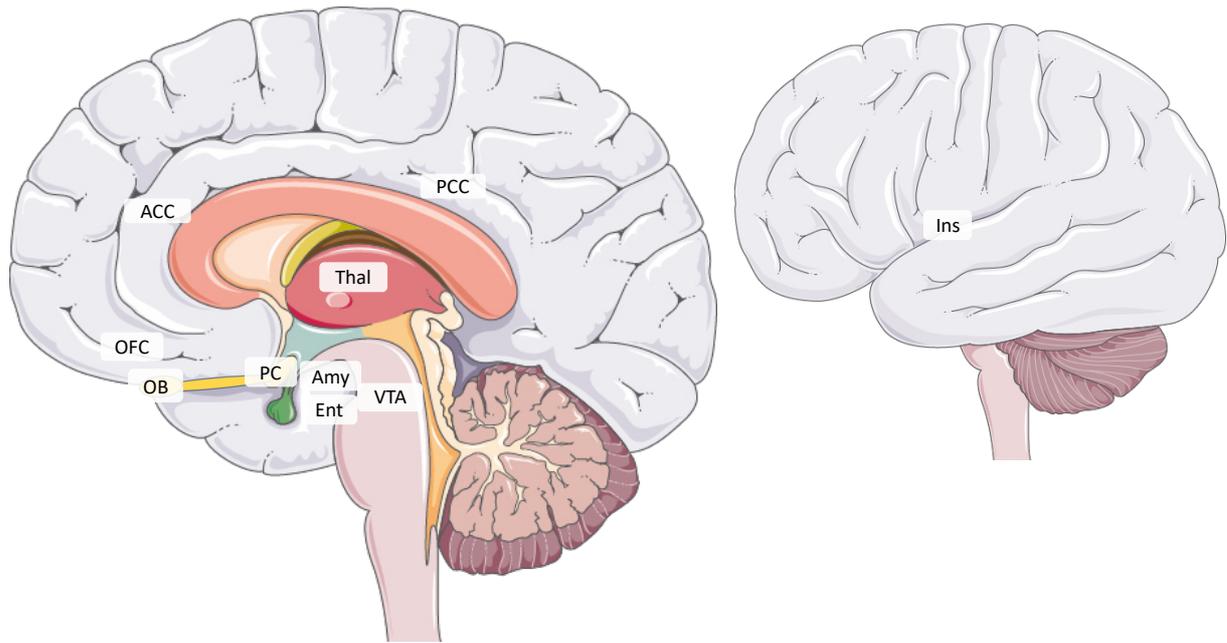
This view was little challenged until the end of the 20<sup>th</sup> century, when it was found that not only humans can discriminate between more than a trillion of odorants<sup>23</sup> (although this number was critiqued, see Gerkin and Castro's response<sup>24</sup>), but they also have detection thresholds comparable to other macrosmatic species for certain compounds (such as sulfuraceous molecules 2,2-dimethylthiethane or 3-mercapto-3-methylbutan-1-ol)<sup>25</sup>. Also, there are evidence for olfactory communication in humans<sup>26</sup>, even if most of it is unconscious. These recent results suggest that, as Mc Gann writes: "poor human olfaction is a 19<sup>th</sup> century myth"<sup>6</sup>. In the following part of this chapter, we will then review the anatomy and functioning of human olfaction as it is currently understood.

## 2. THE OLFACTORY SYSTEM

### 2.1. ANATOMICAL PATHWAYS

In this section, we will briefly explore how odors are processed in the brain from the peripheral receptors to the higher-order areas, as well as the interaction between olfactory and other networks.

Once upon a sniff, there were odorants, volatile compounds that are emitted by various sources, often in a form of a mixture. For example, the scent of a common rose contains around 300 different molecules. The chemical structure of odorants is a major player in how their interact with the receptors, especially regarding their molecular weight, number of rings and number of functional groups<sup>27</sup>. Olfactory receptors are present in the cilia of the olfactory neurons' dendrites, on the surface of the **olfactory epithelium**. This structure is located in the superior part of the nasal cavity, and there are two routes for odorants to reach it: the orthonasal pathway, through the nostrils, and the retronasal pathway, when the volatile molecules are liberated in the mouth and go up to the olfactory epithelium through the nasopharynx. Within the olfactory epithelium, each neuron expresses a single type of receptor, and around 400 functional types have been identified in humans<sup>21</sup>. Note that we have 1000 olfactory genes coding for the receptors, but 63% are pseudogenes and are not expressed in the phenotype. Depending on the individuals, the pattern of receptors varies, which can lead to differences in perception.



**Figure 2. Schematic representation of the olfactory regions in humans.**

*OB = Olfactory Bulb, OFC = Orbitofrontal cortex, PC = Piriform cortex, Amyg = Amygdala, Ent = Entorhinal cortex, VTA = Ventral Tegmental Area, Thal = Thalamus, ACC = Anterior cingulate cortex, PCC = Posterior cingulate cortex, Ins = Insula. Adapted from Mantel et al (2019)*

In general, a single odorant binds to several receptors and a given receptor respond to different molecules, which leads to a combinatorial pattern of activation of the epithelium for each compound<sup>28</sup>. In some cases, however, a receptor will respond to only one molecule or very similar ones. Interestingly, there is a certain mapping of pleasantness even at this early stage of processing. Indeed, Lapid and colleagues<sup>29</sup> showed that areas of the olfactory epithelium that responded maximally to stimulation with a pleasant odorant also responded to other pleasant odorants, and vice versa for unpleasant odorants.

The axons of the olfactory neurons will then cross the cribriform plate to reach the **olfactory bulb**, in bundle structures named glomeruli. Each glomerulus will receive the inputs from neurons expressing the same type of receptors. Although initial studies in mice found a topographical organization of the glomeruli at the macroscopic level<sup>30</sup>, fine-grained electrophysiological investigations did not reveal any particular spatial organization at this level<sup>31</sup>. However, another study in mice showed that the pleasantness of odorants may be represented at the olfactory bulb level<sup>32</sup>.

Note that contrary to other sensory modalities, the information does not go through the thalamus before reaching cortical areas. As the thalamus has been proposed as a crucial structure for the extraction of relevant perceptual information and perceptual consciousness, the case of olfaction suggests that these functions are likely performed in intermediary structures of the olfactory system like the olfactory bulb or the piriform cortex<sup>33</sup>.

After the olfactory bulb, the primary olfactory cortex is the next player in the story. It is constituted of the piriform cortex, the amygdala and the entorhinal cortex, which all receive direct afferences through the olfactory tract<sup>34</sup>. Regarding the **piriform cortex**, several studies

found higher activation of the piriform cortex for unpleasant odors compared to pleasant ones<sup>35,36</sup>. This effect of hedonics is even greater in the anterior piriform cortex compared to its temporal part, for both real stimulations<sup>37–39</sup> and imagined odors<sup>40</sup>. The temporal part instead responds more to intense odors compared to weak ones<sup>41,42</sup>. In addition, it has been shown that the anterior part of the piriform cortex represents physicochemical characteristics of odorants while the posterior part is more involved in the representation of olfactory perceptual qualities<sup>34,43,44</sup>. As for the **amygdala**, it is involved in affective processing regardless of the sensory modality<sup>45</sup>. This area represents the complete spectrum of valence of olfactory stimuli, but also trigeminal characteristics<sup>43,46</sup>. It is more activated for unpleasant odors compared to pleasant ones<sup>35,36</sup>, but also for intense odors<sup>41</sup> and for odors with high emotional value<sup>47</sup>. Finally, the **entorhinal cortex** responds more to intense versus weak odors<sup>42</sup>.

The secondary olfactory cortex mainly comprises the orbitofrontal cortex and the insula. The **orbitofrontal cortex** (OFC) is involved in multisensory integration of hedonics<sup>48–50</sup>. It especially represents the reward value of food, and its activity is modulated by the hunger state of individuals<sup>51</sup>. In addition, the affective dimension of odors is dissociated in this region: pleasant odors tend to activate more its medial part, whereas unpleasant odors activate more the lateral part<sup>41,42</sup>. Activity in the medial part is also influenced by the label associated to an odor, e.g. “food” versus “body odor”<sup>52</sup>. Finally, the OFC represents odor quality and identity<sup>53</sup>. The anterior **insula** is a primary gustatory area, but also plays a role in olfaction. It has been shown that it is activated during olfactory stimulation, with a dissociation between the left and anterior insula more activated for unpleasant odors and the right more activated for pleasant odors<sup>35,54,55</sup>, even for imagined odors<sup>40</sup>. In addition to these main structures, other areas respond differentially depending on odor valence, including the anterior cingulate cortex<sup>42,56</sup>, the ventral tegmental area<sup>57</sup> and the olfactory tubercle<sup>58</sup>.

Note that the olfactory system is not the only one responding to odorants within the nose. The ophthalmic branch of the trigeminal nerve also has ramifications throughout the surface of the nasal epithelium, and is responsible for the perception of heat, cold, irritation and pain associated to many odorants, such as capsaicin or menthol. The cell bodies are in the trigeminal ganglion, and they project to the thalamus. Then, the information goes to the primary and secondary somatosensory cortex, the insula and the orbitofrontal cortex, as well as the piriform cortex<sup>59</sup>, suggesting a significant overlap between the activation of the trigeminal and the olfactory system<sup>60</sup>.

In summary, throughout this brief overview of the olfactory network, we see that it is closely intricated with the trigeminal system, but also with the limbic system, a network involved in general affective and memory processing<sup>45</sup> which includes the amygdala, hippocampus, cingulate gyrus and hypothalamus. We can also notice that pleasantness is represented in each step of olfactory processing. About this point, at the beginning of my PhD, I wrote a bibliographic review of cerebral representation of the hedonic component of odors. This review was published in Brain Topography (see *Article 1*).

## 2.2. THE CENTRAL ROLE OF HEDONIC VALENCE

As we showed in the previous section, pleasantness or hedonic valence is a central element of olfactory processing. It is also an important aspect in people's verbal descriptions of odors, especially when odors are negative<sup>8,61a</sup>. There is a large literature demonstrating the importance of this dimension in people's perceptions<sup>9,62-65</sup>. During my PhD, I was involved in the writing of the second edition of a book chapter about the relation between emotion and the senses. In this chapter, I especially emphasized the tight association between olfaction and emotional processes (see *Article 2*). This happens even in very early stages of life. Indeed, in newborns, we can observe hedonic reactions to unpleasant odors<sup>66</sup>, as well as a preference for the amniotic fluid and odors of foods eaten by the mother during the last weeks of pregnancy<sup>67,68</sup>. Also, children as young as 3 years old are able to point at odors they like or do not like and display similar odor preferences to adults<sup>69,70</sup>. In contrast, odor identification abilities are not fully developed until adolescence<sup>71</sup>, as they necessitate experience and appropriate language skills. And even then, adults are notoriously bad at naming common odors, with a success rate around 40% without any cues<sup>9</sup>. It is thus not surprising that when categorizing odors, individuals tend to group them into pleasant and unpleasant groups rather than separating them according to their source<sup>72</sup>.

In order to investigate the weight of odor pleasantness in olfactory processing, Licon and colleagues<sup>73</sup> asked 22 participants to smell 105 odorants and to rate them on 24 semantic descriptors (e.g., floral, fruity or vegetal) and 8 perceptual dimensions (e.g., intensity, pleasantness, warmth or irritation). Their physiological reactions to odors were also recorded (skin conductance, finger pulse frequency, skin temperature and changes in abdominal respiration). The authors found that pleasantness ratings were highly correlated with the first principal component of the olfactory, semantic, and physiological space, highlighting the importance of hedonic value in all areas of olfactory processing. Note that when it comes to the second component, there was a high correlation with trigeminal features in that case.

A variety of physiological parameters are indeed influenced by odor pleasantness: compared to pleasant ones, negative odors are associated with higher activity of the facial corrugator muscle, higher heart rate variations and smaller volume and duration of sniffs<sup>74-76</sup>. It has also been suggested that skin conductance magnitude is negatively associated with odor pleasantness<sup>77</sup>, although other studies did not find any specific relationship<sup>75,78</sup>. In addition, negative food-related odors are detected faster and more accurately compared to positive and non-food odors<sup>79</sup>. Interestingly, food odors are also better identified compared to non-edible ones<sup>80</sup>. This food-based dissociation is also an important part of odor processing, as edibility is a significant parameter organizing the semantic space of odors as well<sup>65</sup>. Beside edibility, odor pleasantness is also influenced by its intensity<sup>81,82</sup> and its familiarity to the subject<sup>72,77,82</sup>.

This importance of pleasantness, edibility and trigeminal features is not surprising as the main function of the olfactory system is to detect sources of food and to protect the organism from potentially toxic substances<sup>83</sup>. In combination with other sensory channels, smell is indeed a very important part of food behavior, whether at a distant or proximal level. During my PhD,

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<sup>a</sup> A negative odor refers to an odor that is usually perceived as unpleasant and disgusting, in opposition to a positive or pleasant odor.

I co-wrote a review on the contribution of the senses to the overall food emotional experience, which was published in *Food Quality and Preference* (see *Article 3*) and that stresses the interaction between smell, taste, texture and even audition. Regarding the effect of smell alone, Zoon and colleagues<sup>84</sup> asked 29 participants to smell different odors (beef, chocolate, melon and cucumber) signaling either a sweet or savory taste, and either a high or low energy meal. Then, they asked them to rate their appetite for 15 products. The results showed that the presentation of a sweet odor was associated with an increase in appetite for sweet products, but not savory ones, and conversely, a savory odor led to higher appetite for savory foods, but not for sweet ones. It was the same for the energy levels: a high-energy odor led to an increased appetite for high-energy food and conversely. It has also been shown that the hunger hormone ghrelin increases the sensitivity to odors<sup>85</sup>. Humans are even able to follow an olfactory trail of chocolate if they have to!<sup>86</sup>

Smell is also a very useful means to detect dangerous substances. This is reflected in our abilities to process negative odors, which are detected faster and better<sup>79</sup>, and do not decrease with age contrary to positive odors<sup>87</sup>. Sensitivity to potential dangerous compounds such as sulfur is very high, and even superior to other species<sup>25</sup>. A lot of avoidance reactions to olfactory stimuli are learned too. Stevenson and colleagues showed that there was a transmission by the parents of reactions of disgust and avoidance to their children<sup>88</sup>. We learn to avoid immediate threats (such as spoiled food or feces) very early, and animal and body odors in our later development. Such innate and learned avoidance of certain compounds bear an evolutionary significance as it is linked to survival.

Furthermore, odors are a powerful means of communication in a lot of species like mice or dogs, but in humans too. Body secretions like sweat, tears or sperm can be detected by the olfactory system of our peers and may influence their organism. Human leucocyte antigen, or HLA is an ensemble of genes involved in the immune system, and fertile individuals tend to prefer the body odor of people with a dissimilar HLA to theirs<sup>89</sup>. It also appears that sex and sexual orientation can be conveyed through chemosensory channels, although studies are mixed<sup>90</sup>. In the case of babies, they are able to recognize and orient towards their mother's breast in a few minutes after birth<sup>91</sup>. In addition, certain emotional states can be conveyed through body odor. For example, smelling the sweat of individuals exposed to a stressful situation is associated to higher alertness and startle reflex<sup>92</sup>, as well as a higher activity in the amygdala<sup>93</sup>. Finally, body odors are important for kin recognition<sup>90</sup>.

With regards to these main functions of olfaction, an olfactory loss, whether partial (hyposmia) or complete (anosmia) can have severe consequences on one's life. Patients with smell disorders report lower appreciation of food, changes in food intake and appetite, cooking difficulties, inability to detect spoiled foods, smoke and gas, as well as social and hygiene issues<sup>94</sup>. This overall change in quality of life<sup>b</sup> may contribute to symptoms of depression in patients<sup>95</sup>. Conversely, depressed individuals can present olfactory impairment as well<sup>95,96</sup>. This association could be due to the shared neural connections between the olfactory and limbic system.

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<sup>b</sup> In the context of the COVID pandemic, I was involved in two studies measuring the importance of olfactory disorders in the monitoring of the pandemic, as well as the effects of COVID-related anosmia and their influence on quality of life. These articles are respectively presented in Annexes 1 and 2.

In conclusion, odor perception is mainly characterized by its pleasantness, which allows for appropriate approach and avoidance behaviors. In other terms, to like or to not like, that is the -olfactory- question. However, although the affective tone of odors is important, it can bear different significance across individuals depending on several factors of variation.

### 3. INDIVIDUAL VARIABILITY IN ODOR PERCEPTION

In the previous sections, we evoked the general anatomical pathway for odor processing and the predominance of hedonics in smell perception. However, not everyone perceives the olfactory world in the same way. Olfaction has even been considered as a pure subjective sense, depending only on personal experience and thus not comparable between individuals. Although such statement is quite exaggerated, it is true that peoples' perception of the same odor can vary greatly, especially in terms of hedonic valence<sup>97</sup>. As we will see in the next paragraphs, such variability comes from various factors, at different levels of processing.

#### 3.1. AT THE GENETIC LEVEL

As we mentioned in the section on olfactory anatomy, we are not equal regarding the olfactory receptors that we express in our olfactory neurons. Indeed, an analysis of 356 olfactory receptor genes in 26 individuals showed that among their 235 genes expressed in average, only 25% of them were expressed in all participants<sup>98</sup>. This can influence the subsequent perceptual experience since the same compound will not necessarily activate the same set of receptors across individuals. Usually, several molecules can bind to a single receptor and several receptors can be activated by a single compound, but in some cases, there is an exclusive or highly preferential relationship between a given odorant and a certain type of receptor. Depending on the combination of alleles one possesses for the gene coding for such receptor, one may not be able to detect the associated odorant. For example, Keller and colleagues<sup>99</sup> investigated the link between allele combinations for the gene coding for the receptor OR7D4 and the perception of two very similar odorants, androstenone and androstadienone. They showed that individuals presenting RT/RT allele combination smelled both odorants significantly more intensely than individuals with RT/WM and WM/WM combination of alleles, the latter group being unable to detect them at all. Such phenomenon, called *specific anosmia*, has been demonstrated for other compounds and receptors, like beta-ionone and OR5A1<sup>100</sup> or cis-3-hexenol and OR2J3<sup>101</sup>. Specific anosmia can have a significant effect on people's perception of certain foods (e.g. wine<sup>102</sup>, pork<sup>103</sup>) and must be considered when investigating individual differences in odor appreciations.

#### 3.2. AT THE PHYSIOLOGICAL LEVEL

Odor perception is not stable: depending on the context, some odors will bear more or less significance for the individual. Hunger is a major player in the appreciation of food odors. Indeed, Havermans and colleagues compared the pleasantness of odors, one of chocolate and

one of potato chips, before and after participants binged on chocolate<sup>104</sup>. They showed that after stuffing one's stomach with free chocolate, the chocolate odor was rated less pleasant than before, but there was no change for the odor of chips. This phenomenon is called sensory-specific satiety, and is retrieved at the cerebral level, as the OFC is less activated for a food odor that was consumed compared to one that was not<sup>48</sup>. When hungry, individuals better detect food odors<sup>105</sup>, and even non-food odors<sup>106</sup>. They also exhibit longer and larger sniffs for all types of odors<sup>107</sup>.

Another factor of influence is the hormonal state. Indeed, Doty and Cameron showed a positive correlation between the estradiol and estrone levels and olfactory sensitivity in women<sup>108</sup>. More generally, it seems that in the fertile phase, olfactory thresholds are generally lower<sup>109</sup>. However, the use of oral contraceptives does not seem to affect smell abilities<sup>110</sup>. For pregnant women, although higher sensitivity to odors is often reported, the evidence is sparse and such changes seem to be idiosyncratic<sup>111,112</sup>.

Finally, the emotional state of an individual modulates olfactory abilities as well. For example, Pollatos and colleagues<sup>113</sup> showed positive, negative and neutral pictures to a group of subjects, and then presented them with n-butanol. They found that exposure to unpleasant or pleasant images led to a higher detection threshold compared to neutral ones. In addition, participants rated the same odor as less pleasant in the unpleasant condition compared to the neutral and positive conditions. Also, in another study, the authors found that the cortisone level increase in response to a stressful situation was related to a higher capacity to identify odors, but that on the contrary, feelings of anger were associated with reduced identification abilities<sup>114</sup>.

### 3.3. AT THE PERSONAL LEVEL

At the individual level, the main factor of variation is age. Indeed, like other sensory systems, there is a progressive loss of olfactory abilities with age, a phenomenon called *presbyosmia*. All facets of smell perception are affected, whether it is detection, discrimination or identification<sup>115</sup>. This is associated with the drying of the nasal mucosa and olfactory bulb, the diminution of the foramina in the cribriform plate (where the olfactory nerve passes through the cranial bone), the damaging of olfactory receptors, the accumulation of pollutants, and the general cognitive decline<sup>115</sup>. This loss can have severe consequences: indeed, a longitudinal study showed that, controlling for other factors such as dementia, depression or disability, individuals above 70 years old with low odor identification scores had an increased risk of mortality of 36% compared to those who showed higher olfactory abilities<sup>116</sup>. As we saw earlier in this chapter, smell loss is associated with impaired abilities to detect spoiled food or smoke, which can be very detrimental for elderly people living alone.

In addition to quantitative changes in olfactory abilities, age also has an impact on perceived pleasantness of odor, as it was shown by Jousain and colleagues<sup>117</sup>. They compared hedonic ratings for 20 various odorants in young and old adults and found that pleasant odorants were rated as less pleasant by the older individuals compared to the younger ones, but also that age did not affect hedonic judgment of negative odors. This could be explained by the biological importance of detecting potential threats throughout the lifespan.

Another factor of variation is sex. Women tend to have better detection, discrimination and identification abilities than men<sup>118,119</sup>, even though a recent meta-analysis showed that this difference remains relatively small<sup>120</sup>. Several theories have been proposed to explain such results. As we saw in the previous section, hormonal differences could play a role. Also, traditional gender roles encourage women to be more aware of their olfactory environment, through cosmetic products and home cooking for example<sup>109</sup>. Higher verbal abilities and lesser occupational exposure to pollutants in women are also considered as potential mediating factors<sup>120</sup>.

Furthermore, the context associated with the odor can influence its perception. For example, if the same odor of isovaleric acid is presented as a body odor, individuals will rate it as more unpleasant than when it is presented as a cheese odor<sup>52</sup>. Similarly, ambiguous odors positively labeled by the experimenter are rated as more edible by the subject compared to when they are presented negatively by their label<sup>121</sup>. In another experiment, Dalton<sup>122</sup> presented 9 odors to a group of participants, either telling them they were natural healthy extracts or potentially toxic substances. Interestingly, they showed an adaptation of their detection threshold after a continuous exposure when odors were associated with health, but the subjects instead become more sensitive to odors when they thought they were toxic. Overall, these results demonstrate the importance of top-down processes in olfactory perception.

Finally, variations in olfactory abilities can result from certain conditions. For example, patients with neurodegenerative disorders like Alzheimer's and Parkinson's disease have impaired olfaction<sup>123</sup>, a symptom that is often dismissed by healthcare providers but may be an interesting tool for differential diagnosis<sup>124</sup>. Olfactory abilities are also lower in patients with schizophrenia and major depressive disorder<sup>95,96,125</sup>.

#### 3.4. AT THE CULTURAL LEVEL

Individuals' cultural background is also a major factor in their reaction towards odors. Indeed, in a given group, the social significance of smells can vary. For example, Western civilizations tend to prefer asepticized environments and value light and floral perfumes. In other areas, such as the island of Bohol in the Philippines, odors are an important part of one's social life, whether it is in cooking and eating, in medicine, in religious services, and in communication with the ancestors<sup>126</sup>. Body odors are especially important as they indicate identity, sex, and social status. The Boholanos are thus very attentive to such odors, and it is common behavior to tell a stranger that they have a bad smell. Similarly, the Semaq Beri, who live in the Malay peninsula, avoid mixing their body odors with their relatives as it is socially inappropriate. They also have a hunter-gatherer lifestyle and spend a lot of time in the forest. In comparison, the Semelai, who live in the same area, have a more sedentary lifestyle, and do not have specific beliefs about social odors. When asking individuals in these two populations to name different odors<sup>127</sup>, the Semaq Beri do not manifest difficulty and use mostly abstract terms, whereas it is harder for the Semelai who use mainly source-based and evaluative terms, similarly to Westerners.

The place of smell in a given population can be also affected by the olfactory richness of the environment, like the presence of greenery, flowers, animal husbandry, warm and humid climate, and industrial activity. For example, Sorokowska and colleagues<sup>128</sup> compared olfactory sensitivity for n-butanol in several areas: Poland (modern society with high air pollution), the Cook Islands (modern society with low air pollution), and the Tsimane in Bolivia (traditional society with low air pollution). They found that the Polish participants had significantly higher odor detection thresholds compared to the other groups, suggesting that air pollution may play a role in olfactory abilities.

There are also differences in the pleasantness of odors depending on culture, especially for the ones that are food related. Ferdenzi and colleagues<sup>129</sup> compared the responses to common odors in three different countries: Switzerland, England and Singapore. They found significant differences in hedonic ratings between the groups. For example, cinnamon, honey, and mushroom odors were more appreciated in Switzerland compared to the others. However, Singaporeans manifested far less disgust for the odor of durian, a fruit commonly consumed in South Asia, compared to the Europeans who disliked its very strong and pungent smell. Another study<sup>130</sup> compared the perception of mint in French people with an European culture or with an Algerian culture, in which mint is a traditional component of cuisine. The authors found that the Algerian French, who had earlier exposure to mint in their life compared to the European-French, used more references to personal memory when describing the odor and even had a different electroencephalographical activity for the mint odor. However, a recent study investigating the hedonic ratings of 10 monomolecular odorants across 10 diverse populations<sup>131</sup> showed that pleasantness was generally consistent between the group, and that the physico-chemical structure of the stimuli and individual variability explained more variance than cultural factors. However, the odors used in their experiment were not controlled on their edibility or importance in culinary habits for each culture, which does not discard the possibility that food odors could have elicited higher cultural diversity in pleasantness.

Altogether, intercultural studies show that individual olfactory experience is also a social phenomenon, shaped by shared beliefs on odors, culinary habits, and environment. It is interesting to investigate how people verbalize such experience with their counterparts, as we will see in the next section.

## 4. ODORS AND LANGUAGE

### 4.1. THE MUTED SENSE?

Diane Ackerman famously wrote that “olfaction is the muted sense, the one without words”. For Almagor<sup>132</sup>, the subjective experience of odors has its own private language, and there is an inherent incompatibility between the meaning of an odor for the individual and the social norms for it. Thus, contrary to a color or a sound, an odor is not constructed collectively and is rather embedded in personal experience<sup>133</sup>.

This importance of subjectivity is an issue for research on the olfactory language since this area used methodologies and theories from vision even though some concepts are not easily applicable for smell. One major issue is the supposed existence of a veridical (or true) label for anything that is found in the world. However, in olfaction it has been shown that people have difficulties to associate an odor to a name even though this odor may be very vivid in their memory<sup>10,133</sup>. Experimenters often expect participants to give a specific name for an odor, which is considered as the veridical label. It usually corresponds to a common source that evokes an olfactory sensation that is like the one presented to the subject. The issue is that there is not necessarily a consensus between the experimenter and the participant regarding such name, which is very problematic when conducting studies aiming at constructing a semantic theory of olfaction.

Dubois and Rouby<sup>64</sup> thus propose that several elements must be reconsidered in the case of smell. First, a name does not necessarily refer to an objective world entity. Second, an individual does not always have access to a lexicon for stored semantic representations allowing her to retrieve correct labels. Finally, an odor may not be a cognitive representation of objects in the world, but rather a representation of the volatile odorants present in the air, that may not necessarily be associated to a specific object. Therefore, we must reconsider the nature of the relationship between olfactory representation and olfactory language, without resorting to lexical theories constructed from other senses.

So, how do people describe odors if not by their veridical name? David tells us that the most used elements are the source, intensity, associated memories, pleasantness, effect on the individual and use, with a particular focus on the source and the effect<sup>134</sup>. Her French corpus was constituted of subjective accounts, but also of some sort of shared knowledge. This shared experience can manifest in the form of similar reactions for a given odor, the use of a communal vocabulary or the same meaning associated to a descriptor<sup>135</sup>.

To investigate how subjective experiences of odors are shared with others, Baccino and colleagues asked 36 participants to smell an odor and to describe it to another person, who then had to recognize this odor among a selection. The authors showed that correct recognitions were quite low, around 50%. Verbal descriptions involved depictions of source, intensity, valence, and effect, but paradoxically the richer they were, the poorer was the recognition rate. Such failures could be due to unfit descriptions and perceptual misconceptions, from both the participants in the verbal exchange. Regarding the type of names attributed to odors, Huisman and Majid<sup>136</sup> demonstrated that it was easier to name odors with high-frequency names, as well as familiar and edible odors. In another study, Iatropoulos and colleagues<sup>137</sup> showed that common odors are described with high-frequency and non-olfactory-specific terms (often vague or borrowed from other sensory modalities) rather than with olfactory-specific but rare terms.

At the brain level, there is some evidence that the olfactory system is weakly connected with linguistic areas. Oloffsson and Gottfried<sup>138</sup> point out that the cortical elaboration of odor representations is limited compared to other senses, and that their vague format leads to a non-specific activation of semantic concepts and more errors in attributing names to odors. However, when visual cues are provided, there is feedback from the ventral visual stream toward the olfactory areas, which allows for better odor object coding and ultimately better chances to name the odor.

In summary, given the subjective nature of olfactory experience and the difficulty to share a common language for odors, the idea of a muted sense of smell is widely accepted. For Hudson and Distel, this is due to the necessity for the olfactory system to adapt to the extremely large number of stimuli it can encounter. In addition to the combinatorial activity of the olfactory receptors, the system is very flexible, allowing for rapid learning of the relevant information in one's environment. Thus, each individual trajectory will lead to a unique set of representations and meaning for odors, not easily shareable with others<sup>139</sup>. But then, if learning is so important for the olfactory system, what happens when a population is specifically trained to develop a language for odors?

#### 4.2. THE CASE OF EXPERTS

Several professions, like perfumers, cooks, enologists, or coffee specialists routinely work with odors. Such experts have developed an extensive system of classification and characterization of odors, with hours and hours dedicated to learning to detect, discriminate, and identify various olfactory compounds. They developed a restricted number of semantic descriptors, although these cannot be compared to primary colors for example: they designate a set of odors considered as prototypes and the similarity of a given note to these references<sup>140,141</sup>

In a study comparing the verbal descriptions given by novices and experts, Sezille and colleagues<sup>61</sup> asked 64 participants (either novices, flavorists, perfumers or cooks in training) to describe 20 odorants. They found that novices used more hedonic terms to describe the odors compared to the other groups, and that perfumers and flavorists mentioned more chemical terms, olfactory qualities, and sources than novices and trainee cooks. This echoes the learned strategies for perfumers to distance themselves from the pleasantness of odors and instead classify them according to their use for certain perfume compositions<sup>140</sup>. Also, the higher use of metaphorical and abstract terms in trained panelists and experts<sup>61,142</sup> compared to novices, with no changes in hedonic or intensity ratings<sup>61</sup>, suggests a change in cognitive representations of odors rather than a modification of perceptual representations<sup>140</sup>. Interestingly, another recent study showed that wine professionals and connoisseurs use more references to collective experiences when describing wine odors, whereas wine consumers and panelists mainly used individual experiences<sup>143</sup>. This highlights the ambition of a shared linguistic framework in experts compared to non-experts regarding to odors.

However, despite these attempts at a shared language for odors in the community, Pintore and colleagues<sup>144</sup> showed that around 40% of odorants are actually described with very different profiles in two major atlases in the domain, the Arctander and the "Perfumery Materials and Performances 2001" (<http://www.leffingwell.com/programs.htm>). Moreover, these atlases do not contain descriptors for all the possible olfactory space, but rather for a limited set used in the perfumery industry. Another study showed that wine and coffee experts are not more consistent when describing odors compared to novices, even if they display different strategies of verbalizations: when novices used more emotional terms, wine experts used more non-source and abstract terms, and coffee experts less affective terms<sup>145</sup>.

The extensive training of olfactory experts allows them to talk about odors in their professional activity with colleagues sharing a learned lexicon, something very difficult for most untrained people. This shows that the muted aspect of smell is not set in stone, and that we can acquire a form of olfactory language if it is contextually important.

#### 4.3. INTERCULTURAL APPROACHES

In 1916, Henning<sup>146</sup> wrote the following: “*Olfactory abstraction is impossible. We can easily abstract the common shared color – i.e., white – of jasmine, lily-of-the-valley, camphor and milk, but no man can similarly abstract a common odor by attending to what they have in common and setting aside their differences*” (cited by Majid and colleagues<sup>147</sup>).

However, it is not that simple. Indeed, one of the major problems in research on human cognition (and olfaction is no exception), is that the vast majority of the studies are conducted in Western countries, 96% of them to be exact, when they only represent 12% of the world population<sup>148</sup>. Moreover, the participants are undergraduate students in psychology 4 times out of 5. Henrich and colleagues<sup>148</sup> refer to this phenomenon as the WEIRD issue, as general knowledge on cognition is generated only from Western, Educated, Industrialized, Rich and Democratic populations. Given the variability in relationship to smell in social, food, and religious contexts in different communities, the absence of abstract vocabulary for odors in most Western languages does not mean that all other languages are devoid of it as well.

As for Boisson<sup>149</sup>, there is great diversity in olfactory language across cultures, as their environment may vary depending on climate, vegetation, animal husbandry and food habits. In a study comparing 60 various languages on their olfactory lexicon, the linguist found a common trend of a lack of usual terms referring to odors, and an importance of pleasantness in the vocabulary (especially negative terms). He also noticed a significant anthropocentrism in the olfactory space, with higher frequency of terms related to body odor, urine, feces, and in a lesser extent to spoiled food and animals.

More recent studies show evidence for odor abstraction in some languages. For example, the Jahai, who live in Malaysia and Thailand, have a dozen of olfactory verbs, that are psychologically salient and do not refer to one source or category only<sup>150</sup>. When asked to name an odor, English speakers predominantly use source-based descriptors (e.g. flower, food), whereas the Jahai use almost exclusively abstract terms (e.g. *p[ʔeŋ]* to refer to a blood/fish/meat-like smell, or *[tpit]* to refer to a fragrant smell such as flowers, perfumes or bearcat)<sup>150</sup>. Also, although both groups have similar facial responses to the same odor, the Jahai spend around 2s to identify an odor when Dutch speakers spend 13s<sup>147</sup>. This specific olfactory vocabulary does not seem to depend on the language per se, but rather on the lifestyle of a community. Indeed, the Semaq Beri and the Semelai are two groups with similar language (a branch of Malaysian), but with very different lifestyles, as the former are hunter-gatherers and the latter sedentary. The Semaq Beri describe odors mainly with abstract olfactory terms whereas the Semelai use predominantly source-based and evaluative terms<sup>127</sup>. Another example is the case of Boholano, a Malayo-Polynesian language, which differentiates between four types of smells, namely perfume, flowers, axillary smell, and feces. As body odors bear a large significance in their

culture, their language includes abstract general references to body odors and dirtiness, but also abstract gendered references and abstract terms for specific types of body odors<sup>126</sup>.

In a global study investigating the hierarchy of the five senses in 20 languages, Majid and colleagues<sup>151</sup> measured the ability for individuals in a given linguistic community to express a set of sensory properties (color, shape, texture, odor, taste and sound), with the Simpson's diversity index. This index reflects the degree of consensus on a term within a group, also referred to as codability. The authors found that, compared to other senses, olfactory terms were significantly less codable in most of the studied languages. However, in some cases, like in Siwu (Western Africa), Lao (South Asia) and Umpila (Oceania), codability was comparable to other sensory modalities, even if locutors used different strategies to describe the odor stimuli: Siwu-speakers mostly used source-based terms (similarly to most other languages), whereas Lao-speakers mostly resorted to abstract terms and Umpila-speakers mainly to evaluative terms. Interestingly, Aristotle's conception that some senses are more accessible to consciousness and expressible in language, which is commonly accepted in Western philosophy, is not consistent across the 20 languages that were investigated here: although Aristotle ranked the senses from vision, audition, touch, taste all the way down to smell, taste was the most codable sense in half of the cases.

What can we learn from such intercultural approaches regarding olfactory language? Well, despite an apparent poverty of odor lexicons in most languages, some cultures maintain a strong connection with their olfactory world, either because to their hunter-gatherer lifestyle or because of the social meaning of certain smells. This is translated into their language in the presence of a dedicated, commonly used vocabulary for odors that bear significance. This is not surprising given the high plasticity of the olfactory system, which is shaped by the cultural environment of individuals and their need to share an experience with their counterparts.

## 5. CONCLUSION

In this first part of the manuscript, the aim was to review the general principles of olfactory processing in humans, complemented by three review articles written during my PhD. We showed that the sense of smell had a significant social and cultural importance in the history of the Western civilization, despite many philosophers belittling it as a manifestation of animality, sexuality and intuition, in opposition to higher-order forms of perception like vision. Within the biological sciences, olfaction was considered as underdeveloped in humans until very recently, although modern studies show that odors are still a major part of our lives. Our nose allows us to detect food, to avoid threats and to communicate with our peers. Odors are highly emotional, which is reflected at the cerebral level with a large overlap of the olfactory and limbic areas. This does not mean that everyone feels the same way about a given odor though, as many factors can affect olfactory processing and perception. Smell is also very subjective, which is reflected in our limited abilities to talk about smells without training.

From this overview of the olfactory system, one may wonder how actually diverse we are in our perception of odors. Is it true that smell is purely idiosyncratic? What is the actual weight of the factors of variation that we identified? Do people still share a common experience for certain odorants? In the next chapter, we will focus on these issues, and especially the

distinction between the shared and individual aspects of odor processing. We will also approach the complicated issue of the structure-percept relationship in olfaction, to better understand how the chemical features of odorants are related to a given perception.

## Chapter 2 - DIVERSITY AND UNIVERSALITY IN OLFACTION

### - Different strokes for different folks? -

In the previous chapter, we presented an overview of the sense of smell as we understand it today, including the olfactory neural system, the importance of hedonics, the functions of smell, its relationship with language and factors known to influence the perception of odors. We showed that the same odor can evoke different experiences both intra-individually and inter-individually. To what extent and why do people differ in their perception of odors? Are all odorants prone to such perceptual diversity or are there some that are universally pleasant or unpleasant? In this chapter, we will further explore these questions of diversity and unity in the olfactory experience, through a series of studies. First, we will take advantage of a database collected in a large-scale study on the prevalence of smell deficits in France<sup>c</sup> to uncover the factors involved in interindividual variability. Next, we will discuss the stability of perception through the issue of the stimulus-percept, a major problematic within the olfactory community, and how accounting for inter-individual variability in the perceptual experience of odors may help to better understand this relationship.

### 1. FACTORS OF VARIATION IN SMELL PERCEPTION: A PORTRAIT OF OLFACTION IN FRANCE

#### 1.1. CONTEXT AND OBJECTIVES

As we saw in earlier sections, the sense of smell is essential for food behavior, social communication, and detection of danger, as well as general well-being. Although other sensory deficits are well known and studied, olfactory disorders are often overlooked by both the individuals suffering from it and from medical practitioners. However, they are quite common in the population and are associated with serious deficits in some cases. In the article corresponding to *Annex 3*, we present a summary of the studies that estimated the prevalence of smell deficits in different countries, either by directly asking participants to evaluate their sense of smell or by performing psychophysiological measurements. With subjective reports, the average prevalence of olfactory disorders is 9.3% (based on the results of 7 studies in 4 countries). However, when using objective testing, which is more costly and time consuming but more accurate, olfactory deficits are estimated to affect 23.5% of the population on average, including around 16.7% of hyposmia and 3.5% of anosmia (based on the results of 12 studies in 6 countries). In France however, there is yet no large-scale study that investigated the

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<sup>c</sup> The data of this study was collected before starting my PhD. I was involved in the creation and organization of the database and in the writing of the draft of the manuscript (see *Annex 3*). In the context on my PhD, I had the opportunity to perform a complementary analysis on the perceptual data to investigate the factors contributing to the interindividual variability.

prevalence of olfactory disorders in the general population. To this end, our research team launched a national study through a scientific newspaper, inviting participants to smell several odors on scented cards received by mail and then answering an online questionnaire. Contrary to other similar studies, this experiment aimed to compare self-assessment of olfactory capabilities with objective measurement of smell, in a large sample constituted of children, adults and elders. This allowed for the investigation of the benefit of an objective test of olfaction compared to subjective assessment, which has consequences for clinical contexts.

In the context of this thesis, which is not centered around olfactory deficits, we will still present a summary of the original results of this study as they are important to understand the pervasiveness of dysosmia in the general population, and especially the proportion of individuals self-assessing as normosmic when they have a deficit. This element must be accounted for when conducting olfactory studies with non-patients as they could declare to have a normal sense of smell but have a different experience than other participants due to their unknown deficit.

I had a minor contribution to this first study on prevalence, but the data collected was very relevant for my own research, especially to characterize different olfactory profiles and their factors of variation. Indeed, this dataset had many advantages. First, with a very large sample of participants (more than 3000 respondents), we can obtain a very diverse set of perceptual experiences that may not have been caught with the typical sample sizes in psychophysiological experiments on olfaction. Secondly, odors were evaluated with 5 perceptual dimensions, allowing for a limited, but still multi-faceted characterization of one's olfactory experience. Thirdly, the chosen stimuli were very common, and maximized the chances for the participants to have encountered the odorants, with potential various personal trajectories related with them. Also, the stimuli were associated to different olfactory functions and could be associated with food, people, danger, or hedonic pleasure. To differentiate between these types of odors, we chose to analyze the perceptual patterns for each individual odorant. Finally, a total of 23 potential factors influencing perception of odors were also measured in the online questionnaire, which allowed us to assess their impact on individuals' ratings.

In this first part, we will thus briefly present the methodology of the study and the principal results of the original analysis on the prevalence of olfactory disorders (detailed in Annex 3), as well as a second analysis focused on perceptual variability that I conducted during my PhD and that is detailed in *Article 4*.

## 1.2. METHODOLOGY

*Participants.* Participants were recruited in France, through a scientific newspaper ("Le journal du CNRS") which included a set of 8 odors to scratch and sniff at home. They were all provided with a link to a website to take the study. In total, 3685 individuals (2085 women, age 4-89) took the online experiment. We selected a time window from November 25<sup>th</sup>, 2014, to January 28<sup>th</sup>, 2015, to minimize the temporal differences between the participants and the odorants.

*Stimuli.* The 8 odors used in this study were the following (target identification, Compound Identification number, concentration): *L-carvone* (mint, 439570, 22.5%), *trans-anethole* (anise, 637563, 23.5%), *valeric acid* (body odor, 7991, 2.25%), *alpha-pinene* (pine, 6654, 22.5%), *beta-ionone* (flower, 638014, 28%), *cis-3-hexenol* (grass, 5281167, 28%), *isoamyl acetate* (banana, 31276, 5.6%) and *tetrahydrothiophene* (gas, 1127, 22.5%). The odorants were packed into microcapsules, and then printed on cardstock to be scratched and sniffed by the participants.

*Protocol.* For each of the 8 odors, participants were asked to identify them among four choices, and to rate their pleasantness, intensity, familiarity, edibility, and irritation, on a scale from 1 (extremely low) to 5 (extremely high). Other measured variables included sex, age, profession, level of education, laterality, time of last meal, native language and country, smoking habits, medical conditions and treatments, and menstruation cycle for women. In addition, participants responded to questionnaires about parosmia<sup>152</sup>, food neophobia<sup>153</sup> and food habits<sup>154</sup>. Details about the questions are available in *Annex 3*.

*Data analysis.* In a previous pilot experiment, a Linear Discriminant Analysis (LDA) was conducted on a sample constituted of 19 normosmic and 19 patients diagnosed with an olfactory deficit by an ENT physician. This method allows to predict a dependent variable (normosmic or dysosmic) as a linear combination of independent qualitative and quantitative variables. Three models were tested: model A (including the 8 odors and 5 perceptual dimensions, namely intensity, identification, familiarity, edibility and pleasantness); model B, same as A but without odors known to elicit specific anosmia or to highly stimulate the trigeminal system (including only *L-carvone*, *isoamyl acetate*, *trans-anethole* and *alpha-pinene* as odorants, and the same 5 perceptual dimensions); model C, same as B but with the 2 perceptual variables weighing the most in model B (including the same 4 odorants, but with identification and intensity dimensions only). Model A correctly classified 90% of the 38 participants. For model B and C, the rate was 92%. These three models were then used in the present study as a predictor for the olfactory status of each of the 3685 participants, whose olfactory status was unknown this time. In parallel, we created an olfactory space (constituted of the five perceptual dimensions, namely intensity, familiarity, edibility, pleasantness, and identification) and an eating space (constituted of 13 variables, namely neophobia score, willingness to try new foods, eating pleasure, number of added condiments, eating preferences for vegetables, fruits, meat, fish, starch, and dairy products, cooking habits, consumption of prepared meals, and eating in restaurants). Then, we correlated the first two components of each space resulting from a Principal Component Analysis.

For the second analysis on perceptual variability, we identified several clusters of individuals for each odor with a hierarchical clustering (based on Ward distance). Then, we compared these clusters on 17 factors of variation (namely, age, BMI, sex, handedness, profession, level of education, identification score, self-assessment of smell abilities, parosmia score, neophobia score, pleasure in eating, number of added condiments, smoking habits, time since last meal, presence of a cold, olfactory disorder, and sensory disorder), to determine how the clusters would differ. In addition, we computed the skewness and kurtosis of the distribution of the pleasantness ratings to determine odorants with high variability in ratings or low variability.

### 1.3. RESULTS OF THE ORIGINAL STUDY: PREVALENCE OF OLFACTORY DISORDERS

Using the three LDA models constructed from a pilot study, the prevalence of olfactory disorders in the French population was estimated at 17% with model A, 12% with model B and 10% with model C. This was a higher rate than individuals who self-assessed with poor olfaction, which represented 6% of the sample. In fact, around 16% of participants who thought their sense of smell was normal had a deficit. Olfactory disorders were more frequent in older adults (60-89 years old), with 31% of the sample compared to only 10% for the 4-12 years old. Also, men had higher rates of deficits compared to women (13-17 years old:  $X^2(1) = 4.56$ ,  $p = .03$ ; 36-49 years old:  $X^2(1) = 12.8$ ,  $p < .001$ ; 60-89 years old:  $X^2(1) = 4.56$ ,  $p = .03$ ). Regarding qualitative deficits, parosmia was estimated to affect 1.2% of the sampled population. In addition, when comparing the olfactory space and the eating space in each age group, there was a significant relationship for the 60-89 group, with a low willingness to try new food and high neophobia, as well as high consumption of meat and dairy, and less consumption of vegetables and prepared meals ( $r = .25$ ,  $p_{\text{uncorrected}} = .008$ ,  $p_{\text{Bonferroni}} = .06$ ).

What do these results entail? First, the prevalence results are like estimations made in other countries, both in terms of psychophysical measurements and in self-assessment of olfactory capabilities. In this study, we compared these two types of measurements in the same large sample of individuals, and we showed that self-evaluation is not very accurate compared to actual testing with odorants. This can have consequences in clinical contexts: indeed, one of the main issues in ENT consultations is time. A complete psychophysiological assessment with a formal test can include 16 (Sniffing Sticks<sup>155</sup>) to 40 odorants (University of Pennsylvania Smell Identification Test<sup>156</sup>), which may take a major part of the appointment. In this regard, a brief evaluation tool can be of interest. Here, the third model, containing only four odorants and two ratings for each, still had better predictive value of olfactory impairment than self-assessment. This suggests that brief tests of olfactory function could be used in clinical contexts instead of self-assessment alone: even though they have lower predictive value than a complete evaluation, they still allow for detection of severe hyposmia.

Also, the present study gives us some information about the eating habits associated with an olfactory disorder in the elderly. Here, even though the correlation was small, and the results must be taken with caution, it is relevant at a clinical level to be aware of dietary specificities in patients with olfactory disorders, as they can increase risks for nutrients deficits or certain diseases. Interestingly, no relationship between olfactory status and eating habits was retrieved for younger adults and children. One explanation is that eating patterns are influenced by many other sensory, contextual, and social parameters, and that the amount of food behavior affected by smell deficits is larger in older individuals compared to other age groups.

In conclusion, this large-scale study allowed us to draw a portrait of olfactory perception and its disorders within the population. We also found a small association between such deficits and eating patterns in older individuals. Altogether, these results demonstrate a significant presence of dysosmia in the population (17%), suggesting that an important part of individuals have a different or even non-existent olfactory experience for common odors of their environment

compared to their peers. This can partially explain the variability in olfactory evaluations within experimental settings, as recruited individuals may report a normal sense of smell when they have an unknown olfactory impairment that can influence their responses. Many other factors may also be at play in olfactory perception, and the next part of the analysis aimed to identify how common factors of variation may influence the assessment of the 8 odorants tested here, as shown in *Article 4*.

#### 1.4. RESULTS OF STUDY 1: PERCEPTUAL VARIABILITY IN A LARGE POPULATION

Regarding perceptual variability, we decided to analyze each odorant separately. Indeed, as odorants bear different functions for the perceiver (e.g., food, social or hazardous<sup>83</sup>), it may be relevant to study them at the object-level instead of a global analysis. With a hierarchical clustering, we were able to identify between two and five clusters of individuals with a similar perception for each odorant.

Then, we compared the identified clusters on different parameters, to determine what could explain the different perceptual profiles. The first observation is that the clusters identified for each odorant do not necessarily differ on the same variables. Indeed, smoking habits had a small influence on perceptual clusters for GAS and ANISE only. Regarding the presence of cold or olfactory disorders, there was a small influence of this factor for the ANISE, MINT, PINE and BANANA clusters. Willingness to eat new meals and neophilia score had a small impact on the clusters for ANISE and PINE. About pleasure in eating, there was also a small effect MINT and BANANA clusters. Interestingly, although the correct identification of the odor moderately or largely influenced the perceptual clusters for all tested odorants, the total identification score for all odorants was a factor of variation only for ANISE, BANANA, GAS and PINE and always had a small effect size. This suggests that general olfactory abilities play a little role in determining one's perception of a single odorant. The same can be said about self-assessment of such capacities, which had a small effect for all odorants except for MINT.

Regarding age, one of the most important factors influencing smell abilities, it had a small influence for all odorants, except for FLOWER, GAS and PINE. This absence of age-related differences in these cases could be explained by several elements: regarding gas, an odor that is usually perceived as negative and dangerous, it has been shown that perception of negative odorants is not impacted by age, probably because of the evolutionary importance of danger-indicating odorants<sup>157</sup>. The flower odor, constituted of beta-ionone, is particular in the way that there is a consequent amount of the population that has specific anosmia for this compound<sup>100</sup>. In that case, interindividual differences maybe mostly mediated by genetic variations rather than aging or sex (also not influencing the cluster in this experiment). Regarding the pine odor, there is no specific reason for the absence of effect of age and sex, and it seems that differences are driven more by willingness to eat new meals than other variables.

This separate analysis for each odorant suggests that some factors of variation are retrieved for most odorants (like age or sex), and others are more specific to the nature of the odorant (like food-related variables for edible odors). We also showed that all these factors have a quite small influence on the perceptual patterns overall. This means that we need more adequate types

of measures to better understand what drives the perceptual experience of the individuals and its different trajectories. Finally, the fact that we were able to characterize different patterns of perceptual experience for all odorants shows that perception of odors is not a unified object. This diversity in people's subjective experience of an odor is often left aside in olfactory research. However, we argue that this variability is of major importance for the researchers interested in what we call the stimulus-percept issue, i.e., the relation between the structure of odorants and the perception they evoke.

In the next section of this chapter, we will further develop the implication of perceptual variability in this field of research.

## 2. STABILITY AND DIVERSITY OF THE OLFACTORY PERCEPT

### 2.1. CONTEXT AND OBJECTIVES

#### 2.1.1. WHAT IS THE STIMULUS-PERCEPT ISSUE?

One of the hardest – and thus most fascinating – questions in olfactory research is the following: how does a volatile molecule can evoke an olfactory experience? It is usually associated with other secondary questions, such as: why do not all molecules evoke a smell? Why do molecules with similar physicochemical structures do not necessarily evoke the same perception, and conversely why two close odors can be evoked by very structurally different molecules? Solve this, and you will be a legend in the olfactory community<sup>158</sup> and probably beyond.

In practice, many studies aimed at relating certain chemical characteristics with semantic or perceptual features of odorants. For example, the molecular complexity of odorants is positively correlated with the pleasantness of the associated odor, as well as the number of associated olfactory notes<sup>159</sup>. Also, pleasant molecules tend to be larger and to contain oxygen, whereas carboxylic acids and sulfurous compounds are commonly rated as unpleasant<sup>160</sup>. Regarding semantics, Gutierrez and colleagues were able to predict descriptors for a set of molecules characterized in perfumers' atlases with moderate accuracy<sup>161</sup> using a model based on natural language descriptions. In addition, by reducing physicochemical features and semantic descriptors of 144 odorants from the Dravnieks' atlas<sup>162</sup> to a few principal components with PCA analysis, Khan and colleagues<sup>163</sup> were able to predict the position of new odorants of the first semantic component (mainly associated with pleasantness) from their position on the first chemical component, with a correlation of .50. Furthermore, the DREAM<sup>164</sup> olfaction challenge aimed at predicting intensity, pleasantness and 19 semantic qualities of a set of 476 odorants through machine learning algorithms from different teams. The best models were able to predict intensity and pleasantness from chemical features with an accuracy of about 0.5 and 0.4 respectively. However, semantic descriptors were poorly predicted, with an average of 0.2, except for the number of sulfur atoms which was highly associated with descriptors "garlic" and "fish.

More recently, we conducted in our team a study investigating the relationship between chemical features of 1700 molecules and their associated semantic descriptors, to uncover descriptive structure-percept rules, in which I had a minor involvement (see *Annex 4*). We especially found that there was more than one simple rule for most of the olfactory qualities, except for a few simple relationships, like the presence of sulfur in the odorant and the descriptor “sulfurous” like in the previous study. Thus, contrary to a particular wavelength associated with a specific color, or a sound frequency with pitch, this is not that straightforward in the case of olfaction.

Through all these experiments, the parameter that seemed to be predicted the most by chemical features of odorants is their pleasantness. After all, this makes a lot of sense as we saw in the earlier section that the hedonic value is the most relevant feature of an odorant and determine one’s behavior. The pleasantness would thus be associated with certain molecular features cueing the nature of the compound and its potential toxicity. However, we also showed the high variability in pleasantness that exists for some odorants. Knowing this, how can algorithmic models account for such variability? Taking the mean hedonic rating of an odor at face value can present a biased version of the actual diversity in people’s experience, and even the best estimations did not predict pleasantness of odorants that highly. This suggests that we may have to review the stimulus-percept issue to better understand this relationship. In the next section, we discuss two aspects of the problem that must be reconsidered.

### 2.1.2. RECONSIDERING THE PARAMETERS OF THE EQUATION

The first element in the stimulus-percept problem is, well... the stimulus. In the studies described here, the physicochemical structure of the odorant was the input, whether as simple models only including molecular weight or complexity, or as very large datasets with thousands of characteristics. However, the interaction between the odorants and the olfactory receptors located in the nasal mucosa, is also an important part of what we call the stimulus. Humans have around 400 types of receptors, whose combinatorial activity allows for a unique pattern of response for thousands of molecules. Thus, what may be of interest for an analytic chemist may not be the case for a biologist interested in olfactory research. Poivet and colleagues<sup>165</sup> proposed that tested odorants should be socially or evolutionary relevant rather than randomly chosen depending on their chemical characteristics, which simplifies the olfactory space. In their study, they used medicinal chemistry to select relevant chemical features for biological processes and investigated how mice olfactory receptors neurons reacted to different esters. This allowed them to characterize crucial molecular features important for odor perception, with better results than chemical-only machine learning algorithms, like the ones presented in Keller and colleagues in the DREAM olfaction challenge we evoked earlier<sup>166</sup>. In addition, this methodology combining chemistry and biology also helped to uncover key physicochemical features related to the discrimination of odorant acetophenone<sup>167</sup>. More recently, a computational study using 34 deorphanized (i.e., for which ligands are known) human olfactory receptors in vitro demonstrated that their activity patterns can accurately predict 146 perceptual characteristics of odorants<sup>168</sup>, with a better performance than chemical-only-based models. The authors also applied their algorithms in vivo on drosophilae, whose olfactory receptors have all

been deorphanized, and showed that the behavioral valence of the same odorants was better predicted with receptor activities compared to chemical features only. These studies thus suggest that the ligand-receptor interaction should be considered in addition to chemical information to better understand the relationship with perception. In practice, studying olfactory receptors in humans *in vivo* is quite difficult. Indeed, I don't know many people that would accept their nose to be cut out. To circumvent this issue, we used an electronic nose as a model of such receptors, as it will be further explained in the next section.

Regarding the second part of the equation, i.e., perception, the output provided to machine learning algorithms usually is a set of semantic descriptors chosen from a list by a group of subjects, as well as ratings of intensity and pleasantness. For example, the DREAM olfaction projects included the rating of 19 descriptors like “fish”, “sweaty” or “woody”. Although these types of measurement are routinely used in studies on olfaction, they have several important flaws. First, they do not cover all aspects of odor perception, as other variables are important for the individuals when they experience an odor, such as edibility, familiarity or trigeminal activation<sup>43</sup>. Secondly, these measures do not allow the individuals to choose their own words to describe the odorants. The provided terms are often taken from professional characterizations of odors (such as Dravnieks' atlas<sup>162</sup>) and are often vague or redundant for non-experts: for example, the descriptor “bakery” can be interpreted in many ways and used differently by naive participants<sup>164</sup>. Keller and colleagues<sup>164,166</sup> themselves acknowledge a great diversity in the use of these descriptors among subjects, which can bias the measures that are then entered in algorithms.

Finally, we already showed that olfactory perception is quite diverse, especially in terms of pleasantness. It is due to many factors, such as age, sex, genetics, cultural background and life experiences<sup>97,129,169</sup>. And yet, it seems that for some odorants, the hedonic value is quite stable among individuals and comparable to other species<sup>170</sup>. This could be related to the biological salience of such stimuli, as they indicate food or potential hazards for example<sup>83</sup>. In sum, olfactory perception comprises a shared, homogenous part for some relevant odorants, but it also includes a highly variable, heterogenous dimension which is often let aside in algorithms relating chemistry with perception. One way to account for this is to investigate the relationship between olfactory receptors responses for odorants evoking similar percepts among individuals and for odorants eliciting diverse experiences. To this end, an electronic nose can be a good model of the receptors' activity patterns, as explained thereafter.

### 2.1.3. AN ELECTRONIC NOSE COMES TO THE RESCUE

An electronic nose (e-nose) is a technological tool used for artificial olfaction, which analyzes volatile compounds present in air samples. Contrary to other methods like gas chromatography, an e-nose's aim is to characterize the qualitative odor profile of a sample rather than its fine-grained molecular composition<sup>171</sup>. As they are easily manipulated, they are a good candidate to replace human panels in certain industries. E-noses have been successfully used in several domains, including food quality control<sup>172,173</sup>, discrimination of food products<sup>174,175</sup>, assessment of pollutants<sup>176</sup>, and discrimination of diseases<sup>177</sup>. Developers tend

to increasingly use peptides as receptors<sup>178</sup> as they are easy to assemble, and this is great news for fundamental olfactory research.

Indeed, biologically inspired devices offer a very promising tool to study the interaction between chemicals and receptors. Newer generations of e-noses are built aiming to mimic natural olfaction, and especially to reflect human perceptual categorizations. Such composition allows for better interpretation of e-nose responses and may constitute a good tool to model the current missing link between ligand-receptor interaction in the olfactory mucosa and perceptual experience evoked by an odorant. For example, with an e-nose and machine learning algorithms, Haddad and colleagues<sup>179</sup> showed that the hedonic value of odorants could be predicted by the response of an artificial nose. However, regarding the semantic dimensions associated to odorants, there is yet no attempt to associate semantic descriptors with e-nose activation.

So, how does an artificial system can mimic natural olfaction? We know that humans and other species have hundreds of types of olfactory receptors, that are mostly non-selective, meaning that they can respond to many stimuli, and that an odor can bind to many receptors. Therefore, manufacturers use in the same manner non-specific peptide receptors, that allow for a combinatorial pattern of activity corresponding to an odor “olfactory code”. By choosing certain peptides over others, electronic noses can thus be tuned to respond to specific types of stimuli or tasks.

Here, we were interested in using a biologically inspired e-nose to relate its response with both chemical properties and semantic descriptors associated to an odorant, in the wake of Haddad’s results predicting pleasantness from an artificial system’s activity. However, to properly relate chemistry and perception with an e-nose, one must closely control the parameters of the apparatus, as well as the experimental protocol if used manually. To this end, we first conducted during my PhD a study with two objectives: to identify experimental sources of variance impacting an e-nose response, and after having them removed as much as possible, to relate this activity with semantic description of odors. We showed that there was indeed a relationship between the e-nose activation patterns and semantic terms for the tested odorants. Then, in a second study, we used the same apparatus to relate its activity with both perceptual ratings and verbal descriptions of odorants. We also investigated the role of interindividual perceptual variability in such relationship. The results showed that the e-nose responses were correlated with these two measures of perception, but only for odorants eliciting little variability in pleasantness judgements between the participants, which we will discuss the consequences. In the next section, we will present a summary of these two experiments, reported in *Article 5* and *Article 6* respectively.

## 2.2. STUDY 2: RELATING ARTIFICIAL AND NATURAL OLFACTION

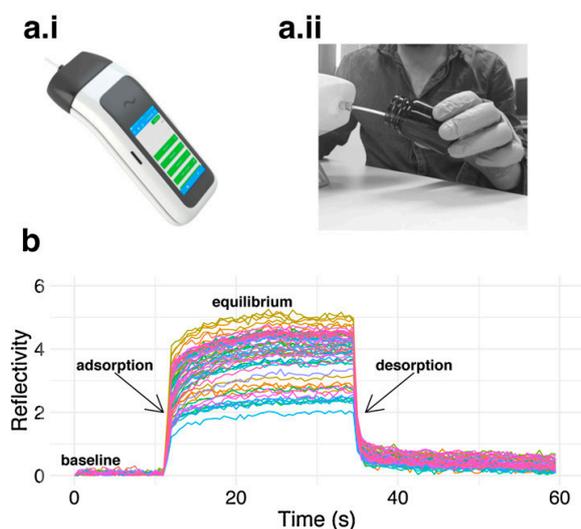
### 2.2.1. METHODOLOGY

In this first study detailed in *Article 5*, our first scientific question was to identify the different source of variance affecting the performance of an opto-electronic nose. We hypothesized that the experimenter, as well as the time between the preparation of an odorized

vial and its testing would have an impact on the response patterns. Our second aim was to relate the activity of the e-nose with human olfactory perception. We hypothesized that e-nose response patterns would be related with odor pleasantness like in Haddad et al<sup>179</sup>, but also to semantic descriptors.

*Opto-electronic nose.* In this study, we used an opto-electronic nose (NeOse Pro, #310 model, Aryballe Technologies SA, Grenoble, France) based on Surface Plasmon Resonance Imaging. It is constituted of 64 peptide sensors reversibly binding to volatile odorants. Its simplified mechanism is as follows: a continuous flux of air arrives to a chamber containing the sensors and a prism coated with gold. The volatile odorants bind to the sensors, and a polarized light is sent through the prism onto the sensors' surface. The binding of the odorants results in the lighting of the sensor spot, with various intensity depending on the strength of the association. A video camera records the dynamic changes in reflectivity, that are then normalized for each sensor to get its relative activity in response to the odorant stimulation.

A full trial includes three steps: first, unodorized air is delivered to the e-nose to get a baseline. Second, the odorants binding to the sensors increase the overall reflectivity of the sensors' surface in what is called the *adsorption* phase. An *equilibrium* is then reached when there are the same number of odorants binding to the receptors as odorants detaching from the sensors. Third, the odorants progressively detaching from the sensors is called the *desorption* phase. The difference between the activity at the time of the equilibrium and the baseline activity provides us with a normalized vector with 64 dimensions (one for each sensor). This vector is the input data for the subsequent analysis. **Figure 3** shows the experimental design for the e-nose acquisition of signal.



**Figure 3. Experimental design for the e-nose signal recording (adapted from Article 4).** a.i. Prototype of the e-nose used in the experiment. a.ii. Example of manual measurement with the e-nose aspiration from an odorized vial. b. Example of a graph representing the changes in relative reflectivity for each sensor as a function of time.

*Stimuli.* In this experiment, we used the dataset of odorants in a previous study from our team (*Annex 4*), that covered well the chemical space, constituted of 105 odorants. It was then reduced to a set of 92 molecules compatible with the e-nose. Each sample contained 1 mL of pure odorant in a colorless, transparent glass flask with a volume of 60 mL. For the solid substances, the mass equivalent of 1 cm<sup>3</sup> was calculated based on the molecule's density. The protocol involved each stimulus to be presented three times to the device in a flask, once per experimenter (2 in total: MM and MP). There was an interval of four minutes between each trial, to allow for complete regeneration of the sensor array.

*Perceptual data.* Perceptual data was obtained from the same previous study<sup>73</sup>, in which 22 volunteers rated 105 odorants (including the ones used in this study) on 8 perceptual variables (here, we considered only intensity and pleasantness among them) and 24 semantic dimensions.

*Data analysis.* All analyses were conducted in R (version 3.5.2) and JASP (version 0.11.1). After data acquisition was completed, we excluded all trials with an insufficient signal strength using threshold values recommended by the e-nose manufacturer, resulting in a final dataset of 88 odorants.

## 2.2.2. RESULTS AND DISCUSSION

*Identification of sources of variation.* A first analysis compared the measurements acquired by the two experimenters. There was a significant yet weak association in the pairwise distance between odorants response patterns for MM and MP ( $r_{\text{Mantel}} = .33$ ,  $p < .001$ ). However, when removing the trials in which the delay of acquisition was superior to 15 odorants between the experimenters (which ending up in 61 remaining odorants), this association became far stronger ( $r_{\text{Mantel}} = .85$ ,  $p < .001$ ). The results thus show an effect of the experimenter on measurements for this handheld device, and an effect of the delay between preparation and measurement with the e-nose. This may be due to several factors, including humidity, storage condition or natural decay.

*Relation between e-nose and chemical space.* A chemical space was constructed with 2603 chemical features (obtained from Dragon software, Talete<sup>®</sup>). Then, the first three Principal Components resulting from a Principal Components Analysis (PCA) in the chemical and e-nose space with correlated. The results showed a significant relationship between PC3<sub>E-Nose</sub> and PC1<sub>Chemical</sub> ( $r = .52$ ,  $p < .001$ ), between PC1<sub>E-Nose</sub> and PC3<sub>Chemical</sub> ( $r = .36$ ,  $p < .001$ ). This suggests that, like in natural olfaction, there is a similarity between the chemical features of odorants and the receptors' patterns of activity.

*Relation between e-nose, perceptual and semantic space.* Then we compared the perceptual dimensions (intensity and pleasantness) with the e-nose principal components. We found a non-significant correlation between pleasantness and PC1<sub>E-Nose</sub> ( $r = .23$ ,  $p = .07$ ), in the general line of Haddad and colleagues<sup>179</sup>, but the weakness of this association should be discussed. One explanation could be the differences in the technology behind the e-noses used in the

experiments. Another would be the fact that the odorants chosen in the present study were supposed to represent the whole chemical and perceptual space of odorants, with no particular focus on their pleasantness contrary to Haddad et al. This would increase the variability between odorants, which could then not be related to the single dimension of pleasantness. Regarding the semantic space, there was a significant relationship between PC1<sub>Semantic</sub> and PC1<sub>E-Nose</sub> ( $r = -.35, p < .001$ ). Interestingly, the descriptors that weighed the most in PC1<sub>Semantic</sub> (i.e., “human”, “decay”, “animal”, “fermentation” on one side and “floral”, “medicinal”, “grassy” on the other) relate to the main functions of smell, namely the detection of danger, social communication, detection of food and hedonic pleasure. Such organization of the e-nose response around biologically relevant odorant features is comparable with the organization of the olfactory receptors in natural systems.

In conclusion, this experiment is to our knowledge the first to show a relationship between the activity of an artificial nose and semantic descriptors provided by humans. This opens the way for newer generations of e-noses centered around human perception and categorization of odors, which could be of importance in the fields of perfumery, agronomy, or other olfaction-related industries as they may help panelists for testing and discriminating new products. In fundamental research on human olfaction, e-noses also seem to be a powerful tool to model the interaction between receptors and volatile odorants. Indeed, like in natural systems, the activity of an artificial array of peptide receptors is correlated with chemical features of odorants, and with perceptual and semantic dimensions as well<sup>29,168,180</sup>.

Following these encouraging results, we decided to include perceptual variability as a potential factor of variation in the response of an artificial nose. Indeed, like we discussed earlier, the current measures of perception used in research on stimulus-percept interaction are not accurately representing the individuals’ experience of odors. Perceptual ratings are usually averaged, which can be problematic if there is high variance in people’s responses. Also, professionally constructed descriptors are presented to the participants, who must rate each one even though they can be vague and not adapted for non-experts in olfaction. In our second experiment, we thus took these two elements into account to better understand the relationship between chemistry, artificial receptors, and olfactory perception.

### 2.3. STUDY 3

In this second study detailed in *Article 6*, our aim was twofold: first, we wanted to compare the activity of an artificial system with human perception depending on its degree of interindividual diversity. Our hypothesis was that the association between the e-nose and perception would be higher for odorants eliciting little variability between individuals compared to odorants evoking diverse perceptions. Indeed, stimuli with high interpersonal perceptual variability would reflect individual trajectories more (including genetics, culture, past experiences...) and would thus be less comparable to the standard response of an artificial system. Secondly, we aimed to use two types of measurement for the perception part: the first would be like current quantitative ratings of odors, and the second would be direct verbal description of odors by the participants, which we hypothesized would be a better representation of their olfactory perception and thus more related to the e-nose activity compared to standard ratings.

### 2.3.1. METHODOLOGY

*Odorants.* In this experiment, we used 20 odorants from the first experiment we presented. They were selected from *Annex 4*, and a pilot study determined the 20 most representative stimuli at the chemical, perceptual and semantic level.

*Opto-electronic nose.* The same apparatus and protocol as in the first experiment were used here. Flasks containing odorants diluted in mineral oil were tested 6 times in total (3 by experimenter MM and 3 by IS), within two days of acquisition.

*Physicochemical characteristics.* The Dragon software (Talete®) was used to extract 82 chemically relevant and easily interpretable structural characteristics for the 20 odorants. We then selected the features with non-null variance only, resulting in 59 descriptors for each molecule.

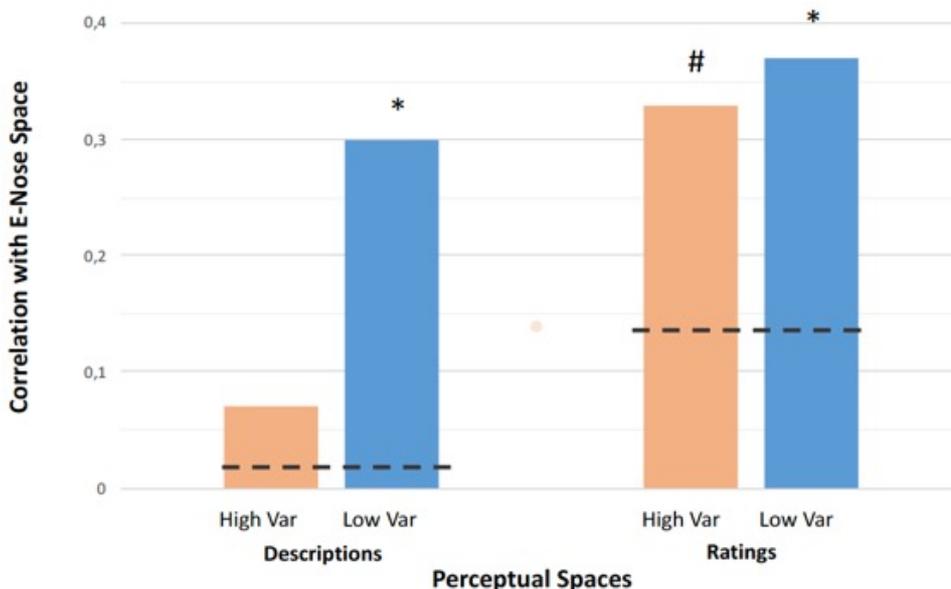
*Human ratings and verbal description of odors.* In total, 74 participants were involved in the experiment. The subjects were recruited from the Technical University of Dresden, Germany (37 participants), as well as in Lyon, France (37 participants). Odorants were this time presented in the same flasks as for the e-nose acquisition, but they contained 1mL of diluted odorant with a concentration corresponding to 1Pa of pressure in the air. The participants were asked to smell and describe their experience of the odors through a short semi-guided interview, in which the experimenter asked generic questions to help them verbalize. The details about the construction and objective of such interview are presented in Chapter 3, as well as the process of the discourse analysis. Here, in the context of this experiment, we will simplify it by considering as verbal description data the number of references made by the participants to 6 types of semantic categories: impact of the odor on the individual, source of the odor, qualitative characterization of the odor, memories associated to the odor, use for the odor and difficulty to verbalize one's experience. Regarding the perceptual ratings, after the verbal description task, the participants rated each odorant on several quantitative scales (intensity, familiarity, edibility, irritation, and pleasantness) from 1 to 9.

*Data analysis.* Like in the first experiment, the odorants were organized into different types of spaces: a chemical space with 59 dimensions, a e-nose space with 64 dimensions, a ratings space with 5 dimensions, and a descriptions space with 6 dimensions. A PCA was conducted on each of these four spaces and the first three resulting Principal Components were compared with each other. Also, we constructed a Euclidian distance matrix of the odorants for each space, and we used a Dissimilarity Matrix Analysis to compare the matrices through a Mantel test. All the statistical analysis were performed with R software (version 3.5.0), with the packages FactomineR for the PCA, and ade4 for the Mantel tests.

### 2.3.2. RESULTS AND DISCUSSION

In a first step of analysis, we compared the ratings and descriptions distance matrices to see if these two measures of perception were related. A Mantel test with 9999 permutations showed that the two spaces were significantly correlated ( $r = .66$ ,  $p < .001$ ). Also,  $PC1_{\text{Description}}$  (34% of the variance) and  $PC1_{\text{Ratings}}$  (59% of the variance) were correlated, ( $r = .84$ ,  $p < .001$ ). Then we compared the e-nose space with both perceptual ones. We found no association between the e-nose and ratings spaces ( $r = .14$ ,  $p = .11$ ) nor between e-nose and descriptions spaces ( $r = .02$ ,  $p = .37$ ).

Next, we performed the same analysis, but this time differentiating between odorants evoking high perceptual variability and odorants with low variability. To this end, we divided the group of 20 odorants on a variability scale, which corresponded to kurtosis (i.e., the tailedness) of the distribution of their pleasantness ratings, as the hedonic value of an odor is the main component driving perception and subsequent behavior. The 10 odorants with the highest kurtosis value (i.e., with a more peaked distribution) were assigned to a “Low variability” group and the 10 with the lowest values (i.e., with a flatter distribution) to a “High variability” group.



**Figure 4. Correlation between the e-nose and perceptual spaces for the Low and High variability group.** The dashed line indicates the correlation between the spaces for all odorants combined. \*:  $p < .05$ , #:  $p < .10$ . (Adapted from Article 5).

When considering the High variability group, we found again a tendential association between the e-nose and ratings spaces ( $r = .32$ ,  $p = .06$ ) and no relationship between the e-nose and descriptions spaces ( $r = .01$ ,  $p = .46$ ).  $PC1_{\text{E-Nose}}$  was nonetheless significantly correlated with both  $PC1_{\text{Ratings}}$  ( $r = -.89$ ,  $p = .04$ ) and  $PC1_{\text{Descriptions}}$  ( $r = -.89$ ,  $p = .04$ ). In contrast, for the Low variability group, we showed this time a significant correlation between the e-nose and ratings spaces ( $r = .37$ ,  $p = .03$ ) and between the e-nose and descriptions spaces ( $r = .30$ ,  $p = .04$ ), as represented in **Figure 4**. Also, there was an association between:  $PC1_{\text{E-Nose}}$  and  $PC2_{\text{Ratings}}$  ( $r = -$

.76,  $p = .01$ ); PC2<sub>E-Nose</sub> and PC2<sub>Ratings</sub> ( $r = -.67$ ,  $p = .03$ ); PC2<sub>E-Nose</sub> and PC1<sub>Descriptions</sub> ( $r = -.87$ ,  $p = .01$ ). We also compared the pleasantness judgements with the E-Nose principal components like in the first experiment and we found a trend between hedonic ratings and PC2<sub>E-Nose</sub>, for the Low variability group only.

Finally, similarly to the first experiment, we found an association between the chemical and e-nose spaces ( $r = .33$ ,  $p < .01$ ), but nothing between the chemical and perceptual spaces (for ratings,  $r = .09$ ,  $p = .20$ ; for descriptions,  $r = .02$ ,  $p = .38$ ).

In conclusion, this second experiment brought us important information about relating natural and artificial systems. Indeed, although our first study did find a significant relationship between the activity of an e-nose and semantic descriptions, the perceptual dimensions of intensity and pleasantness were not related to its response. Here we find that when we consider the degree of perceptual variability evoked by the odors, there is a link between an artificial model of the receptor-ligand interaction and the perceptual experience associated to it. What does this entail? A standard system with an array of peptide receptors, with no specificity to them, is capable to differentiate between different chemical properties of volatile odorants and to provide similar responses for similar molecules. It is also capable to provide similar responses for odorants that are perceptually close (both with quantitative and qualitative characterization) when such odorants are quite universally perceived, but not anymore if the odorants are prone to high variability in the perception they evoke.

These results support our hypothesis that artificial models represent a standard response of the olfactory receptors to odorants, without the inter-individual diversity due to personal trajectories and past experiences. This parameter should be considered for future studies aiming to compare natural and artificial systems of olfaction, as the comparison may be valid only for a certain category of odorants universally liked or disliked, probably because of their biological significance. In the context of this PhD, these findings are even more important as they emphasize the fact that not all odors are subjected to perceptual diversity, contrary to what one may believe at a first glance.

### 3. CONCLUSION

In this chapter, we investigated olfactory perception in different contexts, to determine how universal and variable are people's experiences of odors. In a first study including a very large sample of participants, we were able to characterize several perceptual profiles for each tested odor. We also found that the individual's global olfactory performances (both objective and self-assessed) played a very little role in their olfactory profile for one odorant. In addition, known factors of variation like age, sex, food habits, smoking status... had a small effect on the perceptual groups as well, and did not even necessarily play a part for each individual odor. In other words, it seems that inter-individual variability is driven by personal differences, even though the main known factors of variation on olfactory abilities are not enough to explain it, but also by the type of odorant encountered. In our second and third experiment, we showed that an artificial system can be a useful tool to model the complex relationship between an odorant structure, its interaction with olfactory receptors and human perceptual experience,

given that the odorants are quite universally appreciated as it models the standard biological response of the receptors, not accounting for personal trajectories.

With all this in mind, let us recap where we are in our olfactory journey. We know that people experience odors differently, depending on the nature of the stimuli. We also know that measuring perception - and its diversity - accurately is very important to understand the stimulus-percept relationship in olfactory research. And finally, we know that current measures of perception are limited to fully understand what makes people different in their experience of different odors. In fact, to quote Alexander Graham Bell (1914): *“It is obvious that we have very many kinds of smells, all the way from the odor of violets and roses up to asafetida. But until you can measure their likenesses and differences you can have no science of odor.”* Here, we argue that to measure such likenesses and differences in olfactory perception, we must have a measure of perception that is fine-grained and unbiased enough to capture such variability. This implies that us experimenters must find a way to access the true olfactory experience of participants, or, one may say, their own *subjective* depiction of the odor. There it is, finally, the word that divided the scientific and philosophical communities for centuries, or at least decades of modern science. The subjectivity of one’s perception of the world. Its uniqueness and ineffable nature. The “what it is like to” experience a mental phenomenon. The archnemesis of an objective and quantitative science of the mind. With this unnecessarily dramatic but important distinction, let us investigate the place of subjective experience in experimental research.

## **Chapter 3**

# **THE ISSUE OF SUBJECTIVE EXPERIENCE**

### **- What is it like to smell a bat? -**

In the previous chapters, we investigated the general principles of olfactory perception, as well as the diversity and universality of odor experience, depending on the characteristics of the individuals, but also on the type of odorant they encounter. We discussed the usual methodologies that are used for the measurement of smell, whether they are quantitative with ratings or qualitative with semantic descriptors. These two general kinds of data acquisition have several issues: participants are biased to certain aspects of their experience when experimenters ask them to rate the intensity or the edibility of an odor for example. Also, individuals rarely can use their own words to describe what odors are like to them, as list of descriptors available are arbitrary and not adapted to non-experts. This raises the question of how we can have an accurate measure of the subjective perception of odors while maintaining the necessary rigorous framework of experimental research. This issue of subjectivity has a long history within the field of philosophy of the mind and contemporary cognitive science, as we will further investigate in this chapter.

## 1. CONTEXT AND OBJECTIVES - EXPERIMENTAL RESEARCH AND SUBJECTIVE EXPERIENCE

### 1.1. PHILOSOPHICAL APPROACHES

Like most of research on perception, let us begin with the sense of vision to introduce this philosophical debate. The phenomenal content of visual perception corresponds to the subjective experience of the individual, as in the sensible manifestation to the perceiver<sup>181</sup>. These phenomenal properties are, or at least include specific components which are supposed to be exempted of any reference to the objective reality, and in this way inherently nonintentional. There also are considered as intrinsic, as in independent of the external environment of the individual, as well as ineffable, i.e., beyond expression by common language, and only accessible by introspection and in this sense, private<sup>182</sup>. For example, the sensation of sadness behind blue eyes (poetically reported by The Who) typically is a phenomenal experience, as it is personal and not easily orally described. Nagel<sup>183</sup> formulates the question in animal-friendly terms in his influential article: “what it is like to be a bat?”. Indeed, bats have a system of echolocation that is very biologically different than the visual system: so, what it is like to “see” like a bat? Unless you are a bat, and you can talk to others about it, no one can know what that feels like.

However, most of the reflection on subjectivity and perceptual experience as a whole is based on visual perception<sup>184</sup>. In the case of olfaction, some philosophers claimed that the perceptual experience offered some important particularities, and especially that the representational dimension is absent. It would then be a purely qualitative manifestation, a

“modification of our conscience”<sup>185</sup>. Indeed, how can we perceive the smell of a flower when the flower is absent? Unlike visual perception, there is such a thing as a « floating » olfactory sensation, as it is simply present and disconnected from a particular object<sup>186</sup>. In fact, olfactory experience differs from vision quite a lot. The sense of smell is particular in the sense that we have a dual location of the olfactory sensations: in the nose of course, but also in the mouth, even though we usually do not differentiate spontaneously between what comes from retronasal olfaction or taste, as this is a unified experience. It also lacks a spatiotemporally structure that is usually found in other senses<sup>33</sup>. Finally, contrary to vision and audition, it is difficult to mentally imagine an odor, and not having access to an odor’s name compromises the access to the semantic information associated to the odor while not the case with other senses<sup>187</sup>. However, an odor is rarely presented alone, except in olfactory labs, and most of odors are also bound with visual, auditory or gustatory experience, which allow for an easy access to semantics anyway<sup>188</sup>.

Given the specificities of olfaction, our understanding of the contents of perception may therefore have to be reconsidered to be adequate to the sense of smell as well as other senses. One of the main questions is the nature of smell: do we experience odors as objects or as volatile compounds detached from an object? This philosophical debate is still ongoing<sup>189,190</sup> and aims to give a conceptual framework behind the olfactory experience. The work on smell gives a new light on perceptual processing and challenges existing theories such as the contents of consciousness<sup>187</sup>. In addition, Batty<sup>191</sup> and Lycan<sup>184</sup> argue in favor of the existence of olfactory representations, but that they probably obey to different criteria than those of visual representations. Lycan claims that we experience odors as volatile odorants and that the representation of their source object is constructed at a higher level of processing. As to Batty however, the represented content would indeed be olfactory qualities, but they would not be associated to an object bearing these properties. An important aspect here is the fact that olfactory perception seems to be unique compared to other sensory modalities, in particular because of the importance of its phenomenal dimension. This is in support of our thesis that better characterizing the subjective experience of the individuals is crucial in the experimental study of olfaction. However, it is necessary to question the place of phenomenality in a scientific approach to perception.

In the field of olfaction, several disciplines and approaches have already tackled the issue of individual perception, including historiographies of odors through the centuries<sup>192,193</sup>, the role of smell in social interactions and moral judgements<sup>194–196</sup>, as well as its cultural significance in different populations<sup>127,132</sup>, giving us precious accounts on the subjective experience of smell through space and time. Nonetheless, experimental researchers still lack a proper descriptive model of subjective experience for their protocols, partly due to the traditional opposition between objective experiments and subjective reports. During my PhD, I further discussed issue of subjectivity in olfactory research in an opinion article (*Article 7*).

## 1.2. EXPERIMENTAL APPROACHES

As we just stated, subjectivity of experience is not very well studied in experimental science, and this is not an issue specific to the case of olfaction. In fact, there was a global neglect of

phenomenal experience in modern experimental science, first with behaviorism which denied its mere existence and considered it as an illusion<sup>197</sup>, and then with cognitivism viewing the mind as a succession of information processing steps without the need to include experience<sup>198</sup>. With psychology aiming to consolidate its status as an objective science, researchers in the field resorted to objective and quantitative measures of behavior like response times and constructed theoretical models of information processing during cognitive tasks. Objectivity, as Mascolo<sup>199</sup> puts it, involves an externally observable event, that is unbiased and accurately representing reality.

Introspection, a traditionally used method to obtain knowledge on mind states was thus abandoned as it was not reliable enough, like other types of subjective accounts of one's experience. Indeed, there are multiple sources of bias both from the experimenter and the subject verbalizing its mental state, like social pressure or reconstruction of memories with time. These biases can greatly influence an individual's response and are in contradiction with a reliable, reproducible way to do experimental research. As Jack and Roepstorff<sup>200</sup> ask the question: "why trust the subject" in these conditions? In fact, the cartesian distinction between what is objective and what is subjective is thinner than previously considered. What happens most of the time is what Mascolo<sup>199</sup> calls "intersubjectivity", which refers to the ability to share one's mental state with others. As to him, psychological knowledge is not acquired by either subjective accounts or by objective measurements, but rather by exchanges of experiences between individuals. Therefore, there is no reason to separate objective and subjective events as strictly as modern psychology aimed to do.

Moreover, there is no such thing as a purely objective observation. Indeed, science is made by scientists, who generally happen to be human. We perceive the world through pre-conceptions that will shape our interpretation. Scientists cannot get rid of these frames of mind, but when the data are strong enough, the results will lead to revised pre-conceptions that will be used to create new experiment and so on. Speaking of data, humans are not a senseless combination of limbs and neurons; they are social beings and are viewed as such by scientists, who will infer mental states and behavior based on their own understanding of the world, probably through a kind of mirror system<sup>199</sup>.

Moreover, by focusing on data and methods to interpret data, psychologists may sometimes neglect the necessity to elaborate psychological concepts and framework by means of which they interpret data, to make sense of what is observed in a more general model. In other words, empirical testing is necessary to understand the human mind, but theoretical and philosophical reflection is also an important element to consider. That is why the philosophical considerations about subjectivity and its place in the study of the mind is very important. In olfaction, the conceptualization of the phenomenal experience of odors has not been studied as much as for vision, and it is thus even more crucial to clarify the contents of olfactory perception, both by "armchair" considerations and by experimental research.

Mascolo<sup>199</sup> also brings the issue of measuring perception. In their experiments, researchers often use Likert-type scales to measure certain perceptual or cognitive elements. For example, in olfaction, it is often asked to the participants to rate the intensity of the odor on a scale from "not intense at all" to "extremely intense". This seems like a very easy and publicly observable type of measure, comparable between individuals, thus being the closest we can have to an objective measure of a given aspect of perception. However, it is not a direct measure, as the

subjects must think about what intensity means to them, recollect times in which they experienced different levels of intensity, and match one of these times with what they experience at the moment of the experiment. Through all these steps, there necessarily are modifications compared to their first immediate experience of the odor. In addition, by giving a subject a very specific dimension to focus on, researchers bias his perception in a certain way, depending on the objectives of the experiment and their preconceived ideas about olfactory perception. The use of standardized scales is thus not infallible and may in fact be far less objective than what researchers may think. Other methods of data acquisition have issues too. In olfaction again, participants are also usually presented with a list of possible semantic descriptors of the odors.

Here, we claim that to better understand the subjective perception of odors, olfactory research must take a critical look at its current paradigms and methodologies of perceptual measurement and consider other types of approaches that could help us acquire less biased and more immediate accounts of individuals' perceptual experience.

### 1.3. METHODOLOGIES OF ACQUISITION

As presented in *Article 7*, other fields of research such as sociology, anthropology and philosophy proposed several methodologies to obtain subjective data. One of them is *phenomenology*, based on the work of Husserl<sup>201</sup>. Its partisans claim that it is possible to access reliable content from one's experience, with thorough training and well characterized steps. It involves a temporary suspension of one's beliefs and knowledge to approach experience in a new and unbiased way, and then a series of reduction of one's experience to a few fundamental features. As one may imagine, this is not an easy task and is not often used as it necessitates long periods of training for the participant and an understanding of the concepts behind it.

There are also modern forms of *introspection* that are increasingly used in research, aiming to apply the rigorousness and reliability of experimental science to one's mental states. This renewal of introspective methodologies replies to the need of well-detailed subjective accounts for the study of certain phenomena like dreaming, meditation, pain, or attention. It necessitates less training than the phenomenological approach on the subjects' part. Although some scientists continue to claim the incompatibility of introspection with experimental science, many now acknowledge that this is one of the only ways to obtain valuable data on higher-order cognitive processes<sup>26,27</sup>, and use it to help understand physiological or imaging recordings, as we will see further in Chapter 4.

Finally, clinical psychologists and sociologists often resort to qualitative interviews with their participants, to gather as much as possible information on a particular cognitive process or situation. The *Explicitation Interview*, implemented by Petitmengin<sup>202</sup>, involves the participation of both the participant and the experimenter through an interview in which the experimenter helps the subject putting its experience of a phenomenon into words, especially by using "how" oriented questions, such as "how did you feel", "how did you think about this task to perform it" and so on. This type of interviews was used for example in the report of a sport coaching experience<sup>203</sup>, of a meditative experience<sup>204</sup> and other areas of psychology<sup>205</sup>.

All these techniques may be of interest for olfactory researchers interested in collecting fine-grained subjective accounts of odors. However, as we will see in the next sections, this has not

yet been performed for this kind of experience to our knowledge, and we must consider the specificities of olfactory perception for the application of such methodologies.

#### 1.4. A NEW PROTOCOL FOR THE ACQUISITION OF OLFACTORY DATA

##### 1.4.1. OLFACTORY EXPERIENCE: STAKES AND CHALLENGES

In the first part of this chapter, we showed that the subjective aspect of perceptual experience is a complex issue, that has been discussed within the field of both neurocognitive science and philosophy of mind. The principal issue lays in the incompatibility between the intrinsic subjectivity of the mental states and an objective, measurable experimental science of the mind. This was mainly discussed in the case of visual perception, for which Varela proposed an integrated framework to jointly investigate subjective and objective data, conceptualized as *neurophenomenology*. This methodology first involves a description of the experience of an individual during a certain task to collect data on his or her internal state, that will be then correlated with objective measures as we will further explain in Chapter 4.

However, to apply the principles of neurophenomenology to the field of olfaction, one must account for the particularity of this perceptual modality and adapt certain features that were constructed with visual perception in mind. These elements were further discussed in *Article 7*. Firstly, we must ensure that the olfactory experiences that are proposed to the participants are as rich and diverse as possible, to have an accurate model of smell perception. To this end, we should present different types of odorants, associated to the various functions of olfaction, such as food odors, social odors, hazardous odors, varying in their hedonic valence and degree of familiarity. Secondly, we should be able to use different types of measurements, to ensure that all features of perception are accounted for: this can be done using quantitative measurements, but also qualitative descriptions, either with multiple-choice or free speech. Thirdly, we should be aware and minimize the biases both coming from the experimenter and from the subjects. To this end, the interviewer should ask questions that are open and do not direct to a specific dimension of experience. Also, the participants should be reminded that they are not doing an identification or recognition task, and that there are no bad or incorrect answers, even though they may consider their experience as not accurate or weird. Fourthly, as olfactory vocabulary is scarce and difficult to use, experimenters may have to find ways to encourage participants to verbalize their olfactory experience in their own words, without relying on expert atlases or standardized list of descriptors.

After data collection, researchers need to find a way to structure them for an easier analysis, with different categorizations hierarchically or horizontally organized, with a level of specificity in accordance with the hypotheses. Discourse analysis techniques, as well as artificial intelligence and data mining can be used for qualitative research, with comparison between experimental conditions. Such comparisons could involve autobiographical memories in different stages of life<sup>206</sup>, alternate perceptions settings (such as binocular rivalry in vision or binasal rivalry in olfaction<sup>207</sup>) or description of hallucinations in certain disorders like schizophrenia<sup>125,208</sup>.

#### 1.4.2. A PILOT STUDY TO CONSTRUCT THE PROTOCOL

So, how can we have a protocol of acquisition of the subjective experience of smell considering its specificities? In the context of this PhD, we tried to develop a protocol of such kind, that would fill a certain number of conditions: not biasing the individuals towards one aspect of their olfactory experience in particular, allowing for a consequent verbal description, encouraging the individual to express their experience and what it is like for them to smell an odor, requiring minimum practice for the subjects and for the interviewer and having an easily replicable protocol for future studies. After the data acquisition, we also had to develop a method to analyze in the best way possible the complex and qualitative dataset. We also to face the lack of olfactory vocabulary accessible to the participant, and thus account for the various words that could be associated to one's experience.

In a pilot study, that we present below, we first set up a protocol to determine the optimal conditions for the collection of subjective experience towards odors. We especially aimed to compare the efficiency of a semi-guided interview for the description of the olfactory experience compared to free description. Also, we wanted to estimate the duration of the main experiment and fatigue of the participants with the smelling of many odorants in one session. Finally, we wanted to see if the familiarity of the odorants affected people's descriptions.

#### **Methods**

*Participants.* A total of 12 volunteers (6 women, aged  $23.2 \pm 2.2$ ) were recruited in the Lyon area and randomly assigned to a free or guided condition. In accordance with the declaration of Helsinki, all subjects gave their written and oral consent to the study and were compensated with 5 euros for their participations.

*Stimuli.* We selected 6 odorants for testing and one for training. These odorants were chosen from a previous study in the team by Licon and colleagues<sup>73</sup>, which investigated the principal components organizing the physiological, perceptual and semantic space of 105 odorant molecules. Here, we first selected from this previous experiment the 40 more familiar odorants and the 40 least familiar. Then we selected 3 familiar and 3 unfamiliar molecules to best cover the olfactory space constructed by Licon et al. A t-test showed that the two odorant groups differed on their familiarity ratings, but not on other perceptual dimensions (intensity, pleasantness, irritation, edibility, freshness, heat, and pain). In total, the chosen odorants were the following (Compound Identification number or CID, concentration, common semantic descriptors): for low familiarity group, *phenyl ether* (7583, 13.58%, geranium, green, phenol), *nonanal* (31289, 0.9%, wax, rose, fresh), *butan-1-ol* (263, 0.05%, sweet, balsamic, whisky); for the high familiarity group, *4-terpinen-1-ol* (5325830, 5%, peppery, woody, earthy), *2-butan-1-one* (6569, 0.5%, ethereal, fruity, camphoreous), *MSH* (10130039, 0.003%, passion fruit, blackberry, sweat), and *phenylacetate* (7654, 5.48%, floral, rose, sweet) for training. The training odor was chosen because of its consistence with the example of a rose odor provided in the instructions to the subjects. The concentrations used here were those used in Licon et al, corresponding to 1Pa of pressure in air. The odorants were presented in 15mL opaque vials, diluted in mineral oil to obtain 1mL of solution.

*Protocol.* After reading the conditions of the experiment and giving their consent, the participants were presented 6 numbered vials, in a randomized order. The interviews were audio recorded to allow for further transcription. To explain clearly what was expected from the participants, they were given a written note about what was meant by “olfactory experience”. It was as follows: « *In this study, we are interested in what manifests to you when you smell odors. To better understand what is expected of you, imagine the following situation: a crime happened, and a detective arrives to interrogate the witnesses. During the interviews, he asks them to describe what they saw or heard when the crime happened. He does not want them to make assumptions about what happened, but only to explain to him as clearly as possible what they experienced at this specific time. Here, you are in a position of a witness: we want to hear your own subjective experience and not an interpretation about the source of the odors that will be presented to you. There is thus no good nor bad answer. For example, if you think that a vial smells like a rose to you, the fact that this odor is typically produced by a rose or not is not relevant in this experiment. We are more interested in the fact that, for you, this odor is associated to what you experience when you smell a rose. We are aware that this descriptive exercise may seem difficult, but we ask you to be as attentive as you can to the odors that you will be presented with and to put aside your thoughts external to the experiment. To familiarize yourself with the task, you will have a training vial and you will be able to ask any question that you may have to the experimenter before starting the actual experiment.* »

For each vial, the participants could smell the odor as many times as they wanted and describe their olfactory experience within 2mn, either freely, or with help from the experimenter. In the latter condition, the experimenter said the following to the participants: “*To help you in your description, I will ask you some questions and sometimes repeat what you said to make sure I understood you. If you have trouble to describe an element, don’t hesitate to use your own words or using generic terms like “this thing” or “this feeling”, you might as well come back to it later. When you are ready, smell the first vial and take the time to smell it. Take a few seconds, close your eyes if you want. Focus on your experience. It should become clearer and clearer as you focus on it. Now, try to put some words on this experience. What comes to your mind? What else...? What did you think...? What did you feel when smelling this?*”. After that, the participants rated the overall difficulty they had to describe their experience verbally on a scale from 1 (very easy) to 9 (very hard). There was also a quantitative rating of intensity (from 1 to 9), pleasantness (from -4 to 4), familiarity (from 1 to 9), irritation (from 1 to 9), as well as a free sorting task at the end. The following analysis were centered about the verbalization. The rating task was only used to estimate the duration of the experiment. The free sorting task was not analyzed as well as it took too much time for the subjects to be included in the main experiment.

*Data analysis.* The interviews were transcribed with the ELAN software. Then, we used lexical categorizations of odorants in previous experiments to construct our own grid of analysis. Poncelet and colleagues<sup>130</sup> differentiated between source of the odor, experiences associated to the odors and psychophysical properties of the odor (including its pleasantness). Urdapilleta<sup>209</sup> had categories for objects, personal memories, hedonics, intensity and other characteristics. Sezille and colleagues<sup>61</sup> had three types of references: odor source, olfactory quality and

chemical characterization. Here, we used 11 categories to cover the obtained verbalizations: 1/ references to the odor source, 2/ references to the difficulty of verbalization, 3/ tip-of-the-nose references (i.e. when the odor is very familiar, but the individual is unable to relate it to a name), 4/ references to personal autobiographic memory, 5/ references to episodic memory, 6/ references to the intensity, 7/ references to emotions, 8/ references to hedonics, 9/ references to other sensory modalities, 10/ qualitative descriptors, 11/ chemical features.

## **Results**

First, we compared the difficulty experience by the two groups of subjects in verbalizing their olfactory experience. Participants in the guided condition tended to report less overall difficulty than those in the free condition ( $M_{Free} = 6.2 \pm 1.2$ ,  $M_{Guided} = 5.4 \pm 1.4$ ,  $W = 810$ ,  $p = .057$ ). The most used category was Source (34% of the references), followed by categories related to the effect on the subject, namely Hedonics (12%), Valence (11%), Emotions (11%) and Intensity (9%), then by categories related to memories, namely Episodic memories (7%), Autobiographical memories (5%) and finally by categories related to difficulty, namely Difficulty (8%) and Tip-of-the-nose (3%). Also, the guided group used more references to tip-of-the-nose ( $M_{Free} = 2.1 \pm 11.1$ ,  $M_{Guided} = 3.0 \pm 5.2$ ,  $W = 492$ ,  $p = .009$ ), to emotions ( $M_{Free} = 7.9 \pm 7.9$ ,  $M_{Guided} = 13.6 \pm 10.9$ ,  $W = 455$ ,  $p = .028$ ), to episodic memories ( $M_{Free} = 1.0 \pm 4.7$ ,  $M_{Guided} = 4.8 \pm 8.2$ ,  $W = 455$ ,  $p = .0022$ ), and qualitative terms ( $M_{Free} = 3.5 \pm 7.7$ ,  $M_{Guided} = 9.76 \pm 10.3$ ,  $W = 330$ ,  $p = .00012$ ), compared to the free group. In contrast, the free group used more references to intensity ( $M_{Free} = 15.9 \pm 13.61$ ,  $M_{Guided} = 6.7 \pm 8.3$ ,  $W = 931$ ,  $p = .001$ ) and to autobiographical memories ( $M_{Free} = 10.0 \pm 10.3$ ,  $M_{Guided} = 4.8 \pm 6.1$ ,  $W = 840$ ,  $p = .023$ ). When comparing the number of references to each category for familiar versus unfamiliar odorants, no significant difference was found. There was also no difference between the free vs guided groups ( $M_{Free} = 67.7 \pm 51.7s$ ,  $M_{Guided} = 69.0 \pm 61.9s$ ,  $W = 48602$ ,  $p = .21$ ), nor between familiar vs unfamiliar odorants ( $M_{Familiar} = 69.8 \pm 60.8s$ ,  $M_{Unfamiliar} = 67.2 \pm 56.2$ ,  $W = 51910$ ,  $p = .65$ ).

## **Discussion**

First, these results showed that a guided approach for the verbalization of olfactory experience is perceived as less difficult compared to a free description task, which is an argument in favor of its use in experimental settings as it is notoriously known that odor description and identification are a very difficult task<sup>9</sup>. Without surprise, the source of the odor, its valence and its intensity are the most frequent types of references like in the previous experiments aiming to categorize verbalizations<sup>61,130,209</sup>. The difference between the two types of acquisition of subjective data does not reside in the number of references made, but rather in their type: with a more guided approach, people have more diverse categories of references compared to a free task. Regarding the duration of the experiment, we noticed in our previous experiments in our team that people have difficulties to smell odors for more than 30 minutes, after which they express fatigue. Here, the average duration of verbalization for each odor revolved around 1mn, so we decided to include not more than 20 odorants in the main experiment, to limit the exposure time for the participants while having a decent variability in

the tested odors. Finally, the familiarity of the odors did not seem to affect verbalizations, so we decided to not control for perceived familiarity in the main study.

## 2. STUDY 4 - AN EXPERIMENTAL MODEL OF SUBJECTIVE ODOR EXPERIENCE

Following the above pilot study, we then set up our main experiment during my PhD. The aim was to investigate the subjective experience of a larger sample of odorants and in different populations, to construct a descriptive model of the perceptual experience of smells. Indeed, even if different dimensions of odor perception have been explored, like hedonics, intensity, olfactory memory or semantic description, there is to our knowledge no global model of odor perception that has been proposed in the literature. Such a model will allow to have a general understanding of the structure of olfactory experience and the relative importance of its facets for the individuals. Contrary to other experiments in olfaction, we relied on a semi-guided interview to access subjective experience of odors with a minimization of the experimental biases. Here, we also investigated the importance of language and by comparing French and German participants' experiences, as well as other demographic factors. We used methodologies from various disciplines, including linguistics for discourse analysis and data mining for the characterization of different perceptual profiles within the population. The details of this experiment are presented in *Article 8* (under review).

### 2.1. METHODOLOGY

*Participants.* 74 participants (53 women) were recruited for this experiment (37 from Lyon in France, and 37 from Dresden in Germany). They reported no olfactory disorder nor psychiatric or neurological disorder, they were fluent in either French or German. The mean age was  $24 \pm 6.1$  years old.

Code	Odorant	Concentration	CID
VAL	Isovaleric acid	0,48%	10430
BUT	Butyric acid	0,11%	264
BUTB	Butyl butyrate	0,18%	7983
PROP	Propanoic acid	0,04%	1032
ESAL	Ethyl salicylate	5,49%	8365
OCTN	1-octen-3-one	0,27%	61346
ACE	Acetic acid	0,01%	176
CIS	Cis-3-hexenol	0,24%	5281167
GUA	Guaiacol	2,09%	460
EUG	Eugenol	13,45%	3314
GER	Geraniol	11,29%	637566
BENZ	Benzaldehyde	2%	240
CIN	Cineole	1%	2758

LIN	(+)-linalool	2,17%	6549
BCAR	Beta-caryophyllene	33,64%	5281515
CAR	L-carvone	1,93%	439570
IAA	Isoamyl acetate	0,03%	31276
SAN	Alpha-santalol	Pure	5368797
MYR	Myrcene	0,15%	31253
EOCT	Ethyl octanoate	1,71%	7799

**Table 1.** Characteristics of the 20 odorants. CID is the Compound Identity Number as used on PubChem.

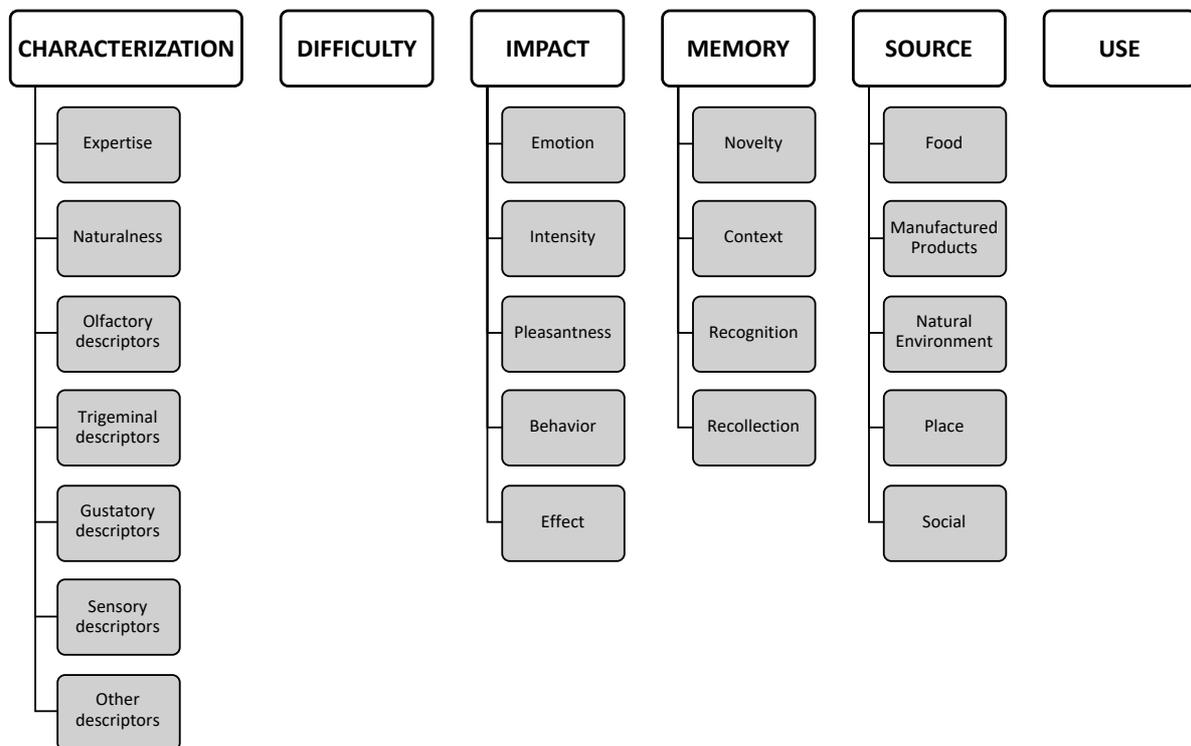
*Stimuli.* 20 odorants were selected for the experiment, based on the 105 odorants dataset used in Licon et al<sup>73</sup> and another pilot testing to narrow it down to the most representative odorants in the chemical, perceptual, semantic and psychophysical space. **Table 1** presents the details of the chosen stimuli. Each odorant was diluted in mineral oil to obtain a total volume of 1mL, and then conditioned in a 15mL opaque vial. The concentrations were taken from Licon et al and correspond to 1Pa of pressure in the air.

*Protocol.* After giving their written and oral consent, the participants filled out a demographic questionnaire, as well as items related to their expertise in certain domains, their exposure to odors in their daily life and the Five Facets Mindfulness questionnaire<sup>210</sup> (aimed to evaluate the capacity to pay attention and describe one's experience). Then, they read a written notice with instructions and what was meant by olfactory experience (see *section 2.3* protocol for the details). They were presented with the 20 odorized vials in a randomized order (with a training vial containing phenylethyl acetate like in the pilot experiment). They could smell them as many times as needed and they were asked to describe within 2 minutes their experience of the odor through a semi-guided interview with the experimenter. The initial instructions by the experimenter were the same as described in the pilot study, but the questions asked to the participants to stimulate their verbalization were more specific and restricted and were as follows: "What does this odor evoke for you?", "What do you think when you smell this odor?" and "If you had to describe what it is like to smell this odor to a friend who never experienced it, how would you describe it to them?". For the French participants, the whole interview was conducted in French, but for the Germans, the questions were provided both in written German and in verbal English, and the subjects' answers were in German. This was due to the lack of a German translator for the interviews as initially planned and the experimenter (myself) was unfortunately not German speaking. The interview was audio recorded for further transcription. For German data, a skilled bilingual researcher translated and transcribed the audio later.

Participants also rated each odor on several quantitative scales including intensity (from 1 to 9), pleasantness (from -4 to 4), irritation (from 1 to 9), edibility (from 1 to 9) and familiarity (from 1 to 9). After the end of the experiment, pleasantness ratings were transformed into emotional saliency (ranging from 0 to 3, corresponding to absolute difference to 0), to match the pleasantness category in the verbalization data as we will see further.

## 2.2. RESULTS

The first and probably main finding of this study was that *people can talk about odors*. Indeed, they used  $9.2 \pm 2.5$  references in average to describe an odor. **Figure 5** represents the structural organization of these references. As the reader may notice, the categories are more detailed than the first pilot experiment, to account for the higher variability in references collected in the main study. Each category is explained in **Table 2**, with corresponding examples. In addition, **Figure 6** shows the relative proportion of use of each of the categories and subcategories. All figures presented here are extracted from **Article 8**. The source of the odor was the most common element in the verbalizations (31% overall), especially in terms of references to food (14%), followed by the impact of the odor on the participants (28%), especially regarding its pleasantness (13%), and finally by the qualitative characterization of the odor (25%). References to memories were less common (9%), like references to difficulty (4%) and use (3%).



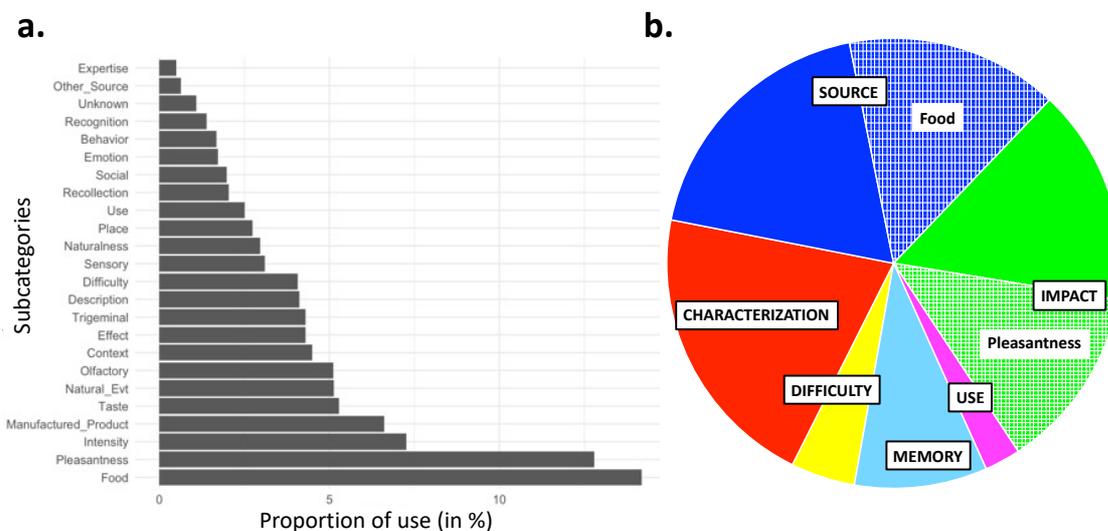
**Figure 5. Descriptive model of the subjective experience of odors.**

Category	Subcategory	Content	Examples
IMPACT	Emotion	Emotions elicited by the odor	“joy”, “wellness”, “nostalgia”, “disgust”
	Intensity	Strength of the odor	“intense”, “low”, “light”, “discrete”
	Effect	Effect of the odor on the individual	“stimulating”, “relaxing”, “surprising”

	Pleasantness	Positive or negative value associated to the odor	“pleasant”, “negative”, “horrible”
	Behavior	Approach or avoidance behavior elicited by the odor	“I want to leave the room”, “I could smell this all day”
SOURCE	Food	Everything edible for humans	“dairy”, “fruits”, “spices”, “vegetables”, “meat”, “sweets”
	Manufactured products	Products fabricated by humans and industrial materials	“medication”, “book”, “soap”, “car”, “metal”
	Natural environment	Elements of nature	“flower”, “soil”, “wood”, “grass”
	Places	Specific place where the odor can be encountered	“hospital”, “garden”, “flower store”
	People	Specific persons and human body odors	“my mother”, “vomit”, “urine”, “transpiration”
	Other sources	Other references	“smoke”, “fire”, “mold”
CHARACTERIZATION	Expertise	Expert terms to describe the odor, its chemical name or characteristics	“butyric acid”, “ester”
	Olfactory descriptors	Olfactory terms, abstract or source-based	“moldy”, “rotten”, “floral”, “vegetal”, “lemony”, “fishy”
	Gustatory descriptors	Terms related to taste	“sour”, “sweet”, “salty”, “pungent”
	Trigeminal descriptors	Terms related to the trigeminal features of the odor	“cold”, “irritating”, “painful”, “spicy”
	Sensory descriptors	Other sensory terms, referring to vision, audition, texture...	“I can see the object”, “green”, “pink”, “wet”, “dry”, “soft”
	Naturalness	Natural or artificial origin of the odor	“natural”, “chemical”, “synthetic”, “artificial”
	Other descriptors	Other descriptors	“complex”, “volatile”, “rare”
MEMORY	Novelty	Odor not previously encountered	“I don’t know this odor”, “new”
	Recognition	Familiar odor not associated with a context	“I know this odor”
	Context	Familiar odor associated with a spatial or temporal context	“This is the odor when I am cooking”, “an odor of Christmas”
	Recollection	Odor associated to a specific event or memory	“I smelled this odor during my trip to Italy”

DIFFICULTY		References to the difficulty for the subject to verbalize, describe or associate something with his/her experience	“I have no words for this”, “I don’t know how to describe”, “I can’t find the name of the odor”
USE		References to the use for the odor	“medical”, “cooking”, “edible”, “it signals danger”

**Table 2. Description and examples for each identified category of references and its subcategories.**



**Figure 6. Use of categories and subcategories of references.**

*a. Proportion of use for each subcategory. b. Proportion of use for each main category. The food and pleasantness subcategories are also indicated into the respective categories of Source and Impact.*

The second main finding was that subjective experience and quantitative ratings of odors share similar characteristics but also have their own specificities. Indeed, as expected, the intensity ratings and the number of verbal references to intensity were related in a quadratic manner ( $F(2,17) = 12,3, p < .001$ ), meaning that the more extreme ratings of intensity, the more the participants talked about intensity. It was the same for references to pleasantness and pleasantness ratings ( $F(2,17) = 9,7, p < .01$ ), as the more extreme ratings of pleasantness, the more references to it. Also, difficulty ratings were positively correlated with references to novelty ( $r = .88, p < .001$ ). When comparing the distance matrices of odorants for the ratings and for the categories of references, there was a significant correlation between these two spaces (Mantel test with 999 permutations,  $r = .66, p = .001$ ). There also was a correlation between the ratings space and the subcategorical space ( $r = .41, p = .001$ ). Taken together, these results show that although the quantitative ratings and verbal descriptions of odors are associated with each

other, they are not equivalent: indeed, verbalizations bring us additional information about the qualitative properties of the odors for the subjects, as well as their potential use.

The third finding of the experiment is that *subjective olfactory experience is differently structured from an odorant to another*. Indeed, people used more references to the source for CIS, BENZ, CAR, CIN, ESAL and GER ( $X^2_{\text{Friedman}}(19) = 124.3, p < .001$ ) compared to the other odors. Similarly, the odorants BUT and VAL were more described in terms of impact compared to other odors ( $X^2_{\text{Friedman}}(19) = 104.8, p < .001$ ). IAA was also more qualitatively described in relation to the other odors ( $X^2_{\text{Friedman}}(19) = 52.6, p < .001$ ). Regarding memories, BENZ, EUG and CIS had more references to them compared to others ( $X^2_{\text{Friedman}}(19) = 122.7, p < .001$ ), and finally, CIN and BUTB were more described in terms of use USE ( $X^2_{\text{Friedman}}(19) = 76.3, p < .001$ ). In sum, even though the general structure of the perceptual experience stayed quite similar across odorants, there can be differences in the relative use of the references depending on the nature of the odor.

The fourth finding of the study is *that data mining can give us information of the fine-grained differences in profiles of experiences* across the individuals. A first standard analysis controlling for other covariables showed that in general, women used more qualitative descriptors compared to men ( $M_{\text{women}} = 2.20 \pm 0.88, M_{\text{men}} = 1.36 \pm 0.98, X^2_{\text{KW}}(1) = 4.34, p = .048$ ). Also, participants that were routinely exposed to odors at work used more references to source ( $M_{\text{exposed}} = 3.23 \pm 1.01, M_{\text{not\_exposed}} = 2.54 \pm 0.92, X^2_{\text{KW}}(1) = 7.13, p = .008$ ) and qualitative descriptors ( $M_{\text{exposed}} = 2.86 \pm 1.11, M_{\text{not\_exposed}} = 2.20 \pm 1.15, X^2_{\text{KW}}(1) = 5.04, p = .03$ ) compared to the ones not particularly exposed. However, the language of the participant had no impact on their types of verbalizations. Then, we applied a subgroup discovery algorithm allowing to characterize overrepresented descriptors in subgroups compared to others. With this technique, we showed that men used mainly descriptors related to the source of odors (e.g., “food” or “plant”) and their impact on them (e.g., “strong”, “discomfort”, “appetizing” or “negative”), whereas women used mainly descriptors referring to the qualitative characterization of the odors (e.g., “fresh”, “chemical” or “acid”). Also, French participants tended to use descriptors mainly related to the impact of odors (e.g., “strong”, “soft” or “aggressive”), whereas the Germans used more qualitative descriptors (e.g., “acid”, “artificial” or “sweet”). Finally, individuals with high exposure to odors used more qualitative descriptors as well (e.g., “sweet”, “acidic” or “fruity”) when those without exposure used more descriptors of difficulty (e.g., “difficulty to identify” or “no evocation”).

The final finding of the present experiment is the fact that *we can identify subgroups of individuals sharing a similar olfactory experience* rather than unique subjective and non-comparable perceptions as it is often thought of odor perception. Indeed, we first conducted a hierarchical clustering analysis on the participants’ verbalizations for each odor, and we found that all 20 of them could be differentiated in two clusters of individuals sharing a similar pattern of perception. Then, using the data mining algorithm of a priori closed, we were able to identify the most frequently used patterns of descriptions within each identified cluster of individuals, and we kept the ones that were at least twice more present in each cluster compared to the other. This allowed to identify the response patterns that characterized most individuals within the clusters for each odor. Here, we will present two examples of such analysis: for odorant ACE, 100% of the individuals in the first cluster mentioned the descriptors “vinegar”, “unpleasant” and “food” to describe it, whereas in the second cluster, 90% of the individuals used the

descriptors “weak”, “difficulty to identify” and “avoidance”. In contrast, for the odorant CIS, although 100% of the individuals in the first identified cluster used the descriptors “grass”, “moment” and “fresh”, the second cluster was far more diverse in the descriptors used, except for the descriptor “natural” which was used by 26% of the individuals. These two examples show us that for some odorants like ACE, the perception is very standardized within a group with the overrepresentation of certain terms to describe the odors, whereas for others like CIS, there is more variability in the descriptions provided by the individuals. Interestingly, this can be related to the distinction we made in earlier chapters between odorants evoking quite universal perceptions and others with high interindividual diversity in responses.

### 2.3. DISCUSSION

The aim of this experiment was to better understand the fine-grained subjective experience of olfaction, with an original methodology combining psychology, philosophy, linguistics, and data mining. The first interesting finding was that contrary to common belief, people can talk about their perception of odors, when they are in an appropriate context and not pressured to identify or characterizing the odor per se. It shows that the experimental settings and the way to present the task can lead to very different results. Here, we wanted to implement a protocol with the least amount of experimental bias, to collect a more directly accessible experience compared to tasks requiring a lot of cognitive thinking, like Likert scales or semantic descriptors lists. Of course, the mere act of verbalizing one’s subjective and private experience influences such experience. As experimental researchers, we must accept that every data we collect has a certain degree of error, whereas it comes from the measuring tools or from the experimenter expectations. The semi-guided interview method is not exempted of such error and biases, but with the opportunity for the participants to talk freely and with their own words, we have access to a complementary source of information coming directly from them. It can be used in conjunction with other quantitative measurements and neuroimaging data to answer a scientific question and may thus be of use for many researchers.

What about the content of the subjective experience of odors? Here, participants described their perception in various terms. As previous studies on olfaction showed it<sup>97,131,211</sup>, pleasantness is one of the main elements of odor perception and brain processing and was mentioned in almost 20% of people’s verbalizations here. Other references to the impact of the odor were also present and are known by the olfactory community as well, like intensity or emotions<sup>77,82,129</sup>. Semantic description of odors is very studied as well, with different atlases, classification, similarity and sorting tasks<sup>212–214</sup>. Here, we found that people qualitatively described the odors they smelled, but they did not use very specific semantic descriptors such as the ones present in atlases: although common source-related terms were used (e.g., floral, fruity...), people also used words from other sensory modalities to compensate the lack of olfactory vocabulary, like gustatory (“sweet” or “acid”), trigeminal (“cold”, “spicy”), tactile (“soft”, “rough”), auditory (“high pitch”) and visual (“green”, “colorful”) descriptors. This shows that it is important to let individuals using their own words to describe odorants or to offer them non-olfactory descriptors to choose from to express their experience. In addition, olfactory memory is also a major field of study, especially with autobiographical memories<sup>206</sup>.

Regarding difficulty, it has been investigated, but mostly through the difficulty of identification<sup>212</sup> and not necessarily through the difficulty to talk about odors per se. Finally, the last main category in our model is use, i.e., how the odors would be used in one's daily life or culture. In our Western sample, odors are not considered as an essential part of our lives and cultural practices, but anthropological work shows that they can bear importance in certain populations, especially in religious and social contexts<sup>11,127</sup>.

In sum, our descriptive model does not necessarily uncover new aspects of perception, but rather allows to combine all the work that was done on specific dimensions to construct a global structure of olfactory perception, and the relative weight of its different facets. Here, we show that the source of odor is the most frequent category of verbalizations, especially if it is considered as food, as well as the hedonic tone of the odor. This is consistent with the main functions of smell in humans, namely food identification and hazard detection<sup>83</sup>.

In this experiment, we also investigated how common factors of variation affected our model. We found an effect of gender and exposure to odors, with women and individuals frequently exposed to odors using more qualitative descriptions. This is again consistent with the scientific literature, as women are generally better than men in olfactory tasks<sup>118,120</sup>, and experts in olfaction use more qualitative terms to describe odors<sup>61,215</sup>. Interestingly, even without being experts, our participants regularly exposed to odors showed a different pattern of verbalization compared to those who did not. We did not observe any strong difference in verbal responses in Germans and French, which can be easily explained as the two languages are linguistically close and do not include a specific olfactory vocabulary. Studies in other systems of language and culture show that certain population have less difficulties speaking about odors as they have a dedicated vocabulary and even abstract terms<sup>127,216</sup>.

We did not focus in this experiment on all the different intra or interindividual factors of variation that affected our descriptive model, as the main goal was to construct an integrative framework for future studies involved in olfactory perception. We applied a series of data mining algorithms to characterize different subgroups of individuals in terms of their verbalizations, but we did not claim to explain why such subgroups were different in their perception. However, we were able to separate odorants with high similarity in people's responses and odorants with much more variations. This distinction between universal and diverse odors has been present throughout this manuscript and is a very interesting point to further explore. It could help us understand how olfactory perception has evolved in both standardized responses to relevant stimuli and interindividual diversity through personal experience.

In conclusion, the present experiment is to our knowledge the first attempt to construct a descriptive model of odor perceptual experience, with less biased method of acquisition based on guided verbal description of subjective experience of smells. It gives us valuable information about the general structure of odor perception and provides us with a basis for future experiments on subjective experience of odors and its variability according to specific factors of interest. More generally, it allows for a better understanding of the complex relationship between perception and language, in the context of olfaction.

### 3. CONCLUSION

With these interesting results, our next step was to investigate the neural basis of olfactory experience. Relating the subjectivity of experience with neurobiological mechanisms is a challenge in cognitive science community. In the next chapter, we will first present this issue and especially the modern attempts to find the neural correlates of consciousness. Then, we will further explain the principles of neurophenomenology, a methodology aiming to provide a framework for the joint investigation of subjective and neurocognitive data. Finally, we will present the results of an experiment conducted during my PhD relating the subjective experience of odors with the pattern of brain activity evoked by odors.

## Chapter 4

# NEURAL CORRELATES OF OLFACTORY EXPERIENCE

- I'll tell you what's in my brain -

### 1. CONTEXT AND OBJECTIVES - RELATING NEURAL ACTIVITY AND CONSCIOUS EXPERIENCE

#### 1.1. THE SEARCH FOR THE NEURAL BASIS OF CONSCIOUSNESS

As we stated earlier in the manuscript, phenomenal experience was long under considered in cognitive science. Indeed, the idea of subjective experience seems incompatible with the principles of natural sciences, which state that everything must be explained by the laws of nature. This issue, also referred as *the explanatory gap*, is one of the greatest challenges in the philosophy of cognitive science.

As Churchland explains it<sup>217</sup>, most mental properties can be reduced to neurobiological processes, meaning an asymmetric dependence of the psychological properties on the neurobiological properties: if the neurobiological state changes, it leads to changes in psychological states depending on it, but the reverse is not true. This position assumes that the reduced property is functional in nature, which is the case for psychological processes but not for phenomenal experience per se. This is the *hard problem of consciousness*: we cannot reduce phenomenality to neurobiological processes, so we cannot naturalize phenomenal experience, i.e., explain it with the laws of nature.

So, what do we do about this hard problem<sup>218</sup>? Some researchers, duly called *eliminativists*, will argue that there is no consciousness in the sense of “what it is like”, and that the concept is poorly defined and could be just a part of folk psychology. Less extreme, *reductionists* like Churchland think that we can reduce the content of consciousness to functional and neurobiological properties, and that the phenomenal aspect of it is not needed to understand the mind. Tenants of the *global workspace theory*<sup>219</sup> argue that consciousness is a framework of mental states available for processing in a cognitive system, which is functionally explainable. Finally for *enactivists*, they consider that consciousness is more than just mental representations and that it is a dynamic process involving the whole body and its interaction with its environment<sup>220</sup>. There is a more recent movement in cognitive science aiming to reintegrate consciousness in the study of cognition, and especially its phenomenal dimension. Roy<sup>221</sup> refers to it as a *phenomenological claim*. To do so, we must first solve a fundamental philosophical problem: “*what do we mean by the concept of consciousness?*”. To this day, there is no clear and undebatable definition of consciousness, which means that empirical research is based on a precarious concept at best, often taken from folk psychology. However, its aim is also to understand what consciousness is, so how can we solve this issue. For Roy<sup>222</sup>, we must first agree on a definition of consciousness, even if it is not perfect, and then use empirical data to sharpen it.

The second question is “*what do we mean by neural correlates of consciousness?*”. When aiming for neural correlates, researchers often confuse it with neural basis, which has not the same implication: the term correlate is neutral whereas a base implies a causation, with neural processes causing conscious states. A correlation is methodologically easy to find, and it is the common paradigm in neurocognitive research today. However, a causation relationship is far more complex and refer to the hard problem as it implies a naturalization of consciousness. Therefore, scientists must be very careful to think in terms of neural correlates rather than neural basis in their work.

*Neurophenomenology* is an approach to the hard problem that has the advantage to account for phenomenal experience in its framework. In the next section, we will present its general principles and how we aim to apply them to olfactory experience. We will also position ourselves with respect to the five questions we introduced in the context of our research hypothesis and paradigm.

## 1.2. GENERAL PRINCIPLES OF NEUROPHENOMENOLOGY

*Neurophenomenology* is based on Husserlian phenomenology, which argues for an account of the immediate aspect of consciousness and aims to transmit an inherently subjective experience to someone else. From this approach, Francisco Varela<sup>223</sup> developed a new framework, neurophenomenology, in an attempt to help solving the hard problem of consciousness: it aims to characterize subjective experience and its neural correlates, with the ultimate goal of finding causal relationship through dynamical processes, but we will not discuss this second aim in the context of this PhD. For Varela, first-person sources of data are as important as neurobiological or psychological measurements and must be considered for the validation of neurocognitive theories. He argues for an empirical double constraint for the use of subjective and objective data: on the one hand, subjective reports must be biologically plausible, and on the other hand, neurocognitive hypotheses must match the individual experience of the subjects during a cognitive task. This mutual enrichment of theories can lead to new discoveries that would not be considered by studying subjective and objective data separately (see *Article 6*).

In practice, several studies applied the principles of neurophenomenology to discover new information on human cognition. For example, a study conducted by Lutz and colleagues<sup>224</sup> investigated binocular rivalry with this approach. Binocular rivalry happens when two different visual stimuli are presented to each eye, resulting in oscillating perception between the two stimuli and a final stable perception. Brain activity during this task varies greatly between and within the subjects and to understand why, the authors collected the experiential variations in vigilance states of the participants. To this end, the participants had a preliminary training in which they learned to identify three types of attentional states for them (a stable preparation state, a fragmented preparation state and a non-preparation state). Then, when undertaking the binocular rivalry task, the subjects indicated for each trial in which attentional state they were at this time. The results of the study showed that there was a synchronization of the cerebral waves only when the participants were correctly prepared for the stimuli, showing that in this

case, accounting for phenomenal experience allowed for a better understanding of cerebral activity measurements.

Other studies use the principles of neurophenomenology, in various experimental fields of research. For example, Modestino<sup>225</sup> reports a case study in which the phenomenal experience associated with the practice of Kundalini meditation (including joy and happiness) was associated with increasing activity in the left prefrontal region, consistent with other studies on meditation. Another case study showed that participants with Post Traumatic Stress Disorder (PTSD) experienced depersonalization and distress during the Rubber Hand Illusion task (a well-known paradigm in experimental research, in which a rubber hand is stimulated at the same time as the real concealed hand of the subject, leading to a temporary sense of body ownership of the rubber hand<sup>226</sup>), which was accompanied by reduced activity of the parasympathetic nervous system and increased activity of the sympathetic nervous system. This account of the subjective experience of the participants during the task was precious to understand depersonalization after traumatic experiences. In sleep research, subjective accounts of dream experiences are progressively taken into account with specific and reproducible methodological conditions, to be analyzed in light of the physiological measurements during sleep<sup>227,228</sup>. Also, in a study investigating hypnosis with EEG measurements<sup>229</sup>, the participants' subjective accounts of hypnosis depth was correlated with global connectivity of the brain. However, neurophenomenological approaches remain quite rare in neurocognitive as it requires some knowledge of the phenomenological method. Furthermore, as mentioned in *Article 7*, because it is individual-centered, neurophenomenological approaches require specific techniques for the analysis of the neurobiological data, beyond the standard fMRI analysis paradigms focusing on changes in groups of individuals. Moreover, if one is interested in the interindividual variability in phenomenal experience, larger samples are necessary to capture this diversity. Although large neuroimaging datasets are available like the Human Connectome Project<sup>230</sup>, they are typically restricted to resting-state or simple cognitive tasks, and do not include the phenomenological accounts of the individuals.

In the context of olfactory research, there is to our knowledge no study specifically aiming to apply neurophenomenology to olfactory perception, or at least to match fine-grained subjective experiences of odors with patterns of cerebral activity. Studies investigating the neural basis of olfaction typically use quantitative scales for each dimension of interest, such as intensity or hedonic value, and relate the ratings with activities in known olfactory areas (e.g., piriform cortex, amygdala, insula, orbitofrontal cortex...) <sup>41,43,58</sup>. Sometimes the individual ratings themselves are used, but in many cases, the group ratings are preferred for the analysis, which negates interindividual diversity, especially in odorants' pleasantness. In addition, the quantitative scales do not cover all aspects of the phenomenal experience of odors as we saw in the previous chapter: the source of the odor, its qualitative characteristics or its use are also important facets of olfactory experience.

With this in mind, we set up during my PhD an experiment inspired by the principles of neurophenomenology to relate phenomenal experience of odors with brain patterns of activity. We will present this study and its results in the next section, corresponding to *Article 9*.

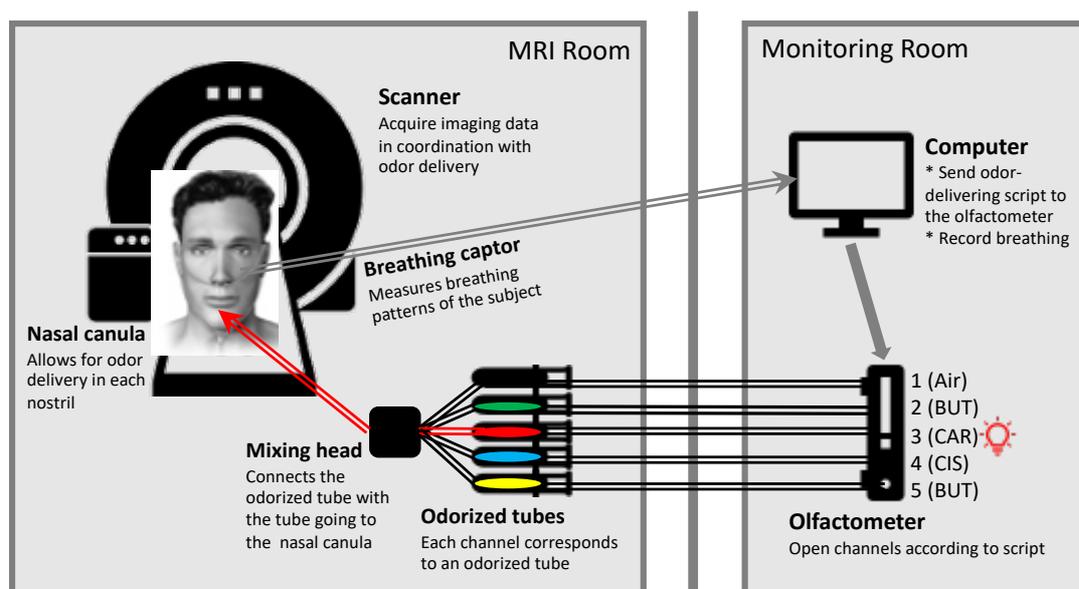
## 2. STUDY 5: PRELIMINARY STUDY ON THE NEURAL CORRELATES OF OLFACTORY EXPERIENCE

In our first behavioral experiment, we constructed a descriptive model of the olfactory experience, using subjective accounts. This second experiment aims to relate the subjective experience a set of olfactory stimuli with the cerebral activity measured with functional magnetic resonance imaging (fMRI). With the information provided by the first-person data, we hypothesize that groups of individuals with different subjective experience of odors will have different patterns of brain activity, both in terms of the global activity within olfactory regions of interest, and in terms of functional connectivity between these cerebral regions.

### 2.1. METHODOLOGY

*Participants.* Among the 37 German subjects that were enrolled in Study 4, 31 of them (23 women, aged  $25.8 \pm 6.6$  years old) came a second time to the laboratory for the neuroimaging part. The inclusion criteria were identical to Study 4. However, we had to remove two participants for the analysis as they undertook the fMRI task but did not describe and rate the odors because of time, resulting in 29 subjects kept for the analysis.

*Stimuli.* The odorants were selected from Study 4, to have access to the most representative odorants of the olfactory space, that would as well evoke diverse subjective experiences in the individuals. The four that were chosen are the following: *Guaiacol* (diluted at 2,09%, CID: 460), *Butyric acid* (diluted at 0,11%, CID: 264), *Cis-3-hexenol* (diluted at 0,48%, CID: 5281167), *L-carvone* (diluted at 4%, CID: 439570).

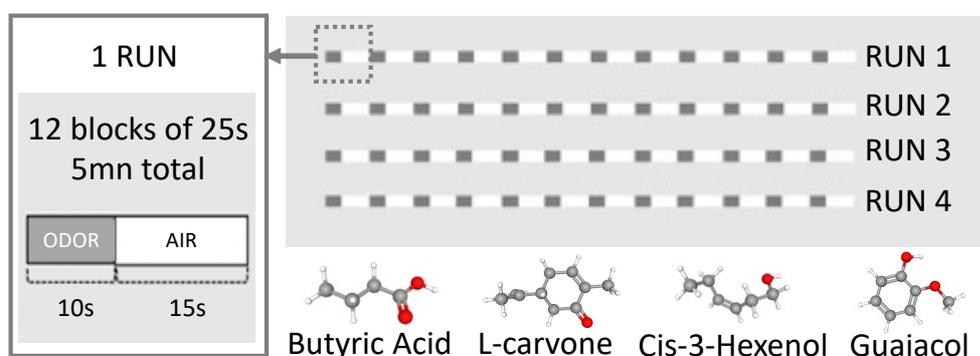


**Figure 7. Schematic representation of the experimental settings.** The different elements used for the odor delivery and acquisition of cerebral data are represented with their function. Red

is an example of the odorized airflow when the CAR channel is open. All tubes are made of polyurethane.

The odorants were presented through a nasal canula to the subjects, with the help of an air-dilution olfactometer<sup>231</sup> (see **Figure 7**). The nasal respiration of the participants was also recorded while they were in the fMRI scanner. The concentration of the odorants was the same as in Study 4, except for CIS and CAR in which it was higher to meet the technical conditions of stimulus deliverance of the fMRI part. A pre-test determined the adequate concentrations needed for iso-intensity between the odorants.

*Protocol.* After receiving the instructions for the task and signing the consent form, the subjects were installed in a fMRI scanner. The experiment was based on a block-design to maximize the acquired signal. There were 4 runs of 5 minutes, each of them constituted of 12 blocks of 10s with odor stimulation and 15s with air only.



**Figure 8.** Experimental design for the fMRI acquisition.

The four odorants were presented 12 times to the participants, in a pseudo-randomized order (see **Figure 8**). The total duration in the scanner for the subjects was around 40min, with 20mn of T2 anatomical acquisition and 20mn of functional acquisition. The participants were instructed to carefully smell each odorant. Also, in the same manner as it was explained to them in Study 4, they had to think about what the odor evoked for them and what it made them think about, and to imagine how they would describe it to someone who did not know the odor. They were orally reminded of what constituted subjective experience, with the same wording as for Study 4.

At the end of the functional session, each of the four odorants was presented to the participants again, this time in a separate room. They were instructed to smell each of them in similar conditions to the fMRI settings: they smelled the odorants from a polyurethane tube connected to a small pump delivering air through an odorized U-shape glass tube. The participants described their perceptual experience for each of the odorants, following the same methodology as in the first study, within 2min maximum per odor. Finally, the four odorants were presented a last time to the participants through the odorized tubes, and they had to rate them on a quantitative scale on several dimensions: intensity (1 to 9), familiarity (1 to 9), edibility (1 to 9), pleasantness (-4 to 4) and irritation (1 to 9).

## 2.2. RESULTS AND DISCUSSION

Our first result of interest was that for each odor we tested, we could identify two main olfactory profiles of individuals: one with a very specific experience and one with more diverse and vague experience. Also, we found that these perceptual subgroups of individuals did not differ in the overall activity of our regions of interest known to be involved in olfactory processing. However, the functional connectivity between such regions was different depending on the subgroups. This suggests that the observed interindividual variability in the perception of a given odor is not related to varying quantitative activation of the olfactory regions, but rather to the functional connectivity within the olfactory network.

Although these preliminary results are encouraging, we acknowledge that the present experiment have some limitations. Indeed, the limited number of subjects involved in the study restricted the number of perceptual subgroups we could compare and the statistical power of our analyses. With a larger sample size, one may expect stronger differences between the groups. It would also allow to capture more interindividual variability and thus more perceptual profiles to compare with brain activity. In addition, we made the choice to collect the subjective reports after the fMRI session rather than during the session, for several reasons. First, participants could really take the time to describe their perception of the odors rather than rushing it because of the stress of being in the machine and the limited amount of time available for the fMRI sessions. Second, we wanted to optimize the acquisition of the brain activity associated with the subjective experience of odors without asking the subject to do an olfactory task, even if this would mean that the verbal reports would be less accurate. Indeed, as they were collected after the fMRI session, with a different experimental apparatus and in a different context, we cannot be certain that the reports are accurately reflecting their subjective experience within the scanner. Unfortunately, we had to make a compromise to obtain the specific brain activity evoked by an experience without linguistic nor motor activity at the expense of the accuracy of verbal descriptions. The weakness of this kind of protocol may be improved with other techniques of acquisition allowing for better collection of subjective data without sacrificing the quality of the imaging.

In fact, in the context of this PhD, we had planned another imaging experiment, this time using a method with a better resolution than functional magnetic resonant imaging, electroencephalography (EEG). This technology has been successfully used to study the dynamics of mental representations<sup>232,233</sup> and can be applied in the context of olfaction experiments. Our aim was to draw temporal windows for which the different olfactory profiles were best represented in the brain, with a better accuracy of the verbal reports as they would have been collected during the EEG session. As it is possible to differentiate between pleasant and unpleasant odors depending on olfactory-related potentials<sup>234</sup>, we expected to find different patterns of EEG activity depending on olfactory profiles. Unfortunately, the soon-to-be superstar COVID-19 virus entered our lives shortly before the start of the experiment, which had thus to be cancelled. We hope that future experiments may be able to relate subjective reports with EEG measurements, as it would allow to overcome some limitations we faced with fMRI.

### 3. CONCLUSION

In this chapter, we were interested in the neural correlates of consciousness, and the conceptual issues related to the place of phenomenal consciousness in experimental research. Although some researchers deny its importance to understand the neural basis of consciousness, others argue in favor of a rigorous integration of subjective reports into neurocognitive research to help solve this “hard problem”. We were especially interested in Varela’s neurophenomenology, and we set up an experiment relating subjective reports of olfactory experiences with odor-evoked cerebral activity using fMRI. Although our results were quite weak and preliminary, they show that the use of first-person data could help understand the differences in cerebral activation and functional connectivity. We hope that researchers in the field will see the potential of a subjective approach and include it in their experimental studies.

## CONCLUSION

There we are. This is the end. Throughout this journey across odor perception, its specificities, its language, and its neural correlates, we tried to answer the following question: can we integrate subjective accounts into experimental research on olfaction, to better understand its perceptual and cerebral variability?

In our first chapter, we presented the sense of smell and its history in Western culture that led to an underestimation of olfactory abilities and especially olfactory language. We also emphasized the perceptual variability that is observed especially at the hedonic level, the main parameter driving olfaction.

In the second chapter, we further investigated the universal and diverse aspects of olfaction through two experimental studies. The first one showed us that in a large sample of individuals, we can find both shared perception and interindividual variability depending on the odorants, that are little affected by the main known factors of variation such as age or gender. The second experiment used an artificial system to test the hypothesis that the relationship between the structure of the odorant and its associated perception depends on the degree of inter-individual agreement on such perception. These two studies show the importance of considering perceptual variability in experimental research on olfaction, especially its part depending on the nature of the odorants and their biological significance to humans. This has consequences for the general research on the stimulus-percept issue in olfactory research.

The third chapter was centered about the place of subjective experience in experimental research beyond olfaction. We presented its complicated history and some methodologies that were proposed to include first-person accounts into experimental protocols. Then, we set up a pilot study followed by our main experiment, using subjective and unbiased descriptions of olfactory experience to construct a descriptive model of odor perception in a large sample of participants from two linguistic backgrounds. By using data mining algorithms, we were able to get a fine-grained characterization of subgroups of individuals sharing similar experience.

Finally, in our fourth and last chapter, we introduced the ongoing debate around the neural basis of consciousness, with the different theories about the place of phenomenal consciousness in neurocognitive research. We then presented our second main experiment, that attempted to relate the subjective experience of odors as modeled in the first main study with the brain activity evoked by odors. Preliminary analyses suggest that inter-individual differences in olfactory subjective experience are likely to be expressed more in qualitative terms (connectivity between brain areas) than quantitative (level of activity between brain areas). They open the way to a new way to construct neuroscientific protocols including first-person accounts into the acquired data, following the principles initiated by the neurophenomenology of Varela.

So, what can we conclude from all these results? As shown by the conceptual theories and discussions around subjective experience and consciousness in general, the issue of subjectivity in experimental research is far from univocal. Although cognitive science has long tried to undermine it, one cannot deny that subjective experience is an essential part of the human mind, and probably what makes it so unique within evolution. Then, we argue that it must be better considered and collected in psychological and neurocognitive research, even though the

objective claim of these disciplines seems to be in contradiction with the inclusion of first-person data. Indeed, scientists remain human, and constantly use their own mind frame and interpersonal knowledge to interpret cognitive data. In this case, the participants' fine-grained subjective insights about their own cognitive and perceptual processes are an essential tool to have a more complete understanding of their performance or their cerebral activity.

In the context of olfaction, a sense that has long been considered as purely sensational, it is quite surprising that subjective approaches have not been developed to accurately collect one's olfactory experience, other than by using quantitative scales or semantic descriptors that are greatly flawed. There are several issues that are yet to solve in the community, including the stimulus-percept problem, or the individual variability in people's perception of pleasantness. Unbiased and detailed first-person reports could be a key player for a better understanding of such issues: for example, we showed that we must include the interindividual hedonic diversity into the equation for relating chemical structure of odorants with percepts. We also showed that rather than completely random experiences, most participants' perception can be organized into a few main profiles, especially for biologically relevant odors. Future studies on olfactory perception may thus benefit from fine-grained subjective reports in addition to the traditional tools for measuring perception to better understand diverse reactions to olfactory stimuli, for example in the context of food acceptance, or in pathological contexts. Regarding neural correlates of olfactory perception, our functional imagery experiment's results were difficult to interpret, but they should be viewed as a proof-of-concept for the inclusion of subjective data into neurocognitive studies. We hope that researchers of the field will see the potential of a first-person approach to implement in their future experiments, with better methodological settings and other imaging techniques such as EEG.

Nonetheless, we understand that the discourse analysis technique used here is quite time-consuming and may not be realistic for most studies. That is why we propose a descriptive model that can be used as a categorical tool for participants to express their experience, either in its global form or in sections depending on the experimenter's question of research. Machine-learning algorithms automatically sorting olfactory discourses could also be developed. In our lab and in collaboration with the LIRIS lab in Lyon, we made some promising attempts for the categorization and description of verbal discourse associated to odors.

In addition to experimental research on olfactory processing, this PhD also provided linguistic information of interest for the research on the language of smell. Although humans are often considered as bad at naming and describing odors, we showed here that in the right context, without any pressure to identify the odors that are presented to them, individuals are more than capable to describe their subjective experience of odors, as long as we extend our vision (sic) of odor perception: even though hedonics and source are the main elements of peoples' discourses, they also evoke emotions, effects, naturalness, trigeminal and other sensory aspects, memories, difficulty and use for odors. In sum, language descriptions of odors may indeed be richer than what we think. Of course, the descriptive model that we developed here was constructed from reports from Westerners with languages notoriously poor in olfactory-specific terms. Future research should investigate the olfactory discourse in other contexts, like in experts or in languages with an abstract olfactory vocabulary, so we could develop a more appropriate model of odor experience.

Finally, the results of this PhD are especially important for the industries relying on consumers' perceptions, such as perfumery, food-processing, wine, or coffee industries. The field of sensory analysis mainly use scales and descriptors, but descriptive sensory analysis is more and more used to better assess the future successes of food products<sup>235-237</sup>. The results presented in this manuscript and the descriptive model of olfaction may be of use for training panelists and get a more accurate experience of the products.

Subjective descriptions could be also important in a clinical context: for example, with the recent pandemic and the high rates of olfactory disorders among the patients, medical practitioners could benefit from subjective depictions of olfactory changes and their impact on the individuals' quality of life. For example, our team recently showed that the COVID-related loss of smell had significant impact on the patients' life (*Annex 2*). An approach centered on subjectivity and first-person accounts could help better characterize such impact and thus help to respond to it appropriately.

In conclusion, this PhD aimed to better understand olfactory experience, by integrating concepts and methodologies from many areas of research, including philosophy, linguistics, experimental psychology, sensory analysis, and data mining. This multidisciplinary approach allowed us to get an accurate apprehension of our object of study, including a fundamental reflection about the concept of subjective experience in itself and its place in scientific research. To our opinion, progress in experimental research relies on a more integrative account of its subject, and on the challenging of the cartesian limitations between the objective and the subjective.

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