



The role of olfaction in affects and social cognition in humans

Camille Ferdenzi

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Université Claude Bernard Lyon 1

Mémoire pour l'obtention de
l'Habilitation à Diriger des Recherches

Présenté par

Camille FERDENZI

**The role of olfaction
in affects and social cognition in humans**

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"There is very little difference between one man and another; but what little there is, is very important."
William James (1842-1910)

*"Laissez-moi deviner ces subtiles odeurs
Et promener mon nez parfait inquisiteur
Il y a des fleurs en vous que je ne connais pas
Et que gardent jaloux les replis de mes draps
Oh, la si fragile prison ! Il suffirait d'un peu de vent
Pour que les chères émanations quittent ma vie et mon divan
Tenez, voici, j'ai découvert dissimulées sous l'évidence
De votre Chanel ordinaire de plus secrètes fulgurances
Il me faudrait les retenir pour donner corps à l'éphémère
Recomposer votre élixir pour en habiller mes chimères »*
Juliette Nouredine (1962-)

"Sense of smell? [...] I never gave it a thought. You don't normally give it a thought. But when I lost it—it was like being struck blind. Life lost a good deal of its savor—one doesn't realize how much 'savor' is smell. You smell people, you smell books, you smell the city, you smell the spring—maybe not consciously, but as a rich unconscious background to everything else. My whole world was suddenly radically poorer..."
Oliver Sacks (1933-2015)
The man who mistook his wife for a hat

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1. Foreword

I would like to start by mentioning that in this report, I am deliberately focusing on some aspects of my scientific career while omitting others, for the sake of concision and for the sake of consistency with my ongoing work and projects. Therefore, I chose to develop aspects related with chemical communication in humans and olfactory disorders, and gave less space to my previous studies on inter- and intra-individual differences in olfaction.

I became interested in the perception of odors in humans during my studies in agri-food engineering, completed in the early 2000s. After focusing on food behavior and perception at that time, I broadened my olfactory horizon with a cross-cultural approach in my master's degree and a developmental one during my PhD thesis. It is during the latter, with the influence of the stimulating work of my supervisor Benoist Schaal on mother-child interactions, that I started to be interested in social odors: I am particularly thankful to him for these inspiring first years in academic research. I then conducted my first project on human body odor in Liverpool, UK, supervised by Craig Roberts, before continuing with two other postdoctoral projects on the role of human odors in social cognition in Geneva, Switzerland, with David Sander and Sylvain Delplanque, and then in my current lab with Moustafa Bensafi (Centre de Recherche en Neurosciences de Lyon CRNL, France). These three projects, which I initiated and then coordinated, received funding and the approval of ethics committees in each country. I started studying olfactory disorders and their consequences more recently, thanks to the impulse of Moustafa Bensafi, when I started my permanent position at the CRNL. I am very grateful to my current research team Neuropop, and in particular to Moustafa Bensafi and Anne Didier, for supporting me in my efforts to join the team: This now allows me to conduct my research with long-term perspectives in a very favorable scientific environment.

Finally, it is important to acknowledge that all the work I describe in this report would not have been made possible without the work of students that I supervised, and of technicians and engineers. Regarding my research at CRNL, two postdocs whom I co-supervise(d) with Moustafa Bensafi have had significant input in terms of processing of fMRI data, Arnaud Fournel, and of statistical analysis of self-reports about COVID-19-related olfactory disorders, Christophe Bousquet. Also, Cédric Manesse (PhD that I co-supervised during his last year of thesis) has investigated olfactory disorders and their consequences on quality of life, and Stéphane Richard Ortegón (ongoing PhD in a project I am coordinating with an cosmetics industrial partner) has initiated studies on chemical communication of emotion. These projects have benefited from the implication of Marc Thévenet, engineer who has an expertise in odor diffusion, of Anne Lelgouarch and Clément Desoche, engineers at the virtual reality platform, of Danielle Ibarrola and Franck Lambertson, engineers at the brain imaging platform CERMEP, and of Christelle Daudé, laboratory technician in the human olfaction platform of the CRNL. In Dijon and Geneva, I closely worked with research technicians, Sylviane Martin and Ines Mehu-Blantar respectively. Bachelor and Master students have also taken part in my studies, among which I can mention Marta Vondrova (Master student in Liverpool), Olga Voronstova-Wenger, Katharin Mylena Da Paz Cabral and Reni Atanassova (Master students in Geneva), Daphnée Poupon, Mathieu Pinger, Aurélien Kassan, Morgane Joly, Erwan Moussy and Manon Leygnier (Master students in Lyon).

2. Summary

English.

Human olfaction has long been relegated to the background, but scientific advances in recent decades have highlighted the extreme acuity of this sense in humans. My work focuses on the ability of humans to communicate information via their biological odor (produced by the body) and on the influence of these biological odors on the behavior of others. In particular, it is known that human body odor has a significant role in attractiveness, and thus potentially in the choice of a partner. However, the determinants of olfactory attractiveness are not yet fully understood. Moreover, it seems that an emotional contagion occurs via biological odor, at least for negative emotions (and notably fear). The transmission of positive emotions and the mechanisms of such a phenomenon remain to be explored. My work aims at exploring these questions in an interdisciplinary way, by trying to develop an understanding of the chemical basis of this form of non-verbal communication and by favoring ecological approaches, i.e., those that better reflect the real conditions in which this communication takes place. I also address the importance of odor in social interactions and other aspects of the emotional life of individuals in a more indirect way through the study of olfactory disorders. This aspect of my research is part of a collaborative approach with other researchers of the Neuropop team, and consists in working on diagnostic and remediation aspects. This allows us to try to improve the quality of life of patients while studying the impact of olfactory loss on social interactions.

French.

L'olfaction humaine a longtemps été reléguée au second plan, mais les avancées scientifiques des dernières décennies ont mis en évidence l'extrême acuité de ce sens chez l'homme. Mes travaux portent en particulier sur la capacité de l'être humain à communiquer des informations via son odeur biologique (produite par le corps) et sur l'influence de ces odeurs biologiques sur le comportement d'autrui. En particulier, on sait que l'odeur corporelle humaine a un rôle significatif dans l'attractivité, et donc potentiellement dans le choix d'un partenaire. En revanche, on ne connaît pas encore parfaitement les déterminants de l'attractivité olfactive. Par ailleurs, il semblerait qu'une contagion émotionnelle se produise via l'odeur biologique, du moins pour les émotions négatives (et notamment la peur). La transmission d'émotions positives ainsi que les mécanismes d'un tel phénomène restent à explorer. Mes travaux visent à explorer ces questions de manière interdisciplinaire, en tentant de développer la compréhension des bases chimiques de cette forme de communication non-verbale et en favorisant des approches écologiques c'est-à-dire qui reflètent mieux les conditions réelles dans lesquelles se produit cette communication. J'aborde aussi la question de l'importance des odeurs dans les interactions sociales et d'autres aspects de la vie affective des individus de manière plus indirecte grâce à l'étude des troubles olfactifs. Ce volet de mes recherches s'inscrit dans une démarche collaborative avec d'autres chercheurs de l'équipe Neuropop, et consiste à œuvrer sur le plan du diagnostic et de la remédiation. Cela nous permet de chercher à améliorer la qualité de vie des patients tout en étudiant les répercussions de la perte d'odorat sur les interactions sociales.

3. List of abbreviations

2D:4D	Second-to-fourth digit ratio
ABUT	Butyric Acid
AND	Androstadienone
BO	Body Odor
EMG	Electromyography
ENT	Ear Nose Throat
ETOC	European Test of Olfactory Capabilities
fMRI	functional Magnetic Resonance Imaging
GC-MS	Gas Chromatography - Mass Spectrometry
GEFAV	Geneva Faces and Voices Database
HMHA	3-Hydroxy-3-MethylHexanoic Acid
LDA	Linear Discriminant Analysis
IFG	Inferior Frontal Gyrus
LIM	Limonene
MFG	Medial Frontal Gyrus
MHC	Major Histocompatibility Complex
MIP	Mood Induction Procedure
MSH	3-Methyl-3-SulfanylHexan-1-ol
OD	Olfactory Disorder
ODD	Old Deodorized and Desensitized
PCA	Principal Component Analysis
PDMS	PolyDiMethylSiloxane
SBSE	Stir Bar Sorptive Extraction
SFG	Superior Frontal Gyrus
SPME	Solid Phase MicroExtraction
UPSIT	University of Pennsylvania Smell Identification Test
VOCs	Volatile Organic Compounds
VR	Virtual Reality
WEIRD	Western Educated Industrialized Rich and Democratic
WP	Work Package

Note: references of articles that I have written or co-authored are underlined.

4. The role of human body odors (BO) in social interactions

4.1. Foreword

After entering olfaction research via the food pathway, my interest quickly turned to body odors and their role in social interactions. During my PhD supervised by Benoist Schaal, I investigated school-aged children's attention to odors in various everyday-life situations: In the self-reports I collected, there was evidence that the odor of the parents and of self (on the attachment object for instance) had a powerful role in emotional homeostasis of the children. I then submitted a project to the Fyssen Foundation to study developmental changes in parent-child body odor perception. As the application was successful I did a post-doctoral year with Craig Roberts at the University of Liverpool (2007-2008), in an evolutionary psychology research group. There, I learned for the first time how to collect, store and present body odors for rater evaluation, and conducted several studies with children and adults with the help of an Erasmus Czech Master student (Marta Vondrova).

During my second post-doctoral experience in affective sciences at the University of Geneva (supervised by David Sander and Sylvain Delplanque, 2009-2013), after conducting a large-scale cross-cultural study on odor-related emotions for which I was recruited initially, I switched back again to social olfaction on my own initiative. Thanks to the ATTRASCENT project funded by the Swiss National Science Foundation FNS, I studied the role of olfactory, visual and vocal cues in human attractiveness. ATTRASCENT was officially led by Sylvain Delplanque to meet the requirements of the fund, and in practice we both coordinated this project that I initiated and that we jointly wrote. I managed a small team composed of a research technician (Ines Mehu-Blantar) and several Master students (Olga Voronstova-Wenger, Katharin Mylena Da Paz Cabral, Reni Atanassova).

I then joined my current laboratory CRNL thanks to another project in direct continuity (and with similar acronym, ATTRASENS), that was funded by the French National Research Agency ANR as part of a program promoting the return to France of young researchers after a post-doctoral experience abroad. I pursued the study of the role of odors in human attractiveness, by investigating mostly specific compounds of body odor rather than body odor samples. During this project (2013-2016), I worked with a post-doctoral fellow (Arnaud Fournel) and a Master student (Daphnée Poupon), I developed my collaboration network with chemists (Nicolas Baldovini) and genetic anthropologists (Harilanto Razafindrazaka and Denis Pierron), and also repeatedly applied for a permanent position at CNRS until being successful in 2017.

Since I took office in 2017 as a CRNS researcher in the Neuropop team of CRNL, I dedicated most of my work to i) investigate emotional contagion through body odor (thanks to a research collaboration with an industrial partner specialized in the development and production of perfumes and cosmetics) and to ii) develop suitable methods to increase our knowledge of body odor chemical composition in order to relate it to behavior (thanks to a second research grant of the Fyssen Foundation and to the collaboration with the cosmetics industrial partner mentioned above). In order to carry out these two projects that I coordinate, I have developed my collaboration network especially for chemical analysis, and I am managing a small team constituted by a research technician (Christelle Daudé, working for the olfaction platform of the CRNL), a PhD student (Stéphane Richard Ortégón, co-supervised with Moustafa Bensafi) and Master students (Alexia Lamblin, Manon Leygnier).

In the following sections, I am presenting these past and ongoing works, as well as my future project that starts in the fall of 2021 with a new PhD (Valentine Brémond-Bostoen) that I co-supervise with Laurent Dormont, lecturer at the Centre d'Écologie Fonctionnelle et Évolutive in Montpellier. This

4-year project, Biodor-IN, is funded by the French National Research Agency and will also involve three master students and a 18-months postdoc. It is aiming at investigating the role of body odors in human attractiveness by investigating more deeply the chemical underpinnings and by developing new approaches of behavioral testing using virtual reality. Other perspectives of collaborative projects are also presented.

4.2. Human body odor (BO) and attractiveness

4.2.1. Introduction

The human body conveys a complex mixture of hundreds of chemical compounds (alcohols, carboxylic acids, ketones, aldehydes, esters, hydrocarbons, etc.), which are transformed from precursors secreted by excretory skin glands (Leyden et al., 1981; Wilke et al., 2007) through the action of skin bacteria (*Corynebacteria*, *Propionibacteria*, *Staphylococcus*) (Natsch and Emter, 2020) and which constitute body odor. This chemical blend has a fixed fraction, which is genetically determined (Roberts et al., 2005; Kuhn and Natsch, 2009) and used as a marker of individuality (Penn et al., 2007; Marchal et al., 2016). It also possesses a variable fraction, which depends on factors such as on diet (Havlicek and Lenochova, 2006; Zuniga et al., 2017), age (Mitro et al., 2012) or physiological state (Singh and Bronstad, 2001; Olsson et al., 2014). There is empirical and societal evidence that odors produced by human bodies are not just some unwelcome emissions that a large proportion of individuals from many societies try to eliminate with the help of hygienic and cosmetic practices: They are sought, and they clearly affect daily interactions with others, especially the close ones. Scientific studies back up these observations by providing solid reasons to believe that chemical communication occurs in humans, i.e. communication through chemicals emitted by an emitter's body and perceived by a receiver through the olfactory and/or trigeminal systems.

Mother-infant communication, for example, is likely modulated by chemicals produced by the mother and perceived through the olfactory system of her baby. Indeed, mothers' areolar glands produce secretions that are attractive to newborns (Doucet et al., 2009) and that are positively associated with breastfeeding success (Doucet et al., 2012). But human chemical communication has been most extensively studied in the context of mate choice, mostly by investigating perceived attractiveness and preferences for a potential reproductive partner. Studies using self-reports show that body odor is rated as a key factor in a person's attractiveness when compared with several sensory and behavioral characteristics of a potential partner (Herz and Inzlicht, 2002), although mainly in female raters (Herz and Inzlicht, 2002; Havlicek et al., 2008). Studies in patients with olfactory disorders show that olfactory loss has serious adverse effects on the quality of social interactions, such as partnership insecurity or decreased sexual activity (Croy et al., 2014; see also Section 5.2.3.).

While some studies have focused on the behavioral effects of specific molecules present in BO (such as androstadienone; see Section 4.2.4.), other studies using BO samples have revealed preferences for biological odors that provide cues to biological quality of a potential sexual partner with regards to genetics (including the major histocompatibility complex MHC), reproductive status and health. People have been shown to prefer and choose MHC-dissimilar mates based on their body odor (Wedekind et al., 1995), at least in some populations (Chaix et al., 2008), a mechanism believed to favor the production of MHC-heterozygous offspring who are more resistant to pathogens. This outcome is also served by a preference for MHC-diverse (heterozygous) mates, which has been shown to be a more robust phenomenon in a recent meta-analysis (while mixed evidence was found – notably

as a function of samples' ethnical heterogeneity – for MHC-dissimilarity) (Winternitz et al., 2017). Preferences for other indicators of mate fitness, which have been evolved because of their beneficial effects on the offspring (biological quality, contribution to child care), seem to be mediated by body odors. For example, women within the fertile phase of the menstrual cycle prefer the body odors of men with greater body bilateral symmetry (indicating a better developmental stability, which is a marker of good physical condition) (Thornhill and Gangestad, 1999), and for socially dominant men (Havlicek et al., 2005). Men's preference for women's cues of fertility is another adaptive phenomenon that seems to be (in part) mediated by body odor, as shown by men's preference for odor samples collected during women's fertile phase of the menstrual cycle (Singh and Bronstad, 2001; Kuukasjarvi et al., 2004). Additionally, human body odor communicates information about health status, which is one aspect of mate fitness. Compared with healthy donors, the odor of sick persons is more aversive (Olsson et al., 2014) and more intensely activates brain networks involved in odor processing (Regenbogen et al., 2017). Information about body condition related to nutritional state is also conveyed by body odor (Fialová et al., 2019), as well as about gender (Doty et al., 1982; Chen and Haviland-Jones, 1999) and age (Mitro et al., 2012). Finally, body odors are involved in the communication of emotions (meta-analysis in de Groot and Smeets, 2017) and of personality traits (such as dominance and neuroticism) (Sorokowska et al., 2012), both of which being involved in the initiation and maintenance of romantic relationships (Mahmut and Croy, 2019).

Despite these numerous pieces of evidence regarding the existence of a chemical communication in humans, especially in the context of mate choice, the mechanisms of such a communication are poorly documented to date. In a recent position paper (Ferdenzi et al., 2020), I have outlined five challenges that I believe are important to ongoing and future research in this area. These are: 1) to go beyond malodors from the axilla, 2) to increase our knowledge of the chemistry of human BO, 3) extend our studies to different cultures, 4) to better understand possible interferences of contraception and fragrance use on human chemical communication, and 5) to foster interdisciplinary research. In the following sections, I will present several studies I conducted on BO attractiveness and I will explain how I am currently addressing some of the above challenges and how I am intending to address them further in the future.

4.2.2. Developmental changes in BO attractiveness

A first way to investigate the role of body odor in mate choice was to test the following hypothesis: parental odors, potentially involved in parent-child attachment early in development (Winberg and Porter, 1998) could become aversive during sexual maturation (Wathelet and Ferdenzi, 2008), thus guiding adults' mate choice by limiting inbreeding and promoting genetic diversity (Wedekind and Furi, 1997). Results of a previous study were in line with this hypothesis (Weisfeld et al., 2003), although the methods used were not fully adequate. Therefore, during my first post-doc at the University of Liverpool, I revisited this hypothesis by recruiting 9 English families, each including two prepubertal (7-10 years) and/or adolescent (11-18 years) children, the father and the mother. Each family member was asked to provide a body odor sample, i.e. a t-shirt worn for three consecutive nights. They then rated the body odor of all family members as well as that of strangers. We recorded hedonic judgments (pleasantness) and pairwise preferences (familiar vs. unfamiliar odor). This study provided evidence for gender differences: more extreme hedonic judgments and better identification of the donors were observed in women and girls. The hypothesis tested, however, namely the development of an aversion to the body odor of the opposite-sex parent during adolescence, was not

verified (Ferdenzi et al., 2010), which could partly be due to the limited sample size. Since then, other studies showed that i) body odors convey developmental cues (mothers are able to classify developmental status of 0-18 year-old children based on their BO: Schaefer et al., 2020b) and ii) the inbreeding avoidance hypothesis is partially verified in a large sample (mothers' preference for pubertal boys' BO is negatively related to the child's level of testosterone for the own son but not for unfamiliar boys: Schaefer et al., 2020a).

4.2.3. Relationship between attractiveness of BO and other traits

BO attractiveness and digit ratio 2D:4D. In this study conducted at the University of Liverpool, we investigated, in three sensory modalities involved in human mate choice (voice, body odor and face), whether second-to-fourth digit ratio can predict masculinity and attractiveness of men evaluated by women. 2D:4D reflects the degree of exposure and sensitivity to prenatal testosterone and has been shown to be related to a number of behavioral, health and fertility characteristics in adult men (Manning, 2002). Testosterone is involved in the development and maintenance of secondary sexual traits involved in attractiveness and is therefore important for mate choice. In our study, 2D:4D was unrelated with olfactory and vocal attractiveness; However, the lower - namely more masculine - the participants' 2D:4D (i.e., indicative of relatively high levels of prenatal testosterone), the more attractive their faces (Ferdenzi et al., 2011a). Using the same digit length method of measurement (direct), I replicated the latter result in another independent sample of Swiss participants several years later (Ferdenzi et al., 2015a), and only partially in a third study using indirect measurement from photocopies of the hands (Roberts et al., 2011). It is possible that adult facial features (such as bone structure) are more dependent on *in utero* hormonal exposure than voice or body odor features. In general, the link between steroid hormones (fetal or circulating) and body odor attractiveness and composition remains poorly understood and would benefit from further study.

BO, face and voice. The question of how the different sensory modalities involved in attractiveness relate to each other remains unresolved to date. Two different hypotheses, the 'back-up cues' and the 'multiple messages', are debated. In the 'back-up cue' hypothesis, the different sensory modalities convey the same information about an individual reflecting the same underlying mate quality, resulting in a more accurate assessment of mate quality. In the 'multiple messages' hypothesis, multimodal cues provide different information each reflecting different aspects of mate quality (Candolin, 2003). In a study where we collected female attractiveness ratings of male BO and visual samples (photo, video), we found no relationship between BO and facial attractiveness, except when considering only the behavioral attractiveness (attractiveness difference between photo and video; positive correlation) (Roberts et al., 2011). In another study conducted in 2011 at the University of Geneva, we collected BO samples, took facial photographs and recorded the voice of men and women and had them rated for attractiveness. Although at that time we did not publish about the relationships between the 3 modalities, we recently provided our dataset to Vit Trebicky (Charles University, Prague) who conducted a meta-analysis involving ten unpublished datasets from different research groups as well as four published studies (N=806 target stimuli donors and 1350 raters). In the current state of the data analysis (Trebicky et al., article in preparation), the correlations between modalities are very modest and the power to observe significant effects is relatively low (power 57% for odor-face correlation, 25% for odor-voice and 33% for voice-face). We thus found little support for redundancy ('back-up cues') in information provided by the different modalities. The results seem

more in favor of a 'multiple messages' hypothesis pattern where the different modalities provide different information, which for instance enables individuals that differ in mate preferences to choose the most suitable partner.

4.2.4. Role of sexually dimorphic BO compounds

It must be pointed out here that a significant part of the research in this area (mate choice) has been driven and even drifted by the fascination of the scientific community - as well as the public - for pheromones. In particular, many studies have focused on the behavioral effects of male steroid compounds, such as androstenone and more recently androstadienone. But the scientific justification for such a focus - to the detriment of all the other components of human biological odor - is highly debatable (Wyatt, 2015) and, although androstadienone is likely to have psychological effects (Jacob and McClintock, 2000; Bensafi et al., 2004), it does not seem to meet the concept of a sex pheromone (Hummer and McClintock, 2009). In sum, while pheromones have been defined (Karlson and Lüscher, 1959) and identified in several animal species (insects: Butenandt et al., 1959; mammals: Schaal et al., 2003; Roberts et al., 2010), their existence in humans has only been speculated and not rigorously demonstrated. In addition, their functional processing has been a subject of debate. Namely, the widespread belief that they would be processed through the accessory (vomeronasal organ VNO) rather than the main olfactory system has been challenged by the fact that i) occlusion or absence of VNO in humans has no effect on putative pheromone perception (Frasnelli et al., 2011) and that ii) in other mammals (e.g., rabbit) it has been shown that pheromones can be processed through the main (and not the accessory) olfactory system (Hudson and Distel, 1986; Schaal et al., 2003; Baxi et al., 2006). In this context, I have conducted a series of experiments with single compounds, the first one with androstadienone, using a protocol aiming at testing the sex-specific effects of the molecule, and several other ones using other molecules that appeared in the literature as produced in a sexually-dimorphic manner.

Androstadienone (AND). In order to understand the role of body odor in social interactions, I was interested in one of its known components, androstadienone, and its effect on the attractiveness of faces and voices. This compound is a steroidal derivative identified in human axillary secretions, in larger quantities in men on average. It has long been suspected to be a human sex pheromone that would have a positive effect on women in the context of mate selection. The modulation of attractiveness by androstadienone had been tested only incompletely at that time (only in women evaluating male stimuli) and these effects were, moreover, poorly reproducible (Lundström and Olsson, 2005; Saxton et al., 2008). Positing that if this molecule has a function in male-female attraction its effects should be sex-specific, my master student Reni Atanassova and I tested its influence on the attractiveness of male and female faces and voices from the GEFAV (a database of faces and voices with varied levels of attractiveness that I constituted during my postdoc in Geneva: [Ferdenzi et al., 2015](#)). Evaluations were performed by individuals of both sexes.

Compared to a control odorant condition, androstadienone, while not explicitly perceived, had similar effects in males and females: slowing down the responses in a categorization task (i.e., to categorize the stimulus as quickly as possible as attractive or non-attractive), except for non-fertile women (**Fig. 1A**) and increasing the attractiveness of opposite-sex stimuli (**Fig. 1B**) (Ferdenzi et al., 2016). This study confirms that androstadienone has a positive effect on the attractiveness of others, but shows that this effect is not sex-specific: this helps to question the legitimacy of this compound as a possible human pheromone (Doty, 2010; Wyatt, 2015). These results are consistent with another study (Hummer and McClintock, 2009) that suggests that the effect of androstadienone, which is more global than that of a sex pheromone, would be to increase attention to emotional/relevant stimuli (in this case, the faces and voices of people of the opposite sex).

A. CATEGORIZATION TIME		STIMULI	
RATERS		Opposite-sex	Same-sex
	Fertile females	↗ ^f	-
	Non-fertile females	↘	↘
	Males	↗	↗ ^v

B. ATTRACTIVENESS RATING		STIMULI	
RATERS		Opposite-sex	Same-sex
	Fertile females	↗	-
	Non-fertile females	↗ ^f	↗ ^f
	Males	↗ ^v	-

Fig. 1. Summary of the effects of androstadienone on (A) response time in a first impression task where participants had to categorize social stimuli (faces, voices) as attractive or non-attractive, and (B) attractiveness rating of these stimuli. ↗: increase in the presence of androstadienone compared with the control condition; ↘: decrease in the presence of androstadienone compared with the control condition; v: for voices only; f: for faces only. From Ferdenzi et al., 2016.

3-hydroxy-3-methylhexanoic acid (HMHA) and 3-methyl-3-sulfanylhexasan-1-ol (MSH). Convinced that the research effort focused on AND and other related androgenic steroids (androstene, androsteneol) lacks a sound scientific basis (Wyatt, 2015) and needs to be redeployed to other potentially relevant human body odor compounds, I focused on 3-hydroxy-3-methylhexanoic acid (HMHA) and 3-methyl-3-sulfanylhexasan-1-ol (MSH). The precursors of these compounds are secreted in sex-specific quantities in the axillary region: HMHA precursor is produced preferentially by men, and MSH precursor by women (Troccaz et al., 2009). Thanks to a collaboration with the Institute of Chemistry of Nice (Nicolas Baldovini), these compounds were synthesized and used in four experiments performed during my ANR ATTRASENS project and thanks to the Agora program of the FNS (project coordinated by Sylvain Delplanque at the University of Geneva, allowing us to conduct an experiment with the public in a Museum in Lausanne).

First, I studied *how HMHA is perceived* in men and women, in terms of sensitivity (detection thresholds), perceptual ratings (pleasantness) and verbal descriptions. This was performed both in a French sample thanks to the work of a master student Daphnée Poupon, and in a Malagasy sample with slightly different methods, thanks to a collaboration with genetic anthropologists from the University of Toulouse (Harilanto Razafindrazaka and Denis Pierron). The results of this study (Ferdenzi et al., 2019) showed that HMHA, described as a human odor with notes of fermentation and moisture or as a chemical/medicinal product, is not perceived differently by men and women: no differences in odor threshold (**Fig. 2A,Bi**), pleasantness or descriptions. Both cultural groups provided similar responses. The only result that would support the idea that this compound is involved in human attractiveness, is that, when presented at suprathreshold concentrations (0.1%), HMHA was perceived

as more intense by Malagasy women who were in the fertile phase of their menstrual cycle (**Fig. 2Bii**), while this was not the case for a control odor of rose (PEA; **Fig. 2Biii**). Additionally, a striking result was the relatively high percentage of individuals being specifically anosmic to HMHA, i.e. not detecting HMHA at any of the 16 concentrations used in this study: 8% in the French sample, 19% in the Malagasy sample. And among those who detect HMHA, the distribution of sensitivities was bimodal, indicating that these individuals fall into two subgroups. The percentage of anosmic individuals is even greater (25%) for another related molecule also tested in this study, 3-methylhex-2-enoic acid (3MHA). As these carboxylic acids are major constituents of sweat odor [in terms of compound quantity and odor typicality (Zeng et al., 1991; Natsch et al., 2003)], one may wonder about the consequences of such variability on cosmetic and hygienic practices, and on daily interactions with others. Overall, this study provided few converging pieces of evidence towards a potential role of HMHA in inter-sexual attractiveness. Whether HMHA is relevant in the perception of a potential partner thus requires further explorations, with more implicit approaches for example and/or by investigating the repercussions of HMHA specific anosmia on interpersonal relationships. The first aspect (implicit approaches) will be developed later in this report, and we started investigating the second aspect in collaboration with Agnieszka Sorokowska at the University of Wroclaw, Poland (Sorokowska et al., 2021). Notably, we tested whether inability to smell HMHA could be associated with social difficulties – measured here through social isolation. Although it proved not to be the case, other aspects of social behavior could be investigated in the future in relationship with specific anosmias to body odor compounds.

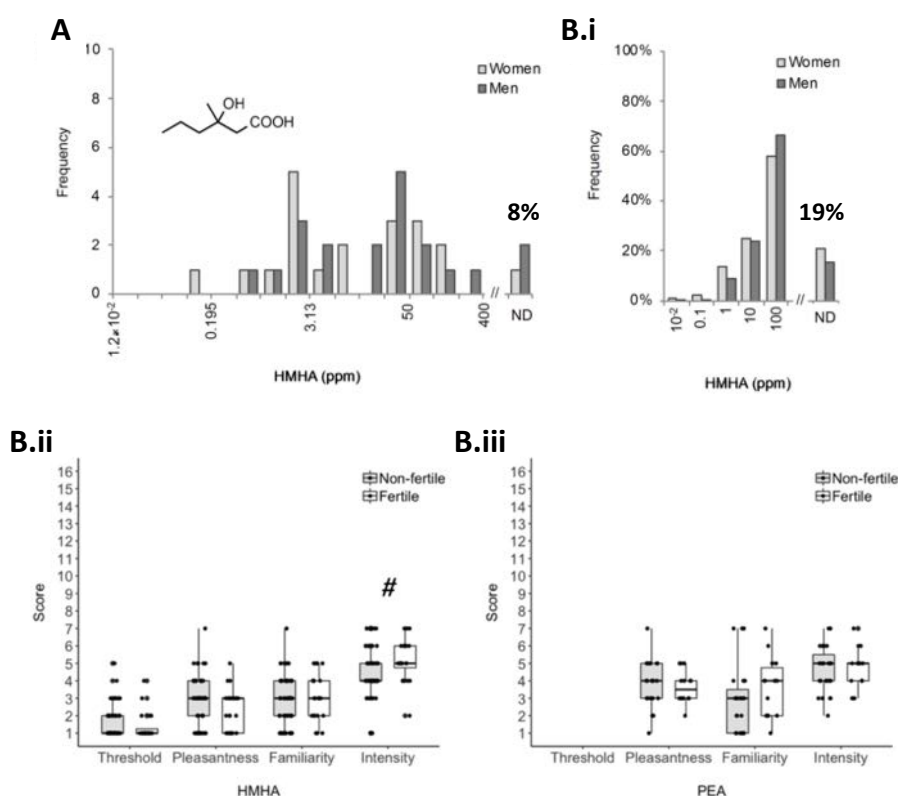


Fig. 2. French sample (N=40): **(A)** Distributions of HMHA detection thresholds in women and men, expressed in parts per million ppm (odor concentration). ND: Not Detected. Malagasy sample (N=280): **(B.i)** Distributions of HMHA detection thresholds, **(B.ii)** Ratings of supraliminal HMHA, **(B.iii)** Ratings of supraliminal PEA. From Ferdenzi et al. (2019).

Second, in another study, we investigated the *conscious perception* of HMHA and MSH to determine whether these molecules are explicitly perceived as masculine (for HMHA) and feminine (for MSH), and whether there would be gender differences in the way they were perceived. Do to so, in collaboration with Sylvain Delplanque and Géraldine Coppin (University of Geneva), we set up a simple experiment during a 1-year exhibition about olfaction at the Musée de la Main (Lausanne, Switzerland). Visitors were presented with two jars containing a t-shirt impregnated one with HMHA (1%) and the other with MSH (0.1%) (**Fig. 3A**). They had to rate the odors on several dimensions, including masculinity/femininity. The responses of 2716 visitors aged 6 to 90 years old were analyzed (Ferdenzi et al., article 1 in preparation). Gender ratings were extremely scattered (**Fig. 3B**) and there was nor a clear gender attributed to the one or the other odor, nor an interaction of rater gender with these ratings. Rather, at these concentrations, liking was a strong predictor of masculinity/femininity (the more liked, the more feminine, see **Fig. 3C**).

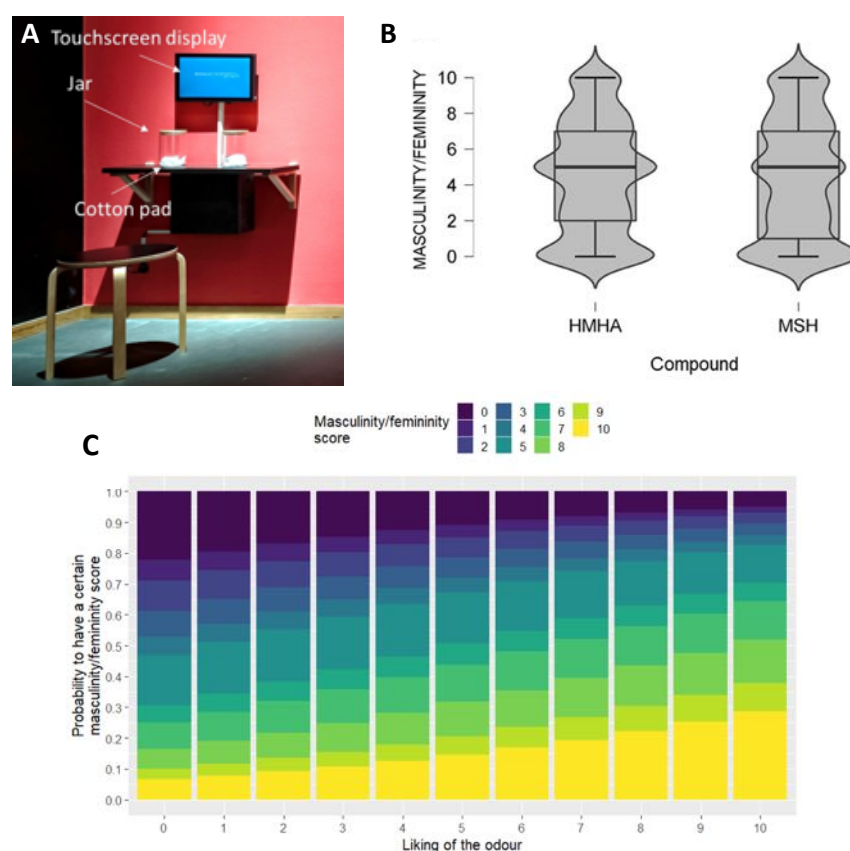


Fig. 3. (A) Experimental setup to test explicit perception of HMHA and MSH at the Musée de la Main exhibition. (B) Violin plot of masculinity/femininity ratings of HMHA and MSH. (C) Relationship between the degree of liking of the odor (x-axis, from 0: not liked, to 10: very much liked) and its perceived gender from very masculine (dark blue) to very feminine (yellow). From Ferdenzi et al. (article 1 in preparation).

Third, *brain processing* of these compounds was investigated on 30 participants using fMRI. HMHA (1%) and MSH (0.05%) were presented repeatedly with other odors from different categories: D-limonene (lemon, LIM), isoamyl acetate (banana, ISO), cis-3-hexenol (grass, CIS), butyric acid (fermented milk/vomit, ABUT), and (-)-Terpinen-4-ol (mold, TER). Participants had to evaluate odor attractiveness during the scan. When examining contrasts between each odor condition and the control (clean air) condition, we found that HMHA only activated visual areas, namely a cluster was found in the striate area and another one was found in the occipital gyrus (**Fig. 4A**). Olfactory areas

were not activated, as this happened to be the case in several other studies on body odors or body-related compounds (see our review in [Mantel et al., 2019](#)). Although being a human odor compound, MSH did not display such a pattern and was associated with activations in the amygdala (**Fig. 4B**). The other odors displayed more classical activations in primary olfactory areas (amygdala/piriform cortex), and in the insula for the most extremely pleasant and unpleasant odors (ABUT, LIM; **Fig 4C,D**). A PCA conducted on the brain activations confirms that HMHA has a distinct pattern compared to the other odors (**Fig. 4E**). There were no gender differences on odor attractiveness ratings but – unlike in the above study at the Museum – men rated HMHA as more masculine than women did. Therefore, we contrasted men’s and women’s brain activations for HMHA. We found that in men two clusters were more activated in the superior and the medial frontal gyrus (**Fig. 5A**), and in women, one cluster was more activated in the inferior frontal gyrus IFG. SFG and MFG have been reported to be activated in olfaction studies in tasks involving attention to odors (e.g., Grabenhorst et al., 2011) and multimodal integration (e.g., odor-name; [Sezille et al., 2015](#); [Fournel et al., 2017](#)). IFG is related with social processing (faces, body odors) and was found to be more activated in socially open women when presented with body odors in another study (Lübke et al., 2014). Activation in SFG and MFG were positively correlated with masculinity ratings (**Fig. 5B.i**) and negatively (significant only for MFG) with the time taken to provide attractiveness rating in the scanner (**Fig. 5B.ii**). These results could be interpreted as a greater allocation of resources in men to process the odor of HMHA and that inter-individual differences exist between them in that the more they allocate these resources the clearer the mental representation of this odor is (higher masculinity ratings, faster attractiveness judgments) ([Ferdenzi et al., article 2 in preparation](#)).

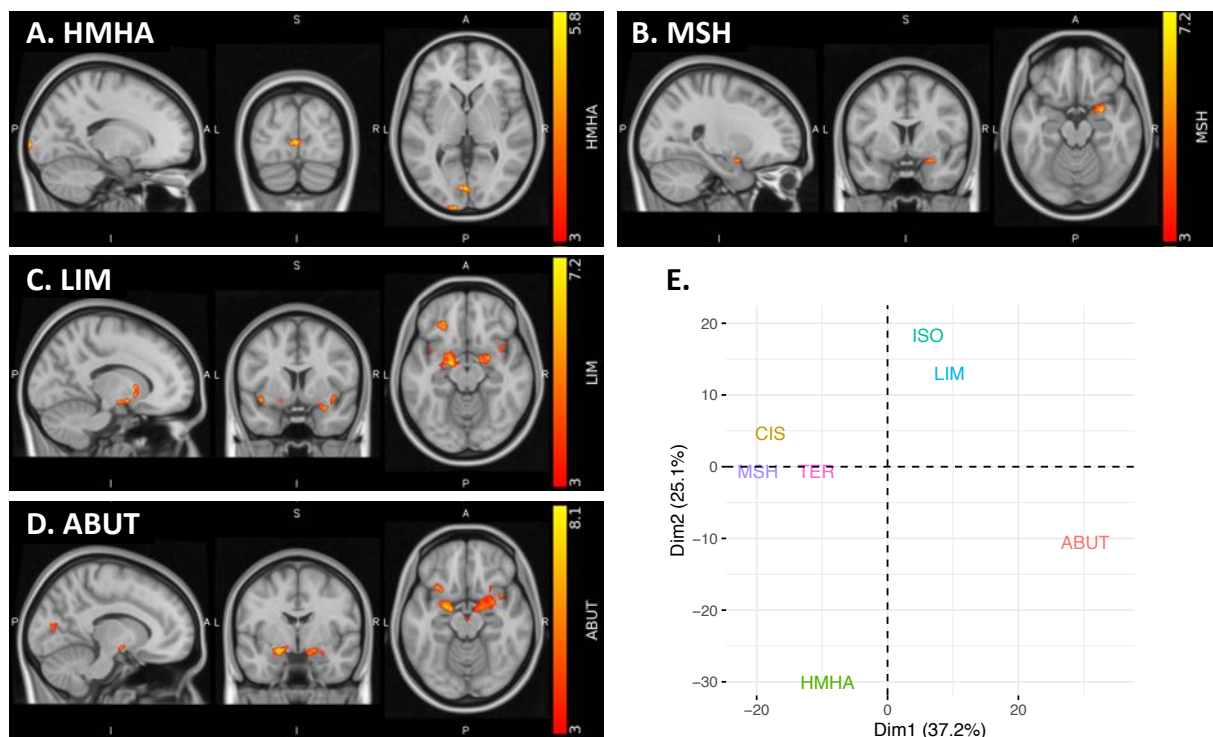


Fig. 4. Brain activations of experimental odors versus clean air (control) for the body odors HMHA (**A**) and MSH (**B**), for a pleasant food odor LIM (**C**) and an unpleasant non-food/non-body odor ABUT (**D**). (**E**) Representation of the seven experimental odors on the first two components of a PCA conducted on the brain activations. From [Ferdenzi et al. \(article 2 in preparation\)](#).

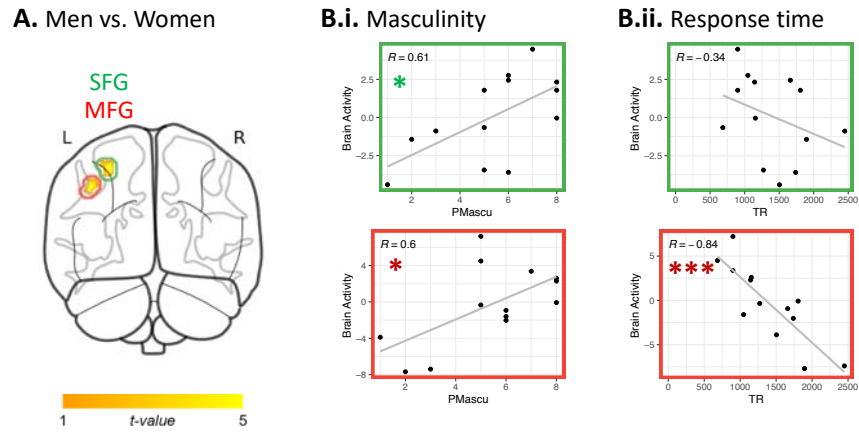


Fig. 5. Contrasts of brain activations in response to HMHA in men versus women (A). Correlation between the level of brain activity in the clusters located in the superior frontal gyrus SFG (in green) and in the medial frontal gyrus MFG (in red) and the ratings of masculinity (B.i.) and the response time to rate attractiveness during the scan (B.ii.). From Ferdenzi et al. (article 2 in preparation).

Fourth and finally, *implicit effects* of HMHA were investigated in a study on face perception. Here, the aim was to test whether HMHA could influence the perceived attractiveness of faces and their gender categorization, and whether differences between male and female raters could occur. An olfactory priming paradigm was used, with odorant stimulation delivered using an olfactometer 3.5 s before the onset of the visual stimulus (face, duration: 100 ms). Faces taken from the GEFAV database (Ferdenzi et al., 2015) were used. Four different identities were used, namely attractive and unattractive composite faces, morphed on a 9-level continuum from feminine to masculine allowing us to have faces with clear or ambiguous gender. They were presented in 3 odorant conditions: HMHA, diacetyl control odor DIA, and unscented air. The participants had to determine the face gender as quickly as possible, and then rate the face's attractiveness on a scale. We hypothesized that HMHA could help categorize the faces as being male (especially the ambiguous ones), and that it could enhance attractiveness (especially in female raters). We found no effect of odor condition and no interaction with rater gender on face gender evaluation. Regarding attractiveness however, we found an effect of HMHA (in men and women indifferently) which was limited to increasing facial attractiveness of the unattractive faces with ambiguous genders (Fig. 6B). This is consistent with

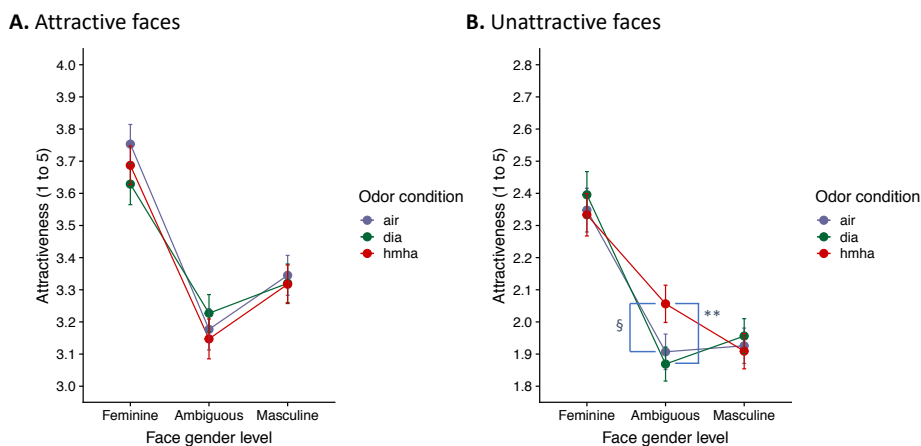


Fig. 6. Representation of the Odor (HMHA vs. control odor DIA vs. control clean AIR) by Face Gender Level (clearly Feminine vs. Ambiguous vs. clearly Masculine) by Face Attractiveness Level (Attractive (A) vs. Unattractive (B)) interaction ($p < 0.05$). **: $p < 0.01$; §: $p = 0.051$. From Ferdenzi et al. (article 3 in preparation).

previous studies showing stronger effects of body odors in ambiguous situations (Zhou and Chen, 2009; Rekow et al., 2021) and suggests that a congruency effect might have occurred with the human odor, increasing the agreeableness of the unattractive/ambiguous faces. Overall, the results of this study do not concur with sex-pheromonal effects of HMHA ([Ferdenzi et al., article 3 in preparation](#)).

➔ Overall, these experiments on sexually dimorphic compounds (AND, HMHA, MSH) showed that they had some effects on the perception of social stimuli (faces and voices) and that some of them (HMHA) seem to be processed in the brain in a distinct manner compared to non-body odors. No clear evidence for sex-pheromonal effect were found, and few gender differences in their processing were found. My position is now to investigate human olfactory attractiveness on a slightly different angle. Studying single molecules has its limits. First, we only have limited knowledge about which compounds could be relevant in human attractiveness. The literature is biased towards malodors, and axillary odors (for historical reasons): there is thus a need to increase our knowledge about body odor composition, while at the same time, to go beyond malodors and axillary sweat. Second, single compounds are never encountered alone in real life, always as a mixture with other compounds. To increase the ecological relevance of our experiments, we should find a way to study single compounds within an odorous matrix (like a standardized artificial human odor). Increasing the ecological validity of the experimental settings in which we are investigating human attractiveness is also crucial: if some attempts towards naturalistic neuroscience have been made (e.g. speed-dating experiments, Saxton et al., 2008), they unfortunately remain anecdotal to date. My future research projects, that I am introducing below, take these considerations into account.

4.2.5. Current and future challenge #1: Increasing knowledge about BO chemistry to relate it with behavioral observations

The challenge. In humans and other mammals, the study of chemical communication is much more recent than in other organisms such as plants or insects. In the last two decades, the chemical composition of human scents has received increasing interest in areas such as medical diagnosis and disease prevention, forensics, emergency search, and more occasionally in the field of cognitive psychology and affective neuroscience (e.g. communication of emotions: Williams et al., 2016; Smeets et al., 2020). The chemical underpinnings of human chemical communication remain mostly unknown, likely because explorations of the characteristics of human scent using analytical chemistry are very heterogenous and generally confined to very specific issues such as malodor management (Haze et al., 2001; Natsch et al., 2005; Starkenmann et al., 2005).

The chemicals emitted by the human body are volatile organic compounds (VOCs, which are targeted when investigating communication through the olfactory system), but also semi- and non-volatile compounds that emanate from the skin, urine, sperm, vaginal secretions, sweat and breath. Various sampling methods have been used to analyze human body odor (see Dormont et al., 2013a, for a review), including solvent extraction, solid-phase micro-extraction (SPME) and stir-bar sorptive extraction (SBSE), or other types of VOC-traps (Tenax, Porapak Q). Analysis is then often performed with Gas Chromatography - Mass Spectrometry (GC-MS) (see review in [Ferdenzi et al., 2020](#), for alternatives). Choosing the most suited technique must be carefully weighted (Drea et al., 2013) depending on the studied substrate (human scents are complex and diverse) and the pursued goal (e.g., understanding individual's full chemical signature for forensic applications versus investigating olfactory detection of airborne attractive compounds).

To date, the knowledge about the chemical composition of human body odor remains heterogeneous and incomplete. Diverse methods are used for sampling and for analyzing. Outcomes are therefore hardly comparable, which is worsened by the small number of donors involved and by the large number of VOCs found (Agapiou et al., 2015). These VOCs are sometimes listed without discussing their origin: it has been estimated that nearly one third of the molecules reported in mammals are either misnamed or not likely to have been produced by the studied organisms (Charpentier et al., 2012), therefore emphasizing the need for a critical attitude towards the origins and roles of the compounds found. The complexity and fluctuations of human body odor (due to physiological state, exogenous sources such as diet, drugs or cosmetics) constitute a serious challenge. More research is needed in this area, and I have modestly started to explore this path thanks to a research grant of the Fyssen Foundation.

Current developments. Since 2018, my aim is to develop a collaboration network and suitable methods to perform chemical analysis of human BO, so that I will be able to relate behavioral observations (odor ratings, behavioral effects of odors) with chemical characteristics of the odor in my future research. There is no consensus and no method in perfect running order to analyze the VOCs emitted by the human body, at least with finer approaches than those implemented to identify the major/most typical compounds of sweat. In my research projects, I would like to be able to explore and detect subtle variations as a function of individual characteristics. Note that the four series of pilot studies presented hereafter have been conducted with my PhD student Stéphane Richard Ortegón, as methodological prerequisites to his project about emotion communication (see Section 4.3) and with the help of 3 bachelor (Liza Brettnacher) and master students (Alexia Lamblin, Valentine Brémont-Bostoen). None of the results have been published yet, and some data is still being analyzed at the time I am writing this report.

First, we performed *solvent extraction* at CRNL, where compounds are collected on a medium and then extracted with a solvent. We conducted two pilot studies in 2019 and 2020 in collaboration with Nicolas Baldovini at the Institut de Chimie de Nice, with the help of two chemistry students (Liza Brettnacher and Alexia Lamblin). We collected BO samples in Lyon, on cotton or gauze pads affixed with metal snaps on the axillary region of a 100% cotton t-shirt (see **Fig. 7**). The pads and t-shirts were

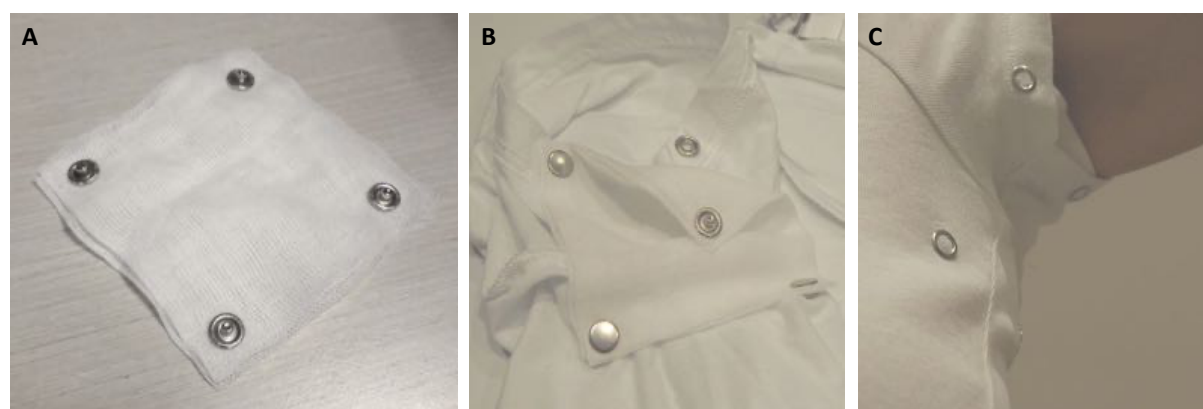


Fig. 7. (A) Cotton gauze pads used for chemical analysis with solvent extraction. (B, C) fixation system with metal snaps on the axillary region of a 100% cotton t-shirt.

rinsed with methanol and dichloromethane, and carefully dried before being used for BO collection. From two days before odor collection, odor donors followed a protocol to prevent odor contamination

and limit unwanted variations (food and other behavioral restrictions, use of non-perfumed cosmetic products). Pads were worn over night and then frozen. Extraction was performed at CRNL following a preliminary protocol designed by Nicolas Baldovini to isolate the acidic fraction of the sweat sample. This consisted in several steps involving addition of solvent (methanol and dichloromethane), sodium hydroxide (NaOH) and hydrochloric acid (HCL), evaporation, centrifugation and drying. Extracts were then sent to Nice to be analyzed with GC-MS. However, this procedure proved to be rather unsuccessful in terms of quality of the obtained chemical profiles, and was difficult to implement (needs chemistry skills and know-hows that we don't have in the Neuropop team, very time consuming, costs and constraints for sample shipping in temperature-controlled conditions). We chose to not give more efforts in this path due to limits, among which the most significant are: 1) cotton/gauze pads contain many undesirable compounds making the interpretation of the chemical profiles difficult, 2) solvent extraction is likely to capture compounds that are not volatile and that are not involved in airborne chemical communication (which is what we are interested in), 3) evaporation steps make us fear that some VOCs are lost in the process.

Second, we initiated discussions with laboratories investigating plant chemistry (Gilles Comte at the Centre d'Étude des Substances Naturelles CESN, Lyon; Sylvie Baudino and Benoît Boachon at the Laboratoire de Biologie Végétale appliquées aux Plantes Aromatiques et Médicinales LBVPAM, Saint Etienne). We conducted a pilot study in December 2019 at the LBVPAM using the same procedure routinely used to analyze VOCs emitted by flowers. The method used is a *dynamic headspace* sampling where air circulates in a headspace thanks to a pump (see **Fig. 8**) and where the outgoing air passes through a small trapping tube filled with a porous polymer adsorbent matrix Porapak™. This matrix is then *eluted with a solvent* (hexane) added with a standardized quantity of camphor (to help quantifying the compounds from the studied sample). Note that although elution with a solvent could be replaced by thermodesorption, this is not a preferred option since it does not allow to reanalyze the sample several times. Overall, this pilot study conducted on BO samples collected on cotton gauze pads revealed a very high level of contamination, again confirming that our collection procedure may not be the best option. After having used indirect sampling (via a medium: cotton gauze pads) in these two series of pilot studies, we concluded that we should use direct sampling near the skin. The challenge was then to invent a new device adapted to the specific configuration of the axilla, that allows the adsorbent material to be near the skin but not in contact with it (to avoid collecting molecules that are not VOCs). We began to address this challenge with new collaborators in the third series of pilot studies.



Fig. 8. (A) Device for dynamic headspace sampling of VOCs produced by roses. (B, C) Same device with BO samples collected on cotton gauze pads.

Third, we then started a collaboration with Laurent Dormont, from the Centre d'Écologie Fonctionnelle et Évolutive (CEFE) in Montpellier. In February 2020, we tested a series of methods: direct and indirect sampling, both in static and dynamic headspace (see **Fig. 9**). For the indirect sampling, we collected BO on gauze pads that we placed in glass flasks covered with a Nalophan film (which was chosen because its high level of inertia allowing to minimize surface interactions with the sampled odor, see Dormont et al., 2013b). For the direct sampling, we created a headspace around the axilla using a Nalophan bag. For both kinds of sampling, we collected VOCs using: 1) a SPME fiber (PDMS/DBV adsorbent) inserted through the Nalophan, 2) a Twister (stir bar, PDMS adsorbent) placed in suspension in the headspace using a hose clamp, and 3) a chromatoprobe (containing a mix of Porapak and Tenax) also inserted through the Nalophan and connected to a tube so that air inside the headspace could be pumped through the chromatoprobe. VOC collection was performed at CRNL on three donors (2 women, 1 man), for 60 minutes (SPME, Twister) and 30 minutes (Chromatoprobe). BO samples were analyzed at CEFE in Montpellier, using thermal desorption in GC-MS, after keeping the adsorbent devices at ambient temperature for a few days. The results again showed that indirect measurement provides low quality profiles due to many contaminants, and that the Twisters and SPME with direct sampling provided the best chemical profiles. Since Twisters have a greater surface of exchange and are easier to use than SPME (i.e., twisters are less fragile, less space consuming, and they have a magnetic property that can be useful), we decided to continue with this device.

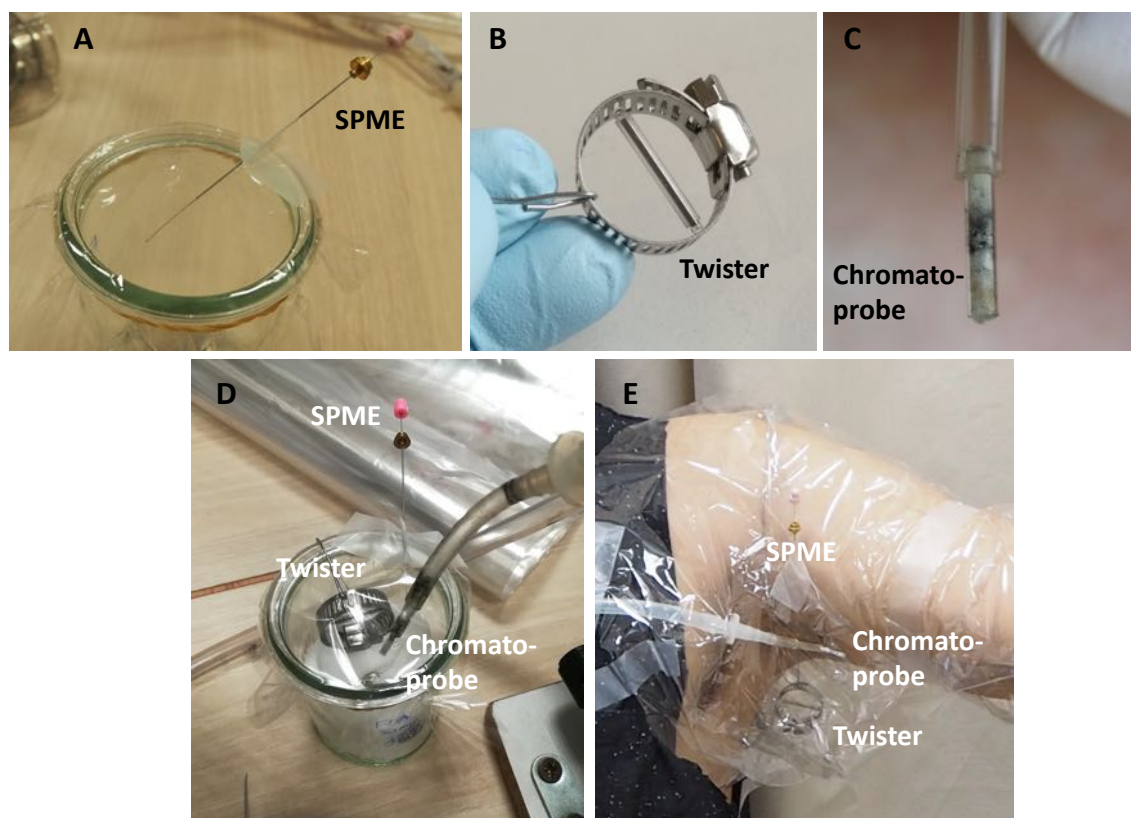


Fig. 9. Adsorbing devices tested: (A) SPME fiber (PDMS/DVB, Supelco), (B) Twister (PDMS, Gerstel), (C) Chromatoprobe (Porapak and Tenax). Experimental setup for (D) indirect sampling on cotton gauze pads, and (E) direct sampling in a headspace near the axilla.

Fourth, during the first semester of 2021, we conducted a series of measurements using the Twisters and other devices – Getxent Biodesiv and Powersorb (similar to the Twisters except that these are single-use and flexible), after having developed a new collection prototype that we called ABOV (Analysis of Body Odor Volatiles) and that meets the following constraints. 1) A headspace is constituted near the skin. 2) The adsorbent phase is not in contact with the skin and thus collects only volatiles. 3) The environmental conditions are modified as little as possible, to preserve the normal functioning of the bacteria. In particular, the bacteria must not be deprived of air. 4) The number of different materials used in the collection device must be reduced to a minimum to limit possible contamination by molecules that could be released. 5) The device is adapted to the axilla, but also allows to collect other odor sources like the neck or any other part of the body. We developed the ABOV device as a home-made version first (**Fig. 10**), and then improved and produce it thanks to local companies specialized in the manufacture of clothing and in stainless steel work (**Fig. 10.C.iii**).



Fig. 10. (A) Our newly developed ABOV device for the collection of VOCs from the human body. (B) Positioning of the device on the axilla and the neck. (C) Detail of the inside of the headspace where springs are used to position the Twisters and Getxent tubes or Powersorbs in suspension in the headspace without touching the skin.

Four studies were conducted in collaboration with Damien Steyer, CEO of Twistaroma in Strasbourg France, and Laurent Dormont, CEFE Montpellier. In the first study (February 2021), we collected VOCs in the neck and axilla of two men and two women using PDMS Twisters and miniaturized prototypes of the Getxent Biodesiv tubes. Using automated analysis, the results showed that Twister (or SBSE) profiles were richer than Getxent profiles and the latter were much less discriminant between the different samples. In the second study (may 2021), repeated collection on two women's axilla allowed to test the possible interactions between adsorbent devices placed in the same headspace (two Twisters or Twister + Powersorb vs. only one device). Results revealed little interaction, therefore allowing to use such a configuration if needed. The third study (Sept 2021) consisted in testing an

artificial odor, namely a mixture of compounds present in human sweat odor, to examine the performance of the method we have chosen for the analysis of the human volatiles (data not analyzed yet). Finally, the last and larger study (June-July 2021) involved 20 donors (9 males and 11 females), collected in neck and axilla of both sides (left and right) with Twisters. Thanks to duplicates, twisters were analyzed in GC-MS at CEFE and at Twistaroma who slightly differ in the materials and methods they use to analyze and interpret the data. As the pre-processing and interpretation of the chemical profiles is currently ongoing, we cannot present any results yet. But our aim here is to perform a distance analysis (see simulation of a Principal Component Analysis on chemical profiles of each sample in **Fig. 11**) between i) sides (left vs. right) for a given odor source of a given individual, ii) sources (axilla vs. neck) of a given side of a given individual, and iii) individuals (#1 to #21). It is expected that inter-side distances would be smaller than inter-source distances, which in turn would be smaller than inter-individual distances. It is also expected that we can identify the molecules that contribute the most to differentiate between the odor sources, and between the individuals or groups of individuals (according to sex, for instance).

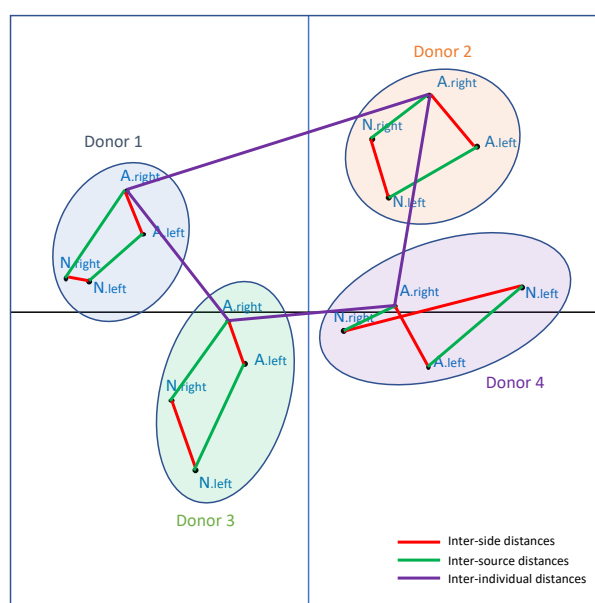


Fig. 11. Simulation of a PCA analysis on the chemical profiles obtained for different individuals (donors) sampled on their left and right axilla (A) and neck (N). An analysis between different categories of distances will allow us to test whether $\text{inter-side distances} < \text{inter-source distances} < \text{inter-individual distances}$.

➔ All together these pilot studies have allowed us to make considerable progress in the identification of suitable scientific collaborators and in the development of suitable methods to investigate the chemical underpinnings of behavioral and perceptual observations that we will make during future experiments on BO attractiveness. I am planning to publish a methodological article presenting both the ABOV device and the results on side, source and individual differences in BO chemical composition. Further, we are going to keep improving and implement these methods in several projects detailed hereafter.

Future project: Biodor-IN (part 1). The current developments presented above in terms of chemical analysis of skin volatiles will serve different future projects that I will present here (regarding human attractiveness) but also later in this document (regarding the communication of emotion, and other information related to individual physiological state). Given that the study of individual molecules of the human body odor (AND, HMHA, MSH) only provides limited information about chemical communication of human attractiveness (see previous sections), I have proposed to investigate this question in a new project, Biodor-IN. Biodor-IN is funded by the French National Research Agency (Young Researchers Programme JCJC) and started in October 2021 with a PhD student (Valentine Brémont-Bostoen) that I am supervising with Laurent Dormont (CEFE Montpellier). A postdoc and three master students will be involved as well. Biodor-IN is going to face several challenges. The aim of the 1st work package of this project (WP1; WP2 will be detailed in the next section) is to develop the knowledge of human biological odors through the study of other relevant odor sources than just the axilla and of other single compounds than the few ones already studied. Indeed, knowledge of human body odor is mostly based on unpleasant smells from the axilla (sweat malodor) while more subtle signals from other odor sources may be crucial in human chemical communication: breast (Doucet et al., 2012), hands (Frumin et al., 2015), tears (Gelstein et al., 2011) or head (Ferdenzi et al., 2020). This entails difficulties related to the necessity to develop new protocols (for body odor collection and analysis), and to gather several disciplines (incl. neurosciences, behavioral sciences, sensory sciences and chemistry) but first steps in these directions have already been made as explained in previous paragraphs. A main aim of Biodor-IN is to identify which parameters of body odor provided by donors may be relevant in human attractiveness, by investigating the responses of receivers according to the characteristics of the donors. We will also investigate how perfumed cosmetic products may modulate receivers' responses to body odors. To achieve this, three experiments are planned.

The *first experiment* will consist in a perceptual and chemical characterization of individual body odor samples. A total of 180 donors including prepubertal children (6-10 years old), young adults (18-35 years old, heterosexual, women not taking hormonal contraception) and older adults (> 50 years old, heterosexual, menopausal women) will provide body odor samples once or twice in young women (during fertile and non-fertile phases of their menstrual cycle). Adult donors will constitute a database serving for the whole Biodor-IN project, and will also be genotyped for MHC (see section 4.2.1.). Samples will be analyzed in GC-MS, but also evaluated by the other adult donors. During the rating sessions, the axillary and head (or neck) odor of individuals differing in age, sex, MHC similarity, and phase of the cycle will be presented, and the raters will provide verbal evaluations (intensity, familiarity, pleasantness, attractiveness, sex typicality, detailed description using specific vocabulary; see Fig. 12).

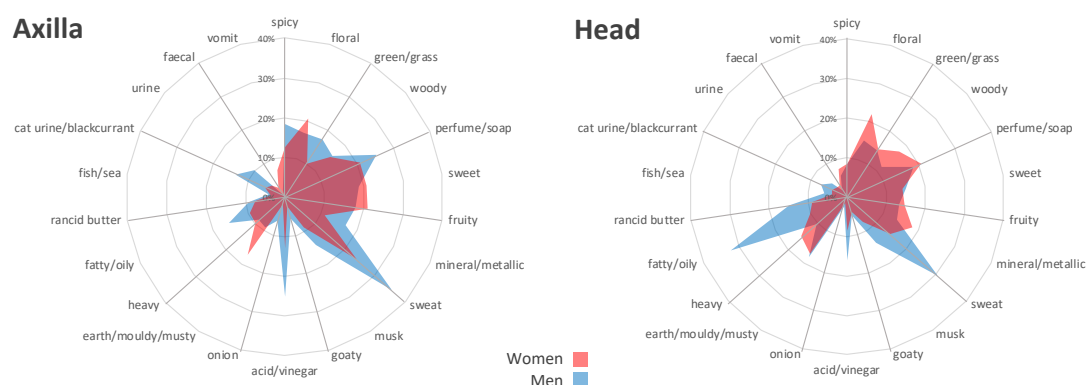


Fig. 12. Perceptual profile of women and men axillary and head odors, based on specific descriptors' use. Data used in [Ferdenzi et al. \(2020\)](#).

Olfactomotor behavior (sniffing) in response to each odor will be recorded, using a home-made apparatus and software (Sezille et al., 2013), as an early measure of affective responses to smells during the first few seconds after odor onset (see Ferdenzi et al., 2014, 2015b). This experiment aims at investigating the factors underlying odor attractiveness (sex, age, hormonal status and MHC-similarity) not only in a perceptual space, but also in more implicit affective responses (sniffing) and with regards to the chemical composition of the odors. Analyses at the individual and at the group level will be performed, searching for general and individual-specific preferences. Importantly, multivariate analyses will be conducted to test whether there is a link between similarity and diversity of the perceptual and chemical profiles on the one hand, and similarity and degree of heterozygosity for MHC on the other hand.

The *second experiment* will evaluate the impact of perfume on the perception of body odors that will have been found as the most relevant in the first experiment. Three conditions will be implemented on the donors: perfumed products forbidden, using the usual perfumed cosmetics, and using a perfumed product imposed by the experimenter.

Finally, the *third experiment* will evaluate neurophysiological responses to composite axillary and head samples (i.e. blends of several individuals) from donors of the opposite sex. It will consist in two sessions, one for autonomic nervous system (heart rate, skin conductance) and motor responses (facial EMG, sniffing), and one for central nervous system responses (fMRI). Anatomical followed by functional sessions with repeated odor stimulations will be implemented during which participants will evaluate odor attractiveness. This part of the project will be conducted by a postdoctoral student. It will provide new knowledge on the physiological and neural correlates of attractiveness, by determining whether odor attractiveness is associated with specific patterns of physiological responses (decreased heart rate, increased skin conductance) and brain activations (larger recruitment of brain circuits involved in sexual arousal such as hypothalamus, fusiform gyrus, orbito-frontal cortex).

→ Combined, the results of these three experiments will hopefully allow identifying which odor source (axilla, head), which individual characteristics, and maybe more precisely which chemical compounds, have a significant role in human attractiveness, in men and women separately. To go further, the other work package of the Biodor-IN project (WP2) tackles another challenge that is presented in the next section: How to increase ecological relevance of the study of human olfactory attractiveness.

4.2.6. Current and future challenge #2: Increasing ecological relevance of the behavioral testing

The challenge. Human chemical communication has been studied using mostly verbal descriptions of how body odour samples are perceived, either with rating scales (pleasantness, intensity, attractiveness, etc.) or with preference tasks. Indirect tasks have also been used, requiring social stimuli (e.g., faces: Ferdenzi et al., 2016; real persons : Saxton et al., 2008) to be rated after being primed by or in the presence of a body odor or a body odor compound. However, how chemosignals influence our biology and cognition, and ultimately our behaviors, is likely to be a covert process, which is not necessarily measurable with conscious verbal methods. Future research would certainly gain in

developing paradigms to measure overt behaviors. For example, motor behaviors are sometimes (but rarely) measured, especially when language is lacking: e.g., head orientation of infants towards odors spatially distributed (Marlier and Schaal, 2005), or reach-to-grasp action towards an object in children with autism (Parma et al., 2013). Other motor behaviors appear to be relevant, such as odor sampling behaviors, measured indirectly, e.g., by recording the frequency with which someone brings his/her own hand near the face after hand-shaking (Frumin et al., 2015), or directly, e.g., by recording airflow variations in the nostrils (sniffing behavior: Mainland and Sobel, 2006). The latter, however, has never been used to our knowledge in the context of social communication in humans (but see Jaenig et al., 2018, for non-human hominids). Ideally, behaviors displayed in real social interactions (e.g., speed dating experiment, see Saxton et al., 2008) and indicating attraction or repulsion towards someone would be very informative. However, although being highly ecologically valid, such approaches face numerous experimental biases, such as uncontrolled sensory and behavioral factors inherent to the interacting person. Therefore, crafty alternatives could be developed, such as associating the diffusion of body odors with artificial standardized individuals, using virtual avatars (Kim et al., 2015) or physically present manikins (Endeveldt-Shapira et al., 2018).

Future project: Biodor-IN (part 2). As an attempt to address this challenge, the project Biodor-IN proposes to develop a virtual social interaction paradigm to test, in close to real life situation, the impact of body odors on person's behavior. Manipulating the body odor of real persons – who never are odorless – is very challenging for scientists who wish to investigate the influence of body odors on social interactions. We propose to lift this barrier by using a strongly innovative protocol involving the use of virtual reality. Thanks to the development of body odor diffusion in neuro-immersion settings, we will be able to attribute the odor of our choice to an odorless interactant. Three experiments are planned in WP2 of the Biodor-IN project.

In the *first experiment*, we will examine the effect of body odor on interpersonal distances using virtual reality. The odorized virtual social interaction setting will be previously developed in collaboration with i) Marc Thevenet, research engineer in the Neuropop team, with whom I will co-supervise a master student to enable odor diffusion to the participant's nose with our olfactometer while the participant is in motion, and with ii) the Neuro-i platform of the CRNL led by Alessandro Farne, where virtual social interactions are already implemented in several projects and will be taken up and adapted to the requirements of our experiment (e.g., for avatars' faces it will be possible to use stimuli from the GEFAV with known levels of attractiveness, [Ferdenzi et al., 2015a](#)) (**Fig. 13**).

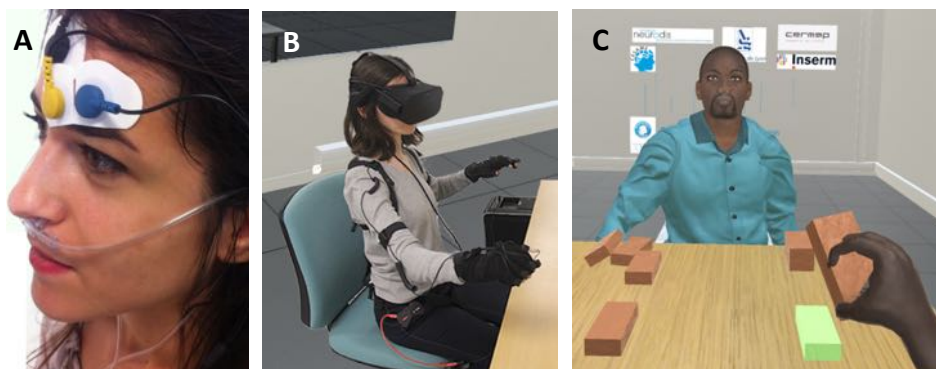


Fig. 13. Example of a setting where odors are diffused under the nostrils thanks to a nasal canula connected to an olfactometer (A) and of neuro-immersion setting developed previously for another project by the Neuro-i platform of CRNL involving a virtual social interaction (B).

In this experiment, participants who will not be intensive virtual reality users will interact with 3 different virtual avatars in 3 odor conditions (1 control, i.e. clean air, and 2 experimental odors) allowing to test the effect of odors in a within-subject design. The experimental odors will be chosen according to the findings of WP1 (Section 4.2.5.) as the most significant for opposite-sex attractiveness. Participants will smell samples from individuals of the opposite sex (composite body odor samples) or one or a mixture of isolated compound(s). Participants will have to evaluate the distance between them and the avatar, and in another task, they will have to approach the avatar. The attractive power of an odor will be illustrated by a shorter perceived distance and by quicker approach and shorter distance maintained between the participant and the avatar.

In the *second experiment*, the effect of context on body odor modulation of social interaction will be tested using virtual reality. A protocol similar to the one of the first experiment will be used. Participants will interact with a virtual avatar in two different odor conditions and four different contexts in which they are totally immersed: no context (no visual stimulation), a context without social interaction in a given place, the same place with a neutral social interaction, the same place with intimate social interaction with someone of the opposite sex. We will record psychophysiological responses of the receivers (heart rate, skin conductance), and motor responses (olfactomotor behavior, EMG, interpersonal distance). The results will indicate how relevant odors influence the perception of a social scene and of interpersonal distance, depending on the context of the social interaction. As evaluations of the odor will also be collected, it will provide information about how the perception of a body odor can be modulated by social context, which is of high relevance both from a fundamental point of view but also from a methodological point of view (many studies on body odors present odor samples in flasks in a decontextualized laboratory context).

In the *third experiment*, we will focus on the effect of gender stereotypes on body odor perception, again using virtual reality. The participants will be presented with twelve composite body odor samples from donors selected according to the gender typicality of their odor. High and low gender typicality will be included, and donors of both sexes will provide body odor samples on 3 occasions: once with no perfumed products allowed, once while using a perfumed product typically female and once while using a perfumed product typically male (both fragrances being imposed by the experimenter). Participants in the virtual reality setting will either be presented with the odors alone (no visual context), or with avatars being either clearly male, clearly female or with ambiguous gender. We will record verbal responses of the receivers (evaluations of the avatar, the odor and the interpersonal distance), and motor responses (olfactomotor behavior, EMG, interpersonal distance). The results of this experiment will provide information about the extent to which olfactory and visual cues of gender interact with each other, and how this can be modulated by perfume use. As donors will provide detailed information about their hygienic/cosmetic habits, this will also allow us to investigate separately whether gender level of atypicality of natural odor is associated to specificities in terms of perfume use.

Combined, the results of these three experiments will allow a deeper understanding of how body odors influence human behaviors during social interactions. Using virtual reality, the experiments will provide naturalistic testing of how the body odors identified as being potentially important in opposite-sex attractiveness influence the perception of others non-consciously (in terms of interpersonal distance) and consciously.

4.3. Human body odor (BO) and communication of positive emotion

4.3.1. Introduction

As mentioned earlier, information about individuals can be communicated through cues contained in their biological odors, including information about their emotional states. For example, BO samples of stress collected on donors during first-time skydiving (Mujica-Parodi et al., 2009) or during academic examinations (Pause, 2004) elicit, when presented to receivers, modifications of the neurophysiological responses (increased activation in the amygdala) and of the ratings of facial expressions, i.e. a facilitated perception of anger in faces with ambiguous facial expression. The responses of the receivers are interpreted as a replication of the emotional state (emotional contagion) that allows the organism to narrow its attentional focus on cues of potential threat and thus to be prepared to adequately respond to it. A meta-analysis was conducted by de Groot and Smeets (2017) on a total of 26 studies investigating the capacity of humans to communicate fear, stress, and anxiety via body odor from one person to another. This study found that communication of these negative emotions is likely to be a true effect, with a small-to-moderate size, and that does not seem to be subject to publication bias or selective reporting.

However, whether positive emotional states can also be chemically communicated is a question that remains to be explored. Indeed, positive affect has traditionally been neglected in psychological studies (Seligman and Csikszentmihalyi, 2000). This may be explained by the fact that they are more idiosyncratic than negative ones and thus more difficult to elicit in laboratory settings. This could also be explained in the light of an evolutionary perspective. Negative emotions have a strong and immediate adaptive function: They allow to quickly answer to threats and thus to survive. Failing to respond appropriately to positive emotions is not likely to have such life-threatening consequences (Pratto and John, 1991), at least not in the short term. However, positive emotions have a major impact on our psychology and our health. Happier people display more stable marriages, have stronger immune systems and are more creative (Lyubomirsky et al., 2005). These relationships are not only correlates: rather, longitudinal studies suggest that there might be a real causal effect of positive emotions (Lyubomirsky et al., 2005).

Very few studies have explored “happy” sweat. In a first study investigating the ability to select the BO samples from happy donors among fearful donors and blanks, Chen & Haviland-Jones (2000) showed that participants were able to do so at an above-chance level (women for samples of all donors, and men for samples of female donors only). Zhou & Chen (2009), using pieces of BO pads tapped underneath the receivers’ nostrils, found that fear sweat – but not happy sweat – biased the recognition of emotions in faces with ambiguous expressions. Namely, receivers interpreted ambiguous expressions as more fearful when exposed to the fear sweat. After investigating implicit effects, these authors used a more explicit approach (Zhou and Chen, 2011). They showed that receivers could discriminate happy sweat from neutral sweat at above-chance level, but that they were less accurate at doing so than when discriminating fear sweat (compared to neutral sweat). They were however unable to verbally identify the donors’ emotion based on their smell. Finally, de Groot and colleagues (2015) highlighted not only the communication of positive emotional information, but also provided evidence of a replication of the donor emotional state in the receivers (i.e., emotional contagion; Hatfield et al., 1993). Indeed, they found that exposure to happy sweat elicited happier facial expressions and a more global processing style, in comparison with fearful sweat. As opposed to local/focused processing style, global processing has been robustly linked with positive affect (Ashby

et al., 1999). During the PhD of Stéphane Richard Ortégón, in collaboration with a cosmetics industrial partner, we conducted several experiments detailed hereafter to better understand the chemical communication of positive emotion, integrating its interaction with perfume use, its chemical underpinnings and its modulation by individual factors.

4.3.2. Positive emotion contagion through body odor

Study 1 – classical emotion induction (videos). In a first study, we aimed at testing whether positive emotions can be communicated through body odor, and to determine to what extent the addition of perfume can modulate this. We collected sweat from male donors during a positive and a neutral Mood Induction Procedure (MIP, 30-min video sequences) performed 2 days apart. The BO samples were cut into small pieces and frozen. During the receiver sessions, BO samples of four donors were put together in a glass U-tube and their odor was diffused to female receivers' nose through a nasal canula using an olfactometer (**Fig. 14A**). Receivers' responses were examined at three levels: verbal descriptions of the odors, peripheral nervous systems' responses (heart rate, skin conductance, **Fig. 14B**), motor activity of the facial muscles (**Fig. 14A**), sniffing (**Fig. 14C**) and performances in creativity and problem-solving tasks (**Fig. 14D**). Indeed, the influence of emotional body odors is more likely to remain below the level of consciousness, and should be measurable on physiological and/or behavioral responses as shown in previous studies (Li et al., 2007; Ferdenzi et al., 2016). Especially, we chose to use creative problem-solving and divergent thinking tasks (Alternate Uses Task, Guilford, 1967; Candle Problem, Duncker, 1945), based on the “broaden-and-build” theory by Fredrickson (1998), which proposes that positive emotions increase attentional scope and allow more flexibility in the thoughts.

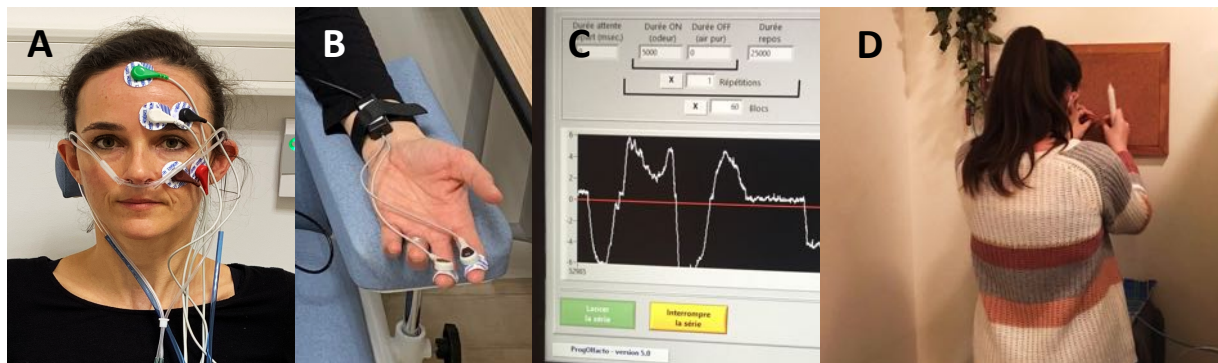


Fig. 14. BO are diffused through a nasal canula connected to an olfactometer (**A**), while physiological responses are recorded (heart rate, skin conductance (**B**)) as well as electromyographic (**A**) and olfactomotor (**C**) behavior. Performances in problem solving tasks are also recorded, such as in the Candle problem (**D**).

In this study, our findings suggest that positive emotions can be transmitted through body odor. They induced modifications at the physiological and behavioral levels. Heart rate slightly decreased (**Fig. 15A**) and skin conductance increased (**Fig. 15B**) in response to the positive versus the neutral BO. Deceleration of heart rate is usually found in response to pleasant stimuli (Alaoui-Ismaïli et al., 1997; Bensafi, 2002) and increase of skin conductance indicates higher arousal (Bensafi, 2002), suggesting that in our study positive BO induced a positively valenced and aroused state. In addition, positive BO was associated to improved performance in creativity tasks: Higher fluency and flexibility scores were found in the Alternate Uses Task (**Fig. 16A,B**), as well as shorter solving time in the Candle Problem

(Fig. 16C). Taken together, the results observed at the physiological and the behavioral level are consistent with each other. They suggest that emotional contagion may have occurred at two levels in the experimental setting, even though the design only provides indirect evidence of it. Interestingly, these effects occur without receivers' awareness since 97% of them reported not to smell anything when presented with body odors alone. Finally, we also tested the effect of perfume by adding one drop of a fragrance to the BO samples when placing them in the glass U-Tube. Note that this was tested only on verbal ratings – that participants were forced to provide even when they did not smell anything – and on physiological and motor responses (within-subject design), but not on creativity performances (between-subject design). Perfume interfered only with verbal evaluations, increasing positive body odor intensity and familiarity compared to the neutral body odor, while both odors were perceptually similar (and mostly not consciously perceived at all) when presented unperfumed. An effect that can be interpreted as a synergy with the positive emotion (Richard Ortegón et al., submitted; Appendix A).

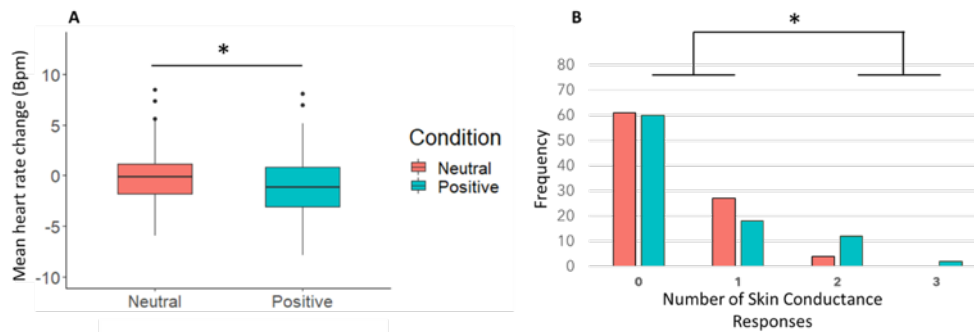


Fig. 15. Heart rate change (A) and number of skin conductance responses (0 to 3) (B) in receivers presented with BO collected either during a neutral (orange) or a positive (blue) Mood Induction Procedure. *: $p < 0.05$ (for a heart rate: main effect of Condition in an analysis with linear mixed models; for skin conductance: Chi-square test comparing 0-1 to 2-3 responses). From Richard Ortegón et al., submitted.

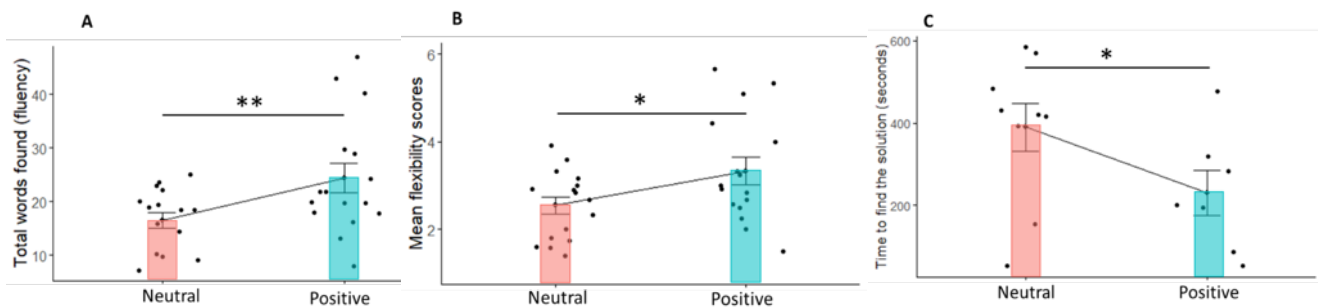


Fig. 16. Performance in creativity tasks when exposed to the BO collected during a neutral (orange) or a positive (blue) Mood Induction Procedure: fluency (A) and flexibility (B) in the Alternate Uses Task, and mean time taken to find the solution in the Candle Problem (C). **: $p < 0.01$; *: $p < 0.05$ (main effect of Condition in an analysis with linear mixed models). From Richard Ortegón et al., submitted.

Study 2 – towards a more powerful emotion induction (with VR). In a second study, we used a protocol very similar to Study 1, except that we investigated another Mood Induction Procedure using Virtual Reality (VR) instead of videos, because immersion was expected to be more powerful (by increasing the feeling of presence to the environment and the vividness of the situation: Steuer, 1992). This new study took place at the Neuro-i platform of CRNL, where we developed a virtual environment with the engineers of the platform Anne Lelgouarch and Clément Desoche. In the positive condition, the donors (**Fig. 17A**) were placed in a pleasant environment (**Fig. 17B**) where they could choose between different activities chosen to induce positive emotions like creative ones or travelling in beautiful places of the world. In the neutral condition, the actual experimental room was reconstituted as a virtual environment (**Fig. 17C**) and the proposed activities were a construction game and the neutral videos used in Study 1.



Fig. 17. Virtual reality setting (A) and environments designed for the positive (B) and neutral (C) Mood Induction Procedures, with examples of activities proposed for each condition on the right.

A first important result of this study is that the ratings of happiness of the donors (who were independent in Study 1 and 2) were significantly higher during the VR induction than during the video induction (**Fig. 18**). VR was thus clearly more powerful than videos to induce positive emotions. However, the results we obtained with the video induction were unfortunately not replicated. Although some results displayed the same pattern as in Study 1 (higher skin conductance and faster problem solving) these effects did not reach significance. An explanation could be that there was not enough contrast (emotionally speaking) between the neutral and the positive emotion induction with VR. Indeed, participants were selected to have very little experience with VR, therefore the neutral condition may not be as neutral as expected and could have been much more arousing than with videos (this can however not be verified since we had no physiological measurement of donor's

arousal). However, in line with this hypothesis, we found that the BO collected during the VR experiment (Study 2) were much more arousing in the receivers than BO collected during the video experiment (Study 1): there were twice more skin conductance responses to BO obtained during induction with VR than to BO obtained with video induction, and these numbers go up to 4 per receiver (instead of up to 3 with videos) (Richard Ortegón et al., article in preparation). Further research is needed to disentangle the effect of arousal, not only valence of the emotion, on the chemical communication of emotion.

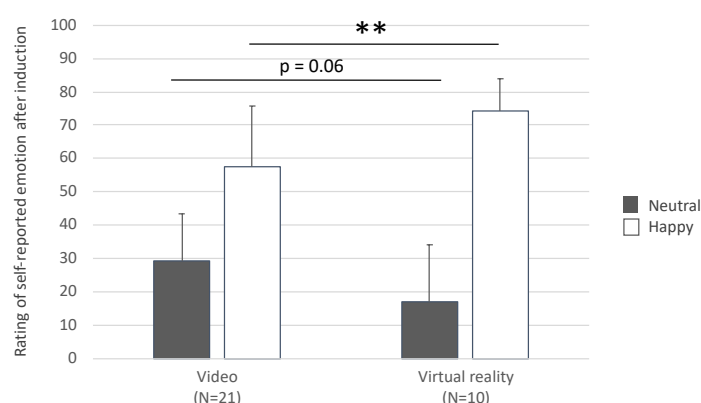


Fig. 18. Average ratings of self-reported neutral and happy feelings following the positive Mood Induction Procedure using video (in Study 1) and virtual reality (in Study 2). From *Richard Ortegón et al. (article in preparation)*.

Perspectives. Many perspectives can be envisaged following these experiments, which are just starting to explore an unresearched area. Although one of them, exploring the chemical underpinnings of emotion communication through body odor, is currently implemented (see Section 4.3.3.), we were forced to give up several of them due to the Covid-19 crisis, given the restrictions applying to presentation of biological samples from one individual to another individual's nose but also to travel. Notably, a cross-cultural study was scheduled in October 2020, aiming at conducting Study 1 in a Japanese sample in Yokohama, Japan, and a fMRI experiment aiming at investigating the neural basis of positive emotion contagion was initially scheduled beginning of 2021. These two experiments may be conducted in a longer-term perspective, providing they will receive funding. Instead, we designed another new experiment that both allows to fit within the safety restrictions imposed by the pandemic and to explore additional questions related with the chemical communication of emotion (see Section 4.3.4). This has been made possible thanks to an extension of the research agreement with the cosmetics industrial partner and of the PhD of Stéphane Richard Ortegón (6 months, until mid-2022).

4.3.3. Current and future challenge #1: Understanding the chemical underpinnings of chemical communication of emotion

This section will be very short since I have introduced the subject in a very detailed manner in Section 4.2.5. Elucidating what changes occur in BO chemical composition when a positive emotion is experienced is an important piece of the puzzle to understand human chemical communication of emotion. To date, we have conducted the first methodological steps that were an obligatory passage given that i) there is no consensus and no existing method routinely used to analyze VOCs from the human body, and ii) this was a brand-new approach for our laboratory, requiring the integration of

multidisciplinary collaborations. While we were working on these methodological steps, one article was published by a group that is well-known in the field of human chemical communication of emotions, in collaboration with another industrial partner (Smeets et al., 2020; see also Preti et al., 2019, for an analytical identification of stress odors). The authors used indirect sampling, putting a Twister in a headspace in presence of an absorbent pad previously worn by donors during 3 types of emotion induction (fear, happiness, neutral). Given that it is ignored which chemical features are associated with emotion signals, an untargeted exploratory approach was used, retaining the chemical compounds that most strongly discriminated between the studied emotions. Their results showed that although the fear samples were well discriminated from the neutral samples, such a clear distinction did not occur for happy samples (vs. fear or vs. neutral). Moreover, most of the compounds that changed the most between happy and fear or neutral samples could not be identified or were identified as non-biological compounds. Thus, many questions remain unanswered to date. Therefore, during the next few months we are going to conduct emotion induction procedures on a new group of participants who will wear the ABOV device (see section 4.2.5.) so that we can collect their VOCs while they experience a positive emotion (within-subject design). Analysis and comparison of the chemical profiles will be performed to identify the chemical changes associated with positive emotion. Providing this step is successful, a longer-term perspective would be to synthesize the compounds identified as “markers” of the positive emotion and to use them in appropriate settings to test and confirm their behavioral effects.

4.3.4. *Current and future challenge #2: Increasing the ecological relevance of the behavioral testing*

In previous Section 4.2.6 on human odor attractiveness, I already pointed at this challenge, which actually applies to the whole field of psychology and neuroscience. The best understanding of human behavior will undoubtedly come from experiments conducted in the most natural situations possible. Contextual effects are not negligible on the performance of participants. For example, many of them are coming to the laboratory for the first time. They are thus likely to experience some stress, facing the novelty of the situation and the unknown of what they will be asked to do. Not to mention that the heightened security measures since Covid-19 can increase their stress. Emotion induction is particularly sensitive in this respect, especially when it comes to inducing positive emotions. This is the reason why we have put in place certain measures to set a more favorable environment for positive emotion induction. For the positive condition of Study 1, donors were seated in groups of 3 which is believed to increase positive emotions thanks to the social interaction and to the sharing of the feelings (as seen in de Groot et al., 2015). In Study 2, with the virtual reality setting, the participants were isolated from their real (laboratory) environment: We relied on the power of immersion, which has indeed proven to be more effective in inducing positive emotion (see **Fig. 18**). In a third experiment, **Study 3**, prepared and launched during the 1st semester of 2021 by Stéphane Richard and a master student Manon Leygnier (and still running), we decided to go further in our naturalistic approach and we designed an at-home experiment, detailed hereafter.

Study 3 – replication of positive emotion communication and factors of variation. The implementation of this study, which was not initially planned, actually responds both to a need for a naturalistic approach and to the experimental difficulties imposed by the current pandemic of Covid-19. Indeed, even if the human experimentation protocols have restarted in French laboratories (after

being interrupted for a few months in 2020), the conduct of experiments must be carried out with reinforced safety conditions and there is still some uncertainty about whether it is safe to present an individual's biological sample (sweat body odor samples) to another individual (see Fathizadeh et al., 2020; Propper, 2020; Santonja et al., 2020; Recalcati et al., 2021). As a consequence, this was a good opportunity to set up a new kind of experiment, taking place in the participants' home, with material (t-shirts, unperfumed products, gloves etc.) sent by parcel post and with an online interface gathering instructions, questionnaires, emotion induction procedure and collection of responses in a variety of tasks. Study 3 involved dyads living together, namely people who are already exposed to each other and therefore not increasing the risk of contamination by Covid-19 by smelling the other person's odor.

With these specific and innovative methodological choices, the aim of Study 3 was to replicate Study 1 (transmission of a positive emotional state of a donor to a receiver via chemical signals) while testing possible factors of variation. Note that for obvious reasons, psychophysiological and motor responses were not recorded and that the focus is on verbal evaluations and on performances in a wide range of creativity tasks (see protocol explained in **Fig. 19**). The main hypothesis is that the duration of the relationship (controlled for the age of the participants) could modulate the ability to "read" the emotional cues contained in the partner's body odor (see Zhou and Chen, 2011). If this ability is partially learned, then we hypothesized that the effect we found between strangers in Study 1 could be enhanced between familiar individuals. As in Study 1, we are also testing the effect of perfume (**Fig. 19D**). Besides these two parameters controlled *a priori* (between-subject long versus short relationships, within-subject perfume condition), we will also investigate *a posteriori* how personality modulates chemical communication (from the donor point of view, i.e. the ability to chemically express emotions; and from the receiver point of view, i.e. the ability to detect and respond to chemical signals of emotion) (see also Section 4.4.). An introversion questionnaire (with questions about how people behave during social experience; Richmond and McCroskey, 1998) and an emotional intelligence questionnaire (about the ability to interpret other's emotions and to manage one's own emotions; Schutte et al., 1998) were used for this purpose. Fifty dyads are expected to be included (N=100 participants) and the first results should be available end of 2021.



Fig. 19. Experimental design for an at-home experiment on chemical communication of positive emotion between members of a dyad living together. During 2 consecutive days where the participants play the role of either the donor or the receiver each in turn, donors wear a cotton t-shirt (**A**) during a video-based Mood Induction Procedure performed on a computer and receivers then perform a series of creativity tasks while smelling the axillary area of their partner's t-shirt (**B,C**). At the very end of the session of each day, a flask containing perfume is placed near the t-shirt while the receivers complete another series of creativity tasks (**D**).

4.4. Personality and BO emission/perception

After having presented my research on human body odor and attractiveness on the one hand, and on chemical communication of emotion on the other hand, I am now exposing more briefly an aspect that is, I believe, transversal, namely the relationship between personality and BO emission and perception. As illustrated by Revelle and Scherer (2009), “personality is to emotion as climate is to weather”. Therefore, for those who want to understand affective responses to stimuli from the environment, including smells, it seems important to investigate the influences of personality. This is something I am interested in since my PhD during which I focused on children’s olfactory perceptions and behaviors and have put a strong focus on inter- and intra-individual differences. In particular, the literature provides contradictory evidence regarding a link between personality (extraversion-introversion and neuroticism dimensions) and olfactory sensitivity (see review in [Ferdenzi, 2013](#)). When I investigated this question in 6-12 year-old children, I found that children higher in extraversion rated a pleasant odor of strawberry as more pleasant than children with lower extraversion, and that children higher in neuroticism rated an unpleasant odor of feet/cheese as more unpleasant ([Ferdenzi, 2013](#)). The effect was moderate but consistent with the higher reactivity of extravert individuals to positively valenced stimuli and of neurotic individuals to negatively valenced ones (Costa and McCrae, 1992). As personality traits are also associated with social attitudes, e.g. extraversion is associated with a tendency to engage in social interactions, it is very likely that there is a relationship with the perception of body odors. Several studies investigated this question by comparing socially anxious versus socially non-anxious individuals. Higher scores on trait social anxiety is associated with higher emotional reactivity to chemosignals (larger skin conductance responses: Adolph et al., 2010; higher startle response: Pause et al., 2009; differences in evoked potentials: Pause et al., 2010) and reduced recruitment of the orbitofrontal cortex (Zhou et al., 2011). Another personality trait, disgust proneness, has been associated with more negative evaluations of sweat odor (Uebel et al., 2017) and with some disorders related with body odor perception (Olfactory Reference Disorder, Schmidt and Grochowski, 2019). These studies mostly tackle responses to negative stimuli, such as fear odor. Investigations of how personality relates to the perception of positive stimuli, such as BO obtained during a positive emotion induction, remains to be conducted (that is what we are currently doing in our Study 3 presented previously in Section 4.3.4).

Not only perception, but also probably emission of body odors may be influenced by personality traits. Some evidence has been published that extraversion, neuroticism and dominance of individuals can be assessed at above chance level based on their body odor (Sorokowska et al., 2012). This ability seems to be partially present in children (Sorokowska, 2013) but is altered by the presence of perfume (Sorokowska et al., 2016). In the same line but using a different (implicit) method, my colleague Arnaud Tognetti and I investigated whether the level of cooperativeness of individuals could be expressed in their body odor and elicit different cooperative behaviors in return. In this study, we collected axillary odors of cooperative and uncooperative male donors through a public good game and used them as olfactory stimuli in a series of tasks examining whether and how they influence ratings of cooperativeness and cooperative decision-making in an incentivized economic game. Our results show that ratings of cooperativeness are unrelated to the donors’ behavioral cooperativeness. However, we did find suggestive evidence that having access to the donor’s body odors provided a strategic

advantage to women: with age, women were more likely to cooperate with cooperative men and to avoid interacting with uncooperative men (**Fig. 20**). Overall, our findings suggest that, as faces and voices, body odors may provide information on the donor's cooperativeness and might be used accurately and in a non-conscious manner to make cooperative decisions, at least by women (Tognetti et al., in revision).

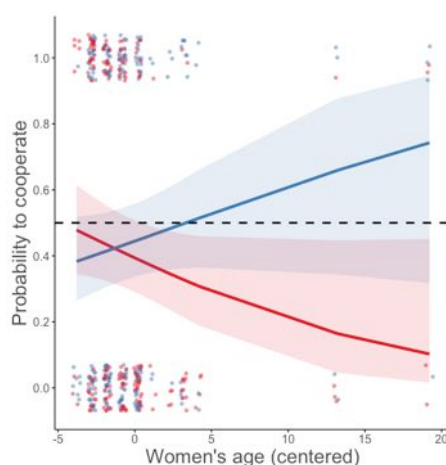


Fig. 20. Predicted probabilities of women's decisions to cooperate or not with the high-cooperative (blue line) and low-cooperative (red line) male BO donors as a function of women's age. Dots: individual decisions to cooperate (1) or not (0) ($N=416$). Dotted black line: random choice (50%). Women's age: $M \pm SD = 21.8 \pm 4.1$ years old (range 18-41). From Tognetti et al. (in revision).

➔ Overall, personality is probably a significant factor of variation in human chemical communication, and taking this parameter into account may help understanding this particular mode of communication, both from the side of odor emission and from the side of the perception of chemical cues present in BO.

4.5. Longer term perspectives

In the previous sections, I introduced my short/medium-term perspectives that I will be able to explore thanks to effective fundings. Here, I am developing two transversal aspects that I wish to keep as research aims in a longer term perspective to better understand human chemical communication: to explore more than just the axilla, and to include different cultures.

To go beyond the axilla. Although many areas of the body produce a smell, most studies on human chemical communication have investigated odors from the axilla. This can be explained in part by the belief that axilla has taken over the communication role from the anogenital region due to the upright human posture (Pawłowski, 1999), but also by cosmetic motives (necessity to understand the formation of malodors to better neutralize them), and by the fact that in adults it is one of the most odorous body regions (richest in apocrine sweat glands) and one of the easiest to collect (discreet sampling, limited contamination by exogenous odors). Other odor sources, largely ignored so far, may be relevant though.

For example, the perception of vaginal and breath odors has been occasionally investigated and found to vary as a function of the donor hormonal status and gender (Doty et al., 1975, 1982). Likewise, very few studies focused on the odor of hands. Individuals can be discriminated on the basis of

olfactory cues from their hands (Wallace, 1977), and another study suggests that greeting by handshaking may be used to sample conspecifics' chemosignals since participants increased the sniffing of their own hands after a handshake (Frumin et al., 2015). It may also be that human (odorless) tears have a deleterious effect on sexual arousal as shown by self-reports, physiological and neural responses of men exposed to such stimuli (Gelstein et al., 2011), although these findings were highly debated (Gračanin et al., 2017b, 2017a; Sobel, 2017). Finally, other body odor sources have been investigated for other purposes than studying human attractiveness to conspecifics, namely i) managing malodorous emanations (e.g., from feet: Caroprese et al., 2009 ; urine : Troccaz et al., 2013; flatus : Ohge et al., 2005), ii) diagnosing diseases (e.g., cancer, from breath : Bajtarevic et al., 2009), iii) forensic applications (e.g. odors from hands: Curran et al., 2010; internal organs: Dubois et al., 2019), to iv) understanding the spreading of diseases (due to blood-sucking insects attracted by human hand odor: Bernier et al., 2000; or feet odor: Verhulst et al., 2013).

Returning to body odor attractiveness, it is crucial to consider odors that may be meaningful during interactions with the partner, namely odors emitted by body parts that are sampled voluntarily or – more likely – in a non-conscious manner. This includes more particularly the head (face, hair, neck, mouth), the hands, the axilla and the genital areas. I have started investigating the odor of the head during my postdoc in Geneva, with a new method of odor sampling for subsequent odor evaluation (see **Fig. 21B**). When comparing the evaluations of the odor of the head and axilla of men and women, we found that both sources were equally intense and attractive, but that their perceptual profiles (based on 22 specific descriptors) were quite different. Both sources were subject to gender differences although descriptive profiles of the axilla seemed to be better discriminated between men and women compared to the head ([Ferdenzi et al., 2020](#); **Fig 21A,B**). Interestingly, head and axillary odor attractiveness were highly correlated in women but not in men (**Fig 21C,D**). It cannot be excluded that a potential greater use of perfumed cosmetics in women may have homogenized the olfactory signature of different body parts. But another possibility that would be worth exploring in the future is that the odor of the head could convey different cues than the axilla in male donors. Some of the most interesting questions for the future are: which information is conveyed by each odor source? by which mechanisms? and which odor source has more weight in determining the attractiveness of a potential reproductive partner?

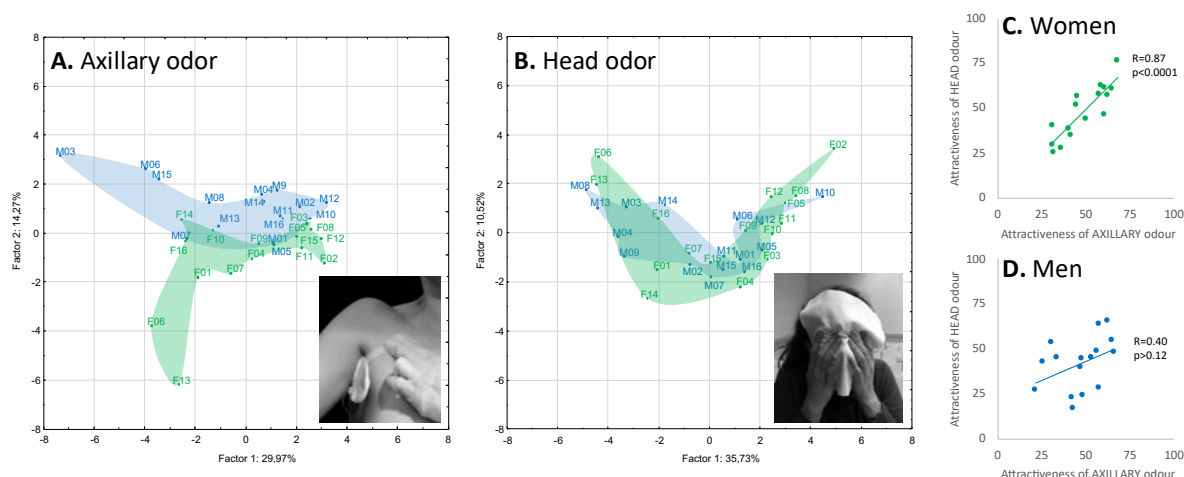


Fig. 21. PCA conducted on the description of odor samples from the axilla (**A**) and head (**B**) of female (green) and male (blue) donors, provided on 22 verbal descriptors specific of body odors. Correlation between attractiveness of the head and the axillary odors in women (**C**) and in men (**D**). Each dot is a BO donor. From [Ferdenzi et al. \(2020\)](#).

To conduct cross-cultural studies. Because interindividual variability has been at the center of my research since my master project, I focused on cultural differences in several studies investigating the perception of odors in general: on children's self-declared attention to odors in everyday contexts (Finland vs. France; [Ferdenzi et al., 2008](#)), on odor descriptions (Vietnam vs. USA vs. France; [Chrea et al., 2007](#)), on self-declared odor-related emotions (Singapore vs. UK vs. Switzerland vs. USA vs. Brazil; [Ferdenzi et al., 2011b, 2013a, 2013b](#)), and on verbal and psychophysiological responses to odors (Quebec vs. France; [Ferdenzi et al., 2017](#)). I would like to implement such approaches in my future research on human chemical communication. In this field, it makes no doubt that studying how body odors may be involved in specific functions – such as human reproduction – should not be limited to the usually studied WEIRD populations (Henrich et al., 2010), namely from Western, Educated, Industrialized, Rich, and Democratic countries, or ODD subjects (Old, Deodorized and Desensitized, which are co-occurring with the WEIRD; Roberts et al., 2020). Including different populations allows testing to what extent hypothesized mechanisms of odor-based attractiveness may be common to the human species, and to describe cultural specificities. For example, it has been proposed that if human body odor contains compounds that are relevant in human attractiveness, then olfactory receptor genes responsible for their detection would be highly conserved in the human species (Wyatt, 2015). In light of this, the extensively studied putative pheromones androstenone and androstadienone seem to be poorly credible candidates. Indeed, at least one in five people cannot detect them (Amoore, 1991; [Ferdenzi et al., 2016](#)) and strong genetically-based interindividual variability has been described for their perceived quality (Keller et al., 2007). Likewise, we found that 8 to 19% of a French and a Malagasy sample were anosmic to an acid compound of BO, HMHA ([Ferdenzi et al., 2019](#)). In line with this, a significant part of the population (80–95% of Asians, versus 0–3% of Europeans and Africans) possesses a non-functional variant of the ABCC11 gene, which has a key function in the formation of BO, resulting in the absence of androgen (and carboxylic acid) compounds and to a much weaker body odor (Martin et al., 2010). These molecules may thus not be as relevant in human mate choice as scientists once thought.

Considering the more complex body odor in its entirety, cross-cultural studies remain scarce. Anthropologists have pointed out ethnicity-related differences in body odor judgments, such as the fact that white and black people perceive the other group as “foul-smelling” (Classen, 1992). A proposed explanation was that such an olfactory classification of people demarcates social groups and contributes to maintaining boundaries between them. However, whether this has biological and perceptual grounds remains under-studied to date probably because this is an ethically sensitive topic. A few studies compared Asian, African and Caucasian people on several aspects, though. African participants were found to have the largest apocrine glands and highest levels of sweat secretion, while Asian participants have fewer apocrine glands and a lower level of axillary odor (Hart, 1980). The emission of some carboxylic acids also differs between ethnic groups (Prokop-Prigge et al., 2016), and differences related to donors' ethnicity were reported in terms of pleasantness and intensity ratings (Parma et al., 2019), which are likely genetic, although diet- and hygiene-related influences cannot be excluded.

Cultural norms and practices may indeed influence body odor emission and perception. For example, rules of interpersonal distances during social interactions (theory of proxemics: Hall, 1966) vary according to culture ([Sorokowska et al., 2017b](#)) and may have a role in chemical communication, as hypothesized in some cultural comparisons of body odor perception ([Schleidt et al., 1981](#); [Ferdenzi et al., 2008](#)). Cultural variations do also exist in emotional responses to odors ([Ferdenzi et al., 2013a](#); [Sorokowska et al., 2018](#)), and cosmetic and drug practices that change from one culture to another

may also be influential. Overall, conducting more cross-cultural investigations of human chemical communication would truly benefit to the understanding of this phenomenon (Ferdenzi, 2019). This could allow identifying universal abilities to perceive and emit odorant compounds that are possibly relevant (e.g., for partner choice), namely abilities that are common to humans in general independently of their culture and environment, because they are involved in the social function of olfaction at the level of the human species. Further, analyzing whether the alteration of these abilities in some individuals (e.g., no perception, no emission) has deleterious consequences on social behavior would help understanding the social function of olfaction. Cross-cultural considerations would also allow having a finer understanding of chemical communication in the way it could point, besides its invariant parts, some variations according to cultural influences.

5. Olfactory disorders (ODs): consequences and remediation

5.1. Foreword

Because the study of the inter- and intra-individual variability of olfactory perceptions has always been at the center of my research and that of the Neuropop team, it is quite natural that we got involved together in the study of olfactory disorders (ODs) or dysosmia. For me, it started in 2014 with the DEFISENS project (coord. Moustafa Bensafi) aiming at measuring the prevalence of ODs in a very large French population, and then with the work of a thesis student Cédric Manesse that I co-supervised with Moustafa Bensafi between 2017 and 2018. The prevalence of ODs in France, their consequences, as well as remediation by olfactory training were investigated, the latter being further studied by a physiotherapy student Aurélien Kassan whose work I supervised in spring 2020. In addition, we started to study the impact of losing the perception of the odor of self and of significant others during interviews conducted by a master student Mathieu Pinger.

With the COVID-19 crisis and given the high prevalence of COVID-19 associated ODs, the team's involvement in this topic has recently been strengthened. I am currently coordinating with Moustafa Bensafi the CORODORAT project (funded by IDEX Lyon, 2020-2021). We co-supervise a post-doc in data science, Christophe Bousquet, with the objective to characterize the COVID-19-related ODs and to understand their impact on the quality of life. At the same time, I am currently the coordinator of a rehabilitation project (2021) with ENT departments of four hospitals in Lyon, involving post-docs Christophe Bousquet and Arnaud Fournel, a research technician of the human olfaction platform of the CRNL Christelle Daudé, and master students in neurosciences (Erwan Moussy) and in speech therapy (Morgane Joly). Our objective is to test the efficiency of several forms of olfactory training in post-COVID dysosmia.

In the following sections, I am presenting these past and current works, as well as my future projects which are directed at strategies to help COVID and non-COVID patients with dysosmia (in collaboration with Moustafa Bensafi), using olfactory training but also assistance with new technologies, such as artificial nose or olfactory prosthesis. At the same time, I will study further the impact of olfactory loss on social interactions.

5.2. ODs: Definition, prevalence and consequences

5.2.1. Definition

ODs can be quantitative or qualitative. The former is characterized by a partial (hyposmia, ranging from mild to severe) or total (anosmia) loss of olfactory perception, and more rarely by a tenfold increase in smell (hyperosmia). Qualitative disturbances are characterized by distortions (parosmia) or olfactory hallucinations (fantosmia). The etiologies of ODs are varied (Hummel et al., 2016): 1) traumatic origin (section of the axons of the olfactory neurons crossing the cribriform plate during a head trauma); 2) naso-sinusal diseases such as nasal polypsis, which can cause an obstacle to the passage of odorant molecules in the nasal cavity and can disrupt the process of binding of odorants to the olfactory receptor neurons due to inflammatory phenomena; 3) normal aging characterized by presbyosmia (by analogy with presbycusis or presbyopia), and neurodegenerative diseases (Parkinson's and Alzheimer's); 4) infections of the upper respiratory tract by bacteria or viruses, which disrupt the sense of smell by simple congestion of the mucosa preventing odorant molecules from reaching the olfactory epithelium, or by causing direct injury of the latter. Other etiologies include congenital anosmia (e.g., in Kallmann's syndrome), exposure to toxic substances that damage the olfactory neuroepithelium, psychiatric and neurological diseases, tumors, and certain systemic diseases. Finally, in nearly one in five cases (Fark and Hummel, 2013), dysosmia is classified as idiopathic because the mechanisms involved cannot be identified.

5.2.2. Prevalence

The prevalence of ODs in the population has been estimated to be around 20-25% in Western populations, which is far from negligible. It is mostly hyposmia, with the rate of anosmia ranging from 1-5% depending on the study and country (see review in Bensafi and Rouby, 2020). A study that we conducted in late 2014 (DEFISENS project, coordinated by M. Bensafi) in collaboration with three hospitals (Nord-Ouest Hospital of Villefranche, Infirmerie Protestante of Caluire and Hospices Civils of Lyon) has provided an estimation of the prevalence of ODs in France (Manesse et al., 2021). We tested the olfactory abilities of 2085 women and 1600 men, aged from 4 to 89 years old, using 8 odors in the form of “scratch-and-sniff” cards (see Fig. 22) that were distributed in France, mainly through a national scientific newspaper ‘Le Journal du CNRS’. A preliminary step consisted in using this test in

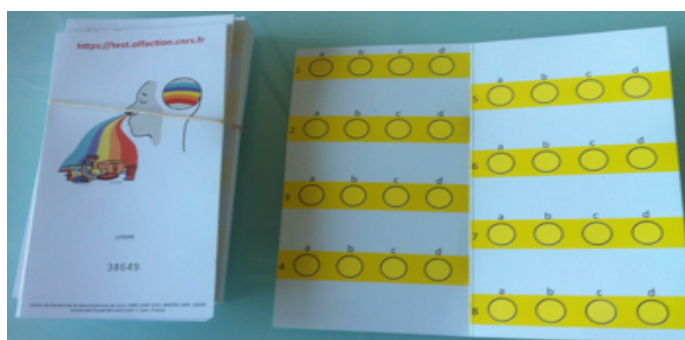


Fig 22. Scratch-and-sniff card used to evaluate the prevalence of ODs in France. Eight odors were used: *l*-carvone (mint), *cis*-3-hexen-1-ol (grass), *trans*-anethole (anise), valeric acid (sweat), α -pinene (pine), β -ionone (flower), isoamyl acetate (banana), tetrahydrothiophene (gas). Odors are trapped in microcapsules and can be released by simply rubbing the printed microcapsule reserve.

individuals with normal olfactory function and in individuals with diagnosed dysosmia. Using a linear discriminant analysis (LDA), we set up the best probabilistic model (based on identification, pleasantness, intensity, familiarity, and edibility ratings) to predict olfactory deficits in a new group of individuals. Using this model, we found that prevalence of smell deficits was 17% in our French sample, and increased with increasing age to reach 31% in people over 60 years old, both percentages being in line with findings in other countries (between 12% and 27% in Spain, Germany, Sweden, Australia and the US, see review in [Manesse et al., 2021](#), and **Fig. 23**). We have noticed that self-evaluation of olfactory abilities by our participants both i) underestimated the presence of a deficit (6% self-reported dysosmia vs. 17% estimated with the scratch-and-sniff cards), and ii) were inaccurate in their evaluation (2/3 of the 6% self-declared dysosmics actually had a normal sense of smell), which is consistent with previous reports (Landis et al., 2003).

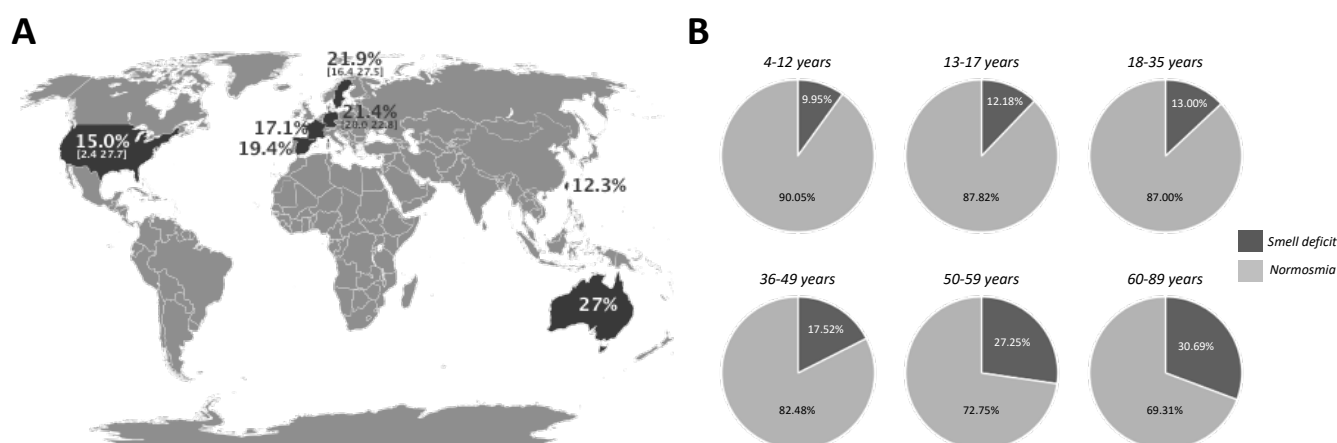


Fig 23. (A) Prevalence of smell deficits in the world using psychophysical testing. The numbers correspond to the prevalence estimated in the general population (mean and 95% CI are mentioned when more than 2 values are available). **(B)** Prevalence of smell deficits and normosmia as a function of age in the French population. From [Manesse et al. \(2021\)](#).

These estimations were obtained before the COVID-19 pandemic. The prevalence of ODs has certainly increased since the new SARS-CoV-2 virus began to spread late 2019. Indeed, loss of taste and smell (and also of trigeminal sensations, see [Parma et al., 2020](#)) was quickly identified as one of the most specific symptoms of COVID-19. In France, almost 6 million cases of COVID-19 have been identified to date, with 46 to 86% of patients experiencing ODs ([Bénézit et al., 2020](#); [Lechien et al., 2020a](#)). Note that the specificity and the prevalence of this symptom are so high that monitoring them at the population level could help anticipate and manage the epidemic (in countries or regions: see our collaborative articles from the GCCR and Smelltracker international projects: [Irvani et al., 2020](#); [Pierron et al., 2020](#)). Prior to the pandemic, post-infectious ODs were known to have variable durations, ranging from a few days for some to longer durations for others, even being permanent in some individuals, suggesting a diversity of viral mechanisms of action ([Doty, 2019a](#)). After almost 2 years of pandemic, there is increasing evidence that many people complain about persistent olfactory loss after having had COVID-19. Follow-up studies are recently starting to be published, evaluating the proportion of patients still experiencing olfactory dysfunction several months after the onset of the disease. At 6 months, 18% self-reported persistent ODs and 60% psychophysically assessed ODs were found in an Italian sample ([Boscolo-Rizzo et al., 2021](#)), 11% with self-reports in a Chinese sample ([Huang et al., 2021](#)) and 5% with a psychophysical test in several European populations ([Lechien et al., 2021a](#)). During the CORODORAT project (coordinated by M. Bensafi and myself), we analyzed the

characteristics of COVID-19 related ODs using a large-scale study involving 3111 French respondents to an online questionnaire¹ over a period of 9 months covering two epidemic waves, from April 8th 2020 to January 13th 2021 (Ferdenzi et al., 2021). Among the respondents (patients with COVID-19 related ODs), some reported having recovered from their OD (N = 609) and in these patients, recovery occurred on average after 16 days and most of the time within one month (“normal” recovery range, **Fig. 24A**). Many respondents had ongoing ODs (N = 2502), and among them N=974 were outside the “normal” recovery range and were considered to have developed a persistent OD with a duration from 1 to 10 months (**Fig. 24B**). Developing a persistent OD was more likely with increasing age and in women, and was more often associated with parosmia (distortion of smells) and phantosmia (olfactory hallucinations). Mechanistically, the discrepancies of recovery times (from a few days to several months) between individuals could be partly explained by how severely the SARS-CoV-2 virus has damaged the olfactory system (Ferdenzi and Bensafi, 2020), even though the mechanisms are still discussed (Lechien et al., 2021b). In the most benign cases, there is only an inflammatory process in the nasal cavity temporarily preventing odorants from reaching the olfactory epithelium (Eliezer et al., 2020), while in the most severe cases basal cells of the olfactory epithelium are infected, thereby compromising the natural regeneration of olfactory neurons (Lechien et al., 2020b).

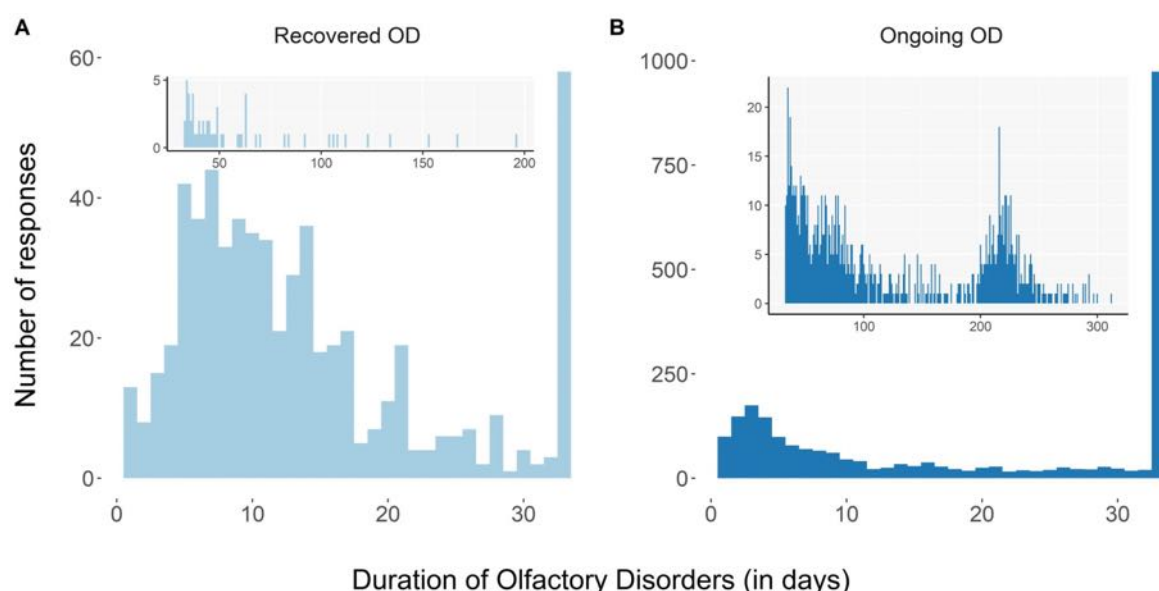


Fig. 24. (A) Distribution of the self-reported OD duration by participants who recovered their sense of smell (N = 609, 90.5% recovered within 32 days or less). (B) Distribution of the self-reported OD duration by the participants who still suffer from OD (N = 2502; 974 participants have persistent OD, i.e. they have not recovered after 32 days). The insets display the distributions of OD durations longer than 32 days. On the inset of panel B, the distribution between 200 and 300 days corresponds to respondents who contracted COVID-19 during the first wave of the disease in spring 2020 (N = 329). From Ferdenzi et al. (2021).

5.2.3. Consequences

Losing one’s sense of smell is generally reported to be less disabling than being blind or deaf, mainly because the consequences are more rarely life-threatening. Consequently, the medical

¹ <https://form.crn.fr/index.php/146862?newtest=Y&lang=fr>

community has long considered that smell disorders are of little importance to the people's health. The growing body of scientific research on this subject and the increasing awareness of the general public since the pandemic have highlighted the fact that losing one's sense of smell is far from being without consequences. Effects of ODs on the patients' safety, health and well-being have been reported in several studies by the Neuropop team ([Manesse et al., 2017, 2021](#); [Ferdenzi et al., 2021](#)) and other groups (review in Croy et al., 2014). Patients with impaired sense of smell are more likely to experience *domestic accidents*, as failure to detect the odors of fire, gas, or spoiled food compromises their safety. Modifications of *food behavior* are often observed. As olfaction is a major component of the flavor of food, a drastic decrease in the pleasure of eating occurs: This leads, on the longer term, to a loss of appetite and/or adding sweet, salty, or fat condiments to make the dishes more appetizing ([Manesse et al., 2017](#)), which may have deleterious nutritional consequences. A lack of motivation to eat and to prepare food also negatively impacts social interactions around meals and may lead to social withdrawal. *Social relationships* are also impacted through the inability to monitor one's own body malodors (sweat, breath), possibly leading to compulsive personal hygiene behaviors and social withdrawal, but also through the lack of stimulation by the odor of the close relatives which are of high importance especially in parent-child attachment and in sexual life. In some cases, smell disorders can lead to a sudden *professional* inadequacy in certain fields such as culinary arts, perfumery and other fields related to chemical senses. Many areas of daily life can thus be impacted, and the deleterious consequences of ODs on physical and mental health (depression, isolation) is now proven. In our online study on COVID-19 related ODs mentioned earlier ([Ferdenzi et al., 2021](#)), we showed that 73% of the respondents considered their OD as incapacitating, and that its deleterious impact on the quality of life was significantly aggravated by OD duration. It was also more pronounced in younger respondents, and in women who were particularly affected in situations involving body odors, meals and flowers. Particular attention was dedicated to social situations and body odor in this study: Here, participants reported seeking close one's odor, controlling own body odor and taking showers more than before having COVID-19 related OD, and wearing perfume less than before.

5.3. Project: improving screening and remediation

5.3.1. Current and future challenges

Given the clear deleterious impact of ODs on quality of life, given their high prevalence in the general population increased recently by the COVID-19 pandemic, and given that a non-negligible proportion of former COVID patients complain about ODs persisting months after their onset, it makes no doubt that proper screening and treatment programs are required. This constitutes a real challenge for the present and for the future. Indeed, in the recent months we (researchers in human olfaction, and our close colleagues in hospitals' ENT departments) have seen an increase in the number of patients requiring medical and rehabilitative support for the recovery of the sense of smell. However, medical advice regarding ODs, which was considered insufficient more than ten years ago ([Landis et al., 2009](#)), seems to still be unsatisfactory. Indeed, in our online study ([Ferdenzi et al., 2021](#)), respondents reported that when they consulted for their sensory loss (GP: 87.5%, specialist: 19.0%) OD mostly served to orient the diagnosis of COVID-19 without being considered as a symptom to treat. Treatment of olfactory loss was rarely evoked. Waiting for a spontaneous recovery was advocated in 18.3% of the consultations, and olfactory training has been recommended by only 3.6% of the GP consultations and 18.4% of the ENT consultations. GPs and ENT specialists are behind in medical

evaluation of ODs mainly because olfactory tests are not part of the usual equipment of the practice. Only a few university centers offer olfactory evaluation based on recognized and validated tests, such as Sniffin' Sticks (Hummel et al., 1997), ETOC (Thomas-Danguin et al., 2003) or UPSIT (Doty et al., 1984). In France, the dissemination of these tests faces a multifactorial problem linked to: i) the non-recognition by health insurance of the medical act of olfactory evaluation (clinical olfactometry) and its cost, ii) the low number of patients who decide to consult ENT practitioners for their OD (outside the period of COVID-19), and iii) the absence of proposal for medical management by the latter. Indeed, not only evaluation but also remediation strategies are lacking. Several techniques have been explored (surgery, acupuncture, Doty, 2019b); Drugs have been tested in clinical trials and may help recover olfactory perceptions (Drews and Hummel, 2016), through oral administration or nasal drops providing they are applied in a specific fashion so that they can reach the olfactory cleft (e.g. using the Kaiteki maneuver; see Mori et al., 2016). However, none of them are routinely used in the practice probably because in most cases there are still many unknowns ranging from the duration of the effects or their physiological bases (Bensafi and Rouby, 2020), and often control groups are lacking. Even olfactory training, which has repeatedly shown beneficial effects (see below), is rarely implemented.

In a position paper that I wrote with my current collaborators, namely four ENT specialists, three speech-therapists working as a team with ENTs, and two physiotherapists (Ferdenzi et al., in revision; Appendix B), we have detailed what we consider being the main current and future challenges. In order to better support patients with dysosmia, a *first challenge* is to improve the knowledge of the medical staff about olfaction, its disturbances and the ways of remediation: We want to contribute to this with this article that we submitted to "La Presse Médicale Formation", a journal in French for hospital doctors who are directly confronted with the difficulties of medical practice in the field. It should be noted that the lack of knowledge of patients is also high (even if it tends to be reduced due to the unprecedented media coverage of COVID-19). The late entry of patients in the treatment of dysosmia is not desirable in itself and works against a possible recovery. I am therefore also actively involved in communication actions towards the general public (conferences during "La semaine du Cerveau" and "La fête de la Science" in 2021). The *second challenge* is to increase the distribution of screening tools in the consultations. A French test developed by our laboratory exists since 2003, the European Test of Olfactory Capabilities ETOC (Thomas-Danguin et al., 2003), and is currently marketed in a very limited way due to insufficient manpower. A post-doc in our team, Arnaud Fournel, is aiming at developing this activity by making this test known to French ENT specialists and by taking the necessary administrative steps to make it a test recognized by the medical authorities. Our team has recently been developing new forms of olfactory diagnostic in the form of single-use scratch-and-sniff cards, which are particularly convenient to test contagious people. Aging of the cards has been tested in our lab for several months now, and the performances of the scratch-and-sniff test to classify someone as anosmic, hyposmic or normosmic are currently compared with those of the ETOC. This aspect, which is coordinated by Moustafa Bensafi in the Neuropop team, will not be detailed further in this report. The *third and fourth challenges* are to develop and validate methods of olfactory rehabilitation, as well as methods of replacement when rehabilitation is unsuccessful or impossible. I will go more into details in the next sections regarding these two challenges, by presenting how I started addressing these challenges and how my future research will go further in these directions.

5.3.2. Olfactory training

Regarding the development and validation methods of olfactory rehabilitation, in the Neuropop team we have focused on olfactory training, which is directly related to our area of expertise unlike other types of possible interventions (using drugs or surgery for instance).

While spontaneous recovery occurs in a proportion of patients who have lost their sense of smell (London et al., 2008), for the others olfactory training is a promising approach. Developed clinically in 2009 (Hummel et al., 2009), it consists of smelling different odorant stimuli daily for several weeks. The frequency of the sessions, the total duration as well as the number and identity of the odors vary from one study to another. Despite these methodological disparities, positive effects of olfactory training have been shown on sensitivity, discrimination, and olfactory identification, according to a meta-analysis (Sorokowska et al., 2017a). Patients who benefit most from olfactory training are those with post-infectious, post-traumatic, or idiopathic olfactory loss (Sorokowska et al., 2017a). The benefit increases as the duration of olfactory training increases, up to 1 year (Konstantinidis et al., 2016). Periodically changing the identity of smelled odors increases the effectiveness of olfactory rehabilitation (Altundag et al., 2015), as does starting olfactory training quickly after the onset of olfactory loss and with high odor concentrations (Damm et al., 2014). To explain olfactory recovery, it has been suggested that olfactory training may have an action i) at the peripheral level (plasticity of olfactory neurons illustrated by increased electrophysiological responses to odors in the olfactory epithelium; Hummel et al., 2018) but also ii) at the central level (increased gray matter volume in the hippocampus and thalamus, possibly related to greater attention to and memory of odors; Gellrich et al., 2018). However, we lack confirmatory double-blind studies with adequate control groups to support these many promising findings (Doty, 2019b). In the Neuropop team, we have implemented different types of olfactory training with the aim to increase the efficiency of the intervention on dysosmic patients.

Study 1. During his PhD Cédric Manesse conducted a proof of concept study where he developed a new training protocol based on daily contextual olfactory exposure. He was inspired by the pioneer protocol of Hummel et al. (2009), which consisted in smelling four odorants twice a day (phenyl ethyl alcohol smelling like rose; eucalyptol smelling like eucalyptus; citronellal smelling like lemon; eugenol smelling like cloves) over a duration of 12 weeks. This procedure allowed them to increase olfactory abilities (measured with the Sniffin' Sticks test) in 28% of the patients, vs. 6% in the control group without training. In our study (Manesse et al., 2018), several adaptations were made compared to Hummel's protocol to try to enhance the efficiency of the training. First, seven odorants were used (the same four as in Hummel et al. (2009) plus terpinen-4-ol smelling damp, cis-3-hexenol smelling like grass, and d-limonene smelling like orange; see **Fig. 25A**). The training consisted in smelling one odorant per day, the seven odors being randomly distributed over the week, and for 12 weeks. Second, instead of just smelling the odors for 10 s and keeping a diary about their overall olfactory abilities, participants were asked to more actively process the olfactory information. Indeed, they had to perform i) a detection task, i.e. to designate the odor among three flasks including two blanks with no odor and one with the target odor, and then ii) ratings of the target odor for intensity, familiarity, pleasantness, edibility and irritation on a 1-to-9 scale. Third, two training sets were implemented: one with contextual cues (a pictorial representation and the name of the source were present on the flasks), and one without. A total of 22 patients diagnosed as dysosmic by ENT practitioners took part in the study, among which only 14 completed the whole training protocol (age: $M \pm SD = 57.4 \pm 4.1$ years;

11 women and 3 men; 8 with context and 6 without). Evaluation of the efficiency of the olfactory training protocols was made by measuring odor identification abilities with the Sniffin' Sticks test before and after the training. The results showed that olfactory identification abilities improved after training, especially in the group with visual context (**Fig. 25B**). Moreover, quality of life (measured through a 15-item questionnaire) was significantly enhanced when both groups were considered (**Fig. 25C**) (Manesse et al., 2018).

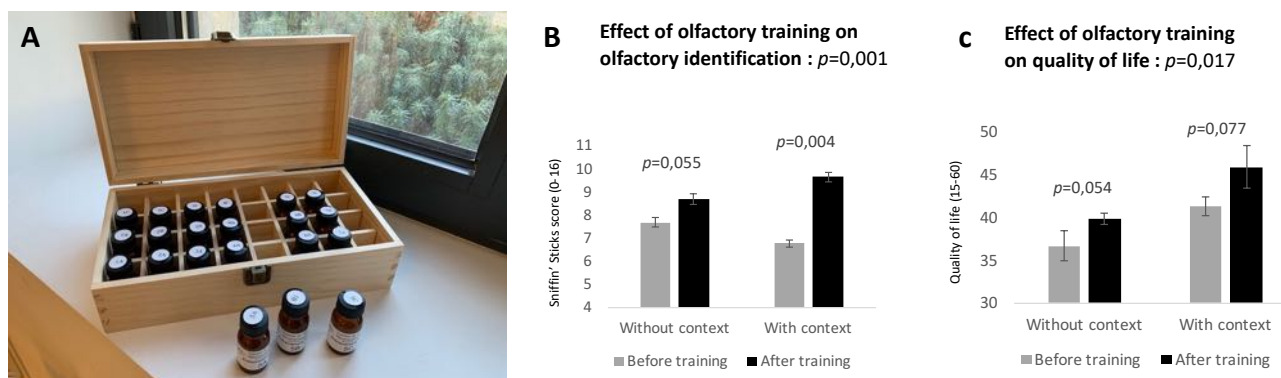


Fig. 25. Effect of olfactory training with seven odorants (**A**) on olfactory identification abilities (**B**) and on the declared quality of life (**C**). From Manesse et al. (2018).

Study 2. A second study was conducted in 2020 by a physiotherapy student, Aurélien Kassan, who was very concerned about the lack of response from the medical profession when he himself lost the sense of smell. He was truly convinced that physiotherapists could play a significant role in the support and rehabilitation of dysosmic patients. The training protocol was similar to the one used in Manesse et al. (2018) except that the tasks were simplified (only detection and intensity rating) to allow patients to smell 3 instead of only 1 odorant a day. Some participants were given precise instructions on how to sniff the odors (to alternate a short, intense sniff with a long, moderate sniff, three times for each odorant) and others were free to sniff however they wanted. Another particularity of this study was the particularly intensive mode of accompaniment: each participant benefited from a weekly appointment of about fifteen minutes in the form of a video call during which the patient carried out his training of the day and could exchange with the practitioner about the progress of his rehabilitation. A total of 26 participants were involved (age: $M \pm SD = 49.6 \pm 14.6$ years; 18 women and 8 men; 17 with controlled breathing and 9 with free breathing). They were diagnosed as dysosmic with the ETOC test (Thomas-Danguin et al., 2003). Although we planned to evaluate the efficiency of the training by comparing the ETOC score before and after the training, the lock-down of March 2020 due to the COVID-19 crisis prevented us to do so since all our protocols were stopped in the laboratory. Therefore, we used another indicator, namely scores of detection and ratings of intensity provided during the daily training, that were averaged over week 1 and over week 12 of the training. While detection abilities remained the same between the first and last week, perceived intensity significantly increased (**Fig. 26A**). When examining individual results, 71.4% of the included patients displayed an improvement of perceived intensity. No difference between the controlled and free breathing were found. Of course, due to the lack of comparison with control group without training, it is not possible to state with certainty that the observed improvement is due to olfactory training rather than spontaneous recovery. However, several studies show the superiority of olfactory training over spontaneous retrieval in improving olfactory abilities (Damm et al., 2014; Sorokowska et al., 2017a), leading us to think that the repeated olfactory exposure has contributed to enhance odor intensity.

Another interesting result was that the intensive follow-up protocol instituted by the physical therapist resulted in a very high compliance rate: 23 out of 26 individuals (i.e. 88%) completed the training in its entirety, compared to only 64% in Study 1 (**Fig. 26B**) where patients received a phone call by the experimenter every 4 weeks ([Manesse et al., 2018](#)). This result argues for intensive follow-up that could typically be implemented by physical therapists or speech therapists. This is an important insight for future strategies of remediation that should be handled by pluridisciplinary teams, for example by including GPs or ENT specialists for diagnostic and orientation towards a remediation protocol, and by actors in the paramedical field such as physical therapists or speech therapists for the monitoring of the training on a regular basis ([Ferdenzi et al., in revision](#); Appendix B).

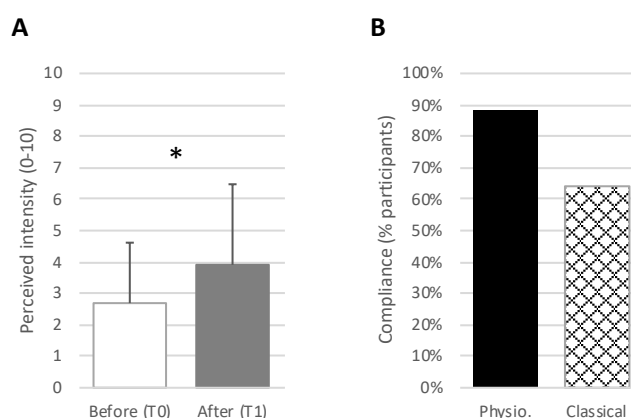


Fig. 26. (A) Changes in perceived odor intensity between week 1 (T0) and week 12 (T1) of olfactory rehabilitation (mean over 7 odors, standard deviation; *: $p < 0.05$, paired t-test). **(B)** Compliance rate as a percentage of participants who completed the entire olfactory training: with intensive follow-up by a physical therapist (weekly video call) and with conventional follow-up (monthly phone call). From [Ferdenzi et al. \(in revision\)](#).

Ongoing study. Currently, I am coordinating a rehabilitation program on post-covid patients, involving four clinical centers: Infirmerie Protestante of Caluire (investigator Dr Frédéric Faure, assisted by the clinical research team), Hôpital Nord-Ouest of Villefranche (investigator Djaber Bellil, assisted by several nurses), Hôpital Lyon Sud (investigator Maxime Fieux, assisted by two speech therapists) and Hôpital Edouard Herriot (investigator Jean-Louis Degraix, assisted by a medical intern). Other key people in this project are our technician Christelle Daudé who weekly follows the patients' inclusions and serves as a relay between the centers and the laboratory, and Arnaud Fournel who implemented the new web interfaces used in this project. In this project, we have made further improvements to the protocol. First, instead of using a paper-and-pencil response sheet, participants are guided in their daily training using a web-interface (on Limesurvey), where they also enter their responses (detection, intensity). Second, given the importance of the follow-up that we highlighted before, we kept the weekly call to the patients and added a visual feedback on the evolution of their olfactory performances throughout the rehabilitation process. A total of 120 patients, displaying COVID-19-related olfactory disorders for at least 6 weeks, will be included in 3 experimental groups: 1) "ReoFlac1": this group smells one odor per day for 12 weeks, 2) "ReoFlac3": this group smells three odors per day for 12 weeks, and 3) "ReoDom": this groups smells five odors per day for 12 weeks. In the two first groups ("ReoFlac"), a case containing numbered vials are provided to the participants, while in the last group ("ReoDom") participants must use domestic products they have at home following some guidelines. For ethical reasons, we have collectively decided not to include a control group without training. Here it must be noted that the absence of a proper control group is a limit of

most studies investigating remediation strategies for ODs, due to the impossibility to implement a placebo condition and to the moral problem raised by the idea of including patients to whom we propose no option. Therefore, we have rather focused on the comparison of the efficiency of different forms of training, with varied levels of intensity of exposure to odors (criteria of evaluation: ETOC and scratch-and-sniff cards test under development, quality of life questionnaire). The “ReoDom” form of training based on domestic odorant products was investigated with the perspective of being able to propose a solution to a larger number of people, because the availability of rehabilitation kits (that have a cost, in time and money) is currently much lower than the demand. In this regard, it must be noted that, in response to the overwhelming patients’ demand since the new virus SARS-CoV-2 virus began to spread, we have written a tip sheet to help patients train themselves at home to accelerate recovery (appearing in Appendix B at the end of the manuscript [Ferdenzi et al., in revision](#)), that we have made available on request and on the “O3 Odorant Odor Olfaction” GDR website (www.gdr-o3.cnrs.fr). Data collection for this project should be completed at the end of 2021.

5.3.3. Future directions for remediation

To me, several areas deserve a special focus in the future.

First, to further understand the *characteristics and the recovery of COVID-19-related ODs*, we will exploit the new answers to our online study mentioned above, in the context of the CORODORAT project and thanks to the useful contribution of the data scientist Christophe Bousquet. For instance, we are currently analyzing the characteristics of phantosmias (qualitatively and in terms of prevalence along the course of the disease). We are also exploring the association between ODs and cognitive disorders. Finally, we will be able to test whether the new variants of the virus are associated with different olfactory symptoms. Finally, a new online study has been recently launched by Moustafa Bensafi to investigate long-term consequences of COVID-19 including long-term olfactory disorders².

Second, for ODs in general, we have seen that a real challenge for the medical community is the *accompaniment of the patients*: it is essential to ensure the maintenance of motivation and thus to increase the effectiveness of olfactory training, as it is for many rehabilitation procedures. For instance, the accompaniment by a practitioner significantly improves olfactory recovery in laryngectomized patients compared to rehabilitation performed independently at home (Ward et al., 2010). It is to address this challenge related to compliance that I intend to keep communicate about the necessity to propose a multi-professional care strategy for OD treatment, together with my ENT, physiotherapy and speech therapy colleagues (in conferences, articles, and during teaching) as well as to conduct new projects with them.

This will be the case in my *third* area of focus, which is the development of *rehabilitation procedures more specifically directed at qualitative olfactory disorders*: parosmias and phantosmias. Treatment options have mainly targeted on the decrease of olfactory perceptions, but are probably not the best suited for olfactory distortions or hallucinations. However, these disorders are highly deleterious for the quality of life and many former COVID-19 patients are concerned. Therefore, we are going to conduct a project in 2021-2022, in collaboration with the speech therapists Luna Denoix and Julie Penavayre from the Lyon-Sud Hospital, with whom I will supervise a Master student in speech therapy, Morgane Joly, from November 2021 onwards. Together we intend to develop a training

² <https://form.cnl.fr/index.php/526179?lang=fr>

protocol with higher order cognitive tasks, mostly based on mental imagery, with the aim to try to reduce parosmias and phantosmias in patients of the olfaction consultation of Dr Maxime Fieux.

Fourth, despite the importance of the follow-up mentioned above, we must acknowledge that this accompaniment will not be available to anyone. I believe it is important to give the opportunity to those who will not have the chance to benefit from a proper follow-up to be able to train their olfaction in autonomy. I am therefore planning to conduct a project on 100 patients to test a *training procedure 100% in autonomy*. This would include the same protocol as in the “ReoDom” group cited above, except that the initial and final evaluation of olfactory abilities would be performed with a self-test using scratch-and-sniff cards test that will be sent by regular mail. It must be noted here that these scratch-and-sniff cards will be developed further for diagnostic and remediation, in the form of connected devices, thanks to a newly funded project ORION (coordinated by Marion Richard, Moustafa Bensafi and myself) that will start in December 2021.

Fifth, because there are some cases where rehabilitation of olfactory abilities is not possible or unsuccessful, our team is aiming at developing solutions thanks to *assistance with new technologies*. I chose to develop this topic, coordinated by Moustafa Bensafi, in the next section since it is funded research that is currently conducted or will be in the following years.

Finally, I would like to better understand the *consequences of ODs on social interactions*. As mentioned earlier, a first series of data have been collected by a psychology master student Mathieu Pinger (who I co-supervised with Moustafa Bensafi), using semi-structured interviews with 11 patients with hyposmia or anosmia, in collaboration with Dr Thomas Hummel (Dresden, Germany). Qualitative data were obtained about the self-reported modifications regarding attitudes towards the odor of self and towards the odor of different categories of others (partner, children, friends, family, colleagues, strangers). Positive and negative consequences were addressed, considering both allocentric and egocentric perspectives (e.g., fear to offend others with one’s own odor / fear to be judged negatively by others). My medium-term objective is to use these qualitative data to develop a questionnaire specifically targeted on social impact of ODs in the future.

5.3.4. Future directions for remediation: Assistance with new technologies

There are some cases where individuals with olfactory loss do not recover. For example, among patients who are consulting a specialist for their olfactory disorder, about 10 to 20% of patients with post-traumatic etiology and about 30 to 70% of patients with upper respiratory infection etiology are found to improve their olfactory abilities over time (Duncan and Seiden, 1995; Reden et al., 2006; London et al., 2008; Fan et al., 2015). Meaning that the others do not improve – although the level of recovery is probably very conservative since it does not include patients who quickly recover after the injury/infection and who therefore do not consult. It must be noted here that, although several case studies report olfactory recovery after several years (5, 7 and 9 years: Mueller and Hummel, 2009), prognosis is generally considered very poor after 2 years olfactory loss. Sometimes in highly damaged olfactory epithelium becoming an aneuronal tissue, respiratory metaplasia may occur, i.e. the replacement of the olfactory mucosa by respiratory mucosa (Child et al., 2018), which may render olfactory recovery even less likely. As mentioned earlier, existing therapies include surgical procedures, pharmacological treatments, and more recently olfactory training. When these therapies fail, artificial systems assisting patients in their daily life could open new therapeutic ways. In the Neuropop team, two directions are favored to explore these new ways: artificial olfaction and development of an olfactory prosthesis.

Portable e-nose. Electronic or artificial noses (e-noses) are electronic devices with the purpose of detecting odorants. They are designed to mimic the human sense of smell. VOCs interact with an array of sensors, which generates a signal (of different nature according to the type of e-nose: electric, optical...). This signal is then transduced and processed by signal processing tools. Increasingly sophisticated e-noses are used in a variety of applications such as quality control in industries, environmental monitoring or diagnosis of diseases (Barbosa et al., 2018). However, they are not offered so far to patients with olfactory deficits. Although to date there is no e-nose capable of reproducing the complete range of performances of the human nose, one can imagine that such devices may yet compensate for some of the human olfactory deficits. The development of a portable e-nose, connected with a smart watch for instance, may be of some help to patients in daily tasks. With Mathieu Pinger, master student, and in collaboration with Thomas Hummel in Dresden, we conducted a study with 45 dysosmic patients (age: $M \pm SD = 57.4 \pm 14.2$ years; 24 women and 21 men) to evaluate how useful e-noses could be in their daily life. Although patients reported being more interested in smell training therapy and new drug treatments compared to surgery, implants and e-noses, 60% of them were interested in e-noses as a therapeutic option. When asked to imagine an e-nose was available that can detect odors around them and display information on the odor quality and intensity (on a watch or inside glasses, for example), patients indicated that this would particularly be helpful in detection of danger and assessment of food edibility, but also for body care, meal preparation and cleaning (Pinger et al., 2021). Thus, putting some efforts to develop this therapeutic approach seems to really make sense with regard to the expectations of the patients. Neuropop has been collaborating for several years (coordination by Moustafa Bensafi) with the company Aryballe Technologies (Grenoble, France) that develops technological solutions to collect, display and analyze odor data (Fournel et al., 2020). Future avenues of collaboration could concern the development of connected, easy-to-use, e-noses whose performances would be in line with the patients' expectations with regards to their health and safety.

Olfactory prosthesis. A step further in using technological progress to assist patients with loss of smell would be to propose an olfactory prosthesis. Scientists have already developed prostheses and implants for hearing impairments and are developing those for vision. However, we have yet to develop such devices to restore the sense of smell, primarily because scientific knowledge linking artificial systems to human biological olfaction is still lacking. First steps in this direction will be taken in the Neuropop team with the 4-year ROSE project (FET-Open European program) that has just started (September 2021). This project coordinated by Moustafa Bensafi is based on a consortium composed of: LETI laboratory (France, nanotechnologies), EPFL (Switzerland, microtechnologies), Aryballe Technologies (France, biotechnology), Politecnico di Milano (Italy, design and mechanics), Technische Universität Dresden (Germany, neurosurgery), Aristotelio Panepistimio Thessalonikis (Greece, clinical olfaction) and the CRNL (France, cognitive neuroscience). This combination of expertise will allow constructing a final proof of concept enabling people with olfactory loss to perceive their olfactory environment. To this end, the consortium will work on the development of a new generation of miniaturized odor sensors, that will be placed inside the nose, and on a module that will stimulate the olfactory system. I am leading one of the seven Work Packages of the project, aiming at testing the technology in normosmic participants and in dysosmic patients all along the project at different steps of the technological developments. A multicentric approach will be used to enable testing enough patients (3 sites in France, Germany and Greece). Several experiments will allow to test the stimulation

device; to examine how dysosmic patients can detect and discriminate a variety of odorant molecules using the stimulation device; to examine their psychophysical and neural responses to odorants; and to investigate the effects of learning with the developed device. This innovative project will help making a considerable leap forward in the domain of sensory protheses, for the benefit of dysosmic patients.

6. Conclusion

In this report, I detailed the two main axes of my current research and the short/medium term projects related to these research themes (human chemical communication and olfactory disorders). Both fields of research illustrate how important odors are in our daily lives, whether for our food behavior, our social interactions, our well-being and our health. It has been very stimulating to see that the research questions I am exploring require multidisciplinary approaches and to develop a network of collaborations (with chemists, health practitioners, etc.), even if this undoubtedly represents a real challenge. Another challenge is the significant impact of the current global health situation, either negative, through the safety restrictions to which we are constrained for BO studies, or positive, by the availability of additional means to study smell loss which has been rather neglected until now. Good adaptability is therefore necessary to move forward. Overall, I hope that my ongoing projects will bring a useful contribution to the understanding of some of the mechanisms involved in the role of olfaction for affects and social cognition in humans.

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8. Curriculum vitae

Degrees

- 2007 PhD in Food Sciences, Université de Bourgogne, Centre Européen des Sciences du Goût, Dijon, France. *“Interindividual variations of olfactory behaviors in 6-to-12 year-old children”*
- 2002 Master’s degree in Food Sciences, Université de Bourgogne, Dijon, France
- 2001 Master’s degree in Food Engineering, INSFA, Rennes, France

Academic positions

- 2017-present CNRS researcher, Centre de Recherche en Neurosciences de Lyon, France
- 2013-2017 Postdoc, Centre de Recherche en Neurosciences de Lyon, France
- 2009-2013 Postdoc, University of Geneva, Switzerland
- 2007-2008 Postdoc, University of Liverpool, UK
- 2002-2007 PhD student, Université de Bourgogne, France

Funding

As a coordinator

- 2021 PAR Region, ORION project, with M. Richard and M. Bensafi (4 years, 200 k€)
- 2021 ANR JCJC, Biodor-IN project (4 years, 346 k€)
- 2020 IDEX Lyon, CORODORAT project, with M. Bensafi (1 year, 60 k€)
- 2018 Industrial grant, including a CIFRE PhD (3 years, 339 k€)
- 2018 Industrial grant (6 months, 26 k€)
- 2017 FYSEN Foundation research grant (12 months, 35 k€)
- 2012 ANR Retour Postdoc, ATTRASENS project (3 years, 271 k€)
- 2007 FYSEN Foundation postdoctoral grant (12 months, 22 k€)

As a partner

- 2021 FET OPEN, ROSE project, workpackage leader, coord. M. Bensafi (4 years, 3 000 k€)
- 2020 CNRS MITI, EXTREM-O project, coord. D. Pierron (2 years, 43 k€)
- 2020 DFG Scientific Networks, Human Chemical Communication project, coord. H. Loos (2 years, 30 k€)
- 2018 ARYBALLE industrial grant, coord. M. Bensafi (1 year, 50 k€)
- 2018 FNS Agora, coord. S. Delplanque (2 years, 200 k€)
- 2016 CNRS MI Défi AUTON, coord. M. Bensafi (1 year, 44 k€)
- 2016 ANR Franco-allemande, MEROD project, coord. M. Bensafi (3 years, 190 k€)
- 2015 CNRS MI Défi GENRE, coord. M. Bensafi (1 year, 5 k€)
- 2015 NESTLE Foundation, coord. D. Pierron (2 years, 76 k€)
- 2014 CNRS MI PEPS, coord. N. Baldovini (1 year, 15 k€)
- 2013 CNRS MI Défi SENS, coord. M. Bensafi (2 years, 70 k€)
- 2010 FNS, ATTRASCENT project, coord. S. Delplanque (3 years, 334 k€)

Collaborations

National

Université de Montpellier – L. Dormont – CEFE UMR 5175

Université Toulouse III – D. Pierron, V. Pereda-Loth, H. Razafindrazaka – AMIS UMR 5288

Université Côte d’Azur – N. Baldovini, J. Golebiowski – ICN UMR 7272

Hospices Civils de Lyon – M. Fieux, J-L. Degraix – ENT Department

Infirmierie Protestante de Caluire – F. Faure – ENT Department

Hôpital Nord-Ouest de Villefranche – D. Bellil – ENT Department
 Institut Paul Bocuse, Lyon – A. Giboreau – Institut Paul Bocuse Research Center
 Université Lyon 1 – F. Gueyffier, F. Vavre – LBBE UMR 5558
 Hospices Civils de Lyon – T. Ferry – Department of Infectious Diseases
 Université de Nice Sophia Antipolis – O. Wathelet – LAPCOS EA 7278

International

Global Consortium for Chemosensory Research (GCCR)
 Human Chemical Communication European Consortium
 Karolinska Institute, Sweden – A. Tognetti, M. Olsson – Department of Clinical Neuroscience
 University of Geneva – S. Delplanque, G. Coppin – Swiss Center for Affective Sciences
 University of Dresden, Germany – T. Hummel – Faculty of Medicine
 University of Wroclaw, Poland – A. Sorokowska – Psychology Institute
 University Hospital of Geneva – F. Bianchi-Demicheli – Sexology Unit
 University of Campinas, Brazil – P. Barbosa – Department of linguistics
 University of California, USA – J-X. Guinard – Department of Food Science and Technology
 University of Beijing, China – T. Guo – Cognitive Neuroscience Laboratory
 University of Stirling, UK – S.C. Roberts – Psychology Department
 University of Singapore – A. Schirmer – Psychology Department
 University of Helsinki, Finland – H. Tuorila – Food Technology Department

Supervision of students and teaching

Supervision of Postdocs (2)

2020-2021 Christophe Bousquet (Neurosciences, Université Lyon 1, France, ANR funding)
 2017-2021 Arnaud Fournel (Neurosciences, Université Lyon 1, France, CIFRE funding)

Supervision of PhD students (3)

2021-2024 Valentine Brémond (Neurosciences, Université Lyon 1, France, ANR funding)
 2018-2022 Stéphane Richard Ortegón (Neurosciences, Université Lyon 1, France, CIFRE funding)
 2015-2018 Cédric Manesse (Neurosciences, Université Lyon 1, France, Région ARC2 funding)

Supervision of Master students - 2nd year (11)

2021-2022 Morgane Joly (Rehabilitation Sciences, Université Lyon 1, France)
 2020-2021 Manon Leygnier (Neurosciences, Université Lyon 1, France)
 2020-2021 Erwan Moussy (Neurosciences, Université Lyon 1, France)
 2019-2020 Aurélien Kassan (Rehabilitation Sciences, Université Lyon 1, France)
 2018-2019 Stéphane Richard Ortegón (Neurosciences, Université Lyon 1, France)
 2017-2018 Mathieu Pinger (Psychology, University of Freiburg, Germany)
 2014-2015 Daphnée Poupon (BioSciences, ENS Lyon and Université Lyon 1, France)
 2011-2012 Reni Atanassova (Affective Sciences, University of Geneva, Switzerland)
 2011-2012 Mylena Da Paz Cabral (Affective Sciences, University of Geneva, Switzerland)
 2011-2012 Olga Voronstova-Wenger (Affective Sciences, University of Geneva, Switzerland)
 2007-2008 Marta Vondrova (Anthropology, Prag University, Czech Republic)

Supervision of Master students - 1st year (7)

2020-2021 Morgane Joly (Rehabilitation Sciences, Université Lyon 1, France)
 2018-2019 Alexia Lamblin (Chemistry, Université Lyon 1, France)
 2014-2015 Déborah Ligout (Biology, Université Lyon 1, France)
 2013-2014 Bérengère Digard (Biology, Université Lyon 1, France)
 2005-2006 Laura Tailhandier (Developmental Psychology, Université de Bourgogne, France)
 2005-2006 Fabien Pacaut (Developmental Psychology, Université de Bourgogne, France)

2004-2005 Charlotte Marinot (Developmental Psychology, Université de Bourgogne, France)

Supervision of Bachelor students (8)

2019-2020 Liza Brettnacher (1st year, Chemistry, Université Lyon 1, France)
2019-2020 Darlène Florentiny (2nd year, Life Sciences, Université Lyon 1, France)
2018-2019 Aicha Chikh (3rd year, Psychology, Université Lyon 2, France)
2017-2018 Aicha Chikh (2nd year, Psychology, Université Lyon 2, France)
2013-2014 Sophie Roblin (2nd year, Psychology, Université Lyon 2, France)
2012-2013 Marisa Domingos Felicio (2nd year, Affective Sciences, University of Geneva, Switzerland)
2011-2012 Mariam Khidasheli (3rd year, Affective Sciences, University of Geneva, Switzerland)
2007-2008 Kirsty Elliott (3rd year, Psychology, University of Liverpool, UK)

Teaching

2020-2021	Master in Physical Therapy, ISTR Université Lyon 1	(12 hrs)
2019-2020	Master in Physical Therapy, ISTR Université Lyon 1	(12 hrs)
2018-2019	Master in Physical Therapy, ISTR Université Lyon 1	(12 hrs)
2017-2018	Master in Neurosciences, Université Lyon 1	(2 hrs)
2017-2018	Bachelor (3 rd year) in Biosciences, ENS Université Lyon 1	(2 hrs)
2016-2017	Bachelor (3 rd year) in Biosciences, ENS Université Lyon 1	(2 hrs)
2015-2016	Bachelor (3 rd year) in Biosciences, ENS Université Lyon 1	(2 hrs)
2015-2016	Bachelor (2 nd year) in Psychology, Université Lyon 2	(21 hrs)

Communications

Peer-reviewed articles (42)

- Ferdenzi C**, Bousquet C, Aguera P-M, Dantec M, Daudé C, Fornoni L, Fournel A, Kassan A, Mantel M, Moranges M, Moussy E, Richard Ortégón S, Rouby C, Bensafi M (2021). Recovery from COVID-19-related olfactory disorders and quality of life: insights from an observational online study. *Chemical Senses*, 46, 1-10.
- Razafindrazaka H, Pereda-Loth V, **Ferdenzi C**, Heiske M, Alva O, Radriamialisoa M, Costedoat C, Signoli M, Talou T, Courtade-Saidi M, Boland A, Deleuze JF, Rouby C, Radimilahy C, Letellier T, Bensafi M, Pierron D. accepted. African gene flow reduces beta-ionone anosmia/hyposmia prevalence in admixed Malagasy populations. *Brain Sciences*.
- Pereda-Loth V, Martínez Pineda A, Tisseyre L, Courtade-Saidi M, Bousquet C, **Ferdenzi C**, Letellier T, Bensafi M, Pierron D. (2021). The autumnal lockdown was not the main initiator of the decrease in SARS-CoV-2 circulation in France. *Communications Medicine*, 1, 7.
- Sorokowska A, Janczak A, **Ferdenzi C**, Baldovini N, Oleszkiewicz A (2021). Blindness, but not HMHA anosmia, predicts loneliness: A psychophysical study. *Personality and Social Psychology Bulletin*, published online.
- Manesse C, **Ferdenzi C**, Mantel M, Sabri M, Bessy M, Fournel A, Faure F, Bellil D, Jomain S, Landis BN, Hugentobler M, Giboreau A, Rouby C, Bensafi M. (2021). The prevalence of olfactory deficits and their effects on food habits from childhood to old age: a large-scale study in a Western population. *Food Quality and Preference*, 93, 104273.
- Midroit M, Chalençon L, Renier N, Milton A, Thevenet M, Sacquet J, Breton M, Forest J, Noury N, Richard M, Raineteau O, **Ferdenzi C**, Fournel A, Wesson DW, Bensafi M, Didier A, Madaïron N (2021). Neural processing of the reward value of pleasant odorants. *Current Biology*. 31(8):1592-605.e9.
- Pinger M, Draf J, Lakner T, **Ferdenzi C**, Rouby C, Hummel T, Bensafi M (2021). Perceived utility of electronic noses in patients with loss of smell. *European Archives of Oto-Rhino-Laryngology*, 278, 2155-6.

- Ferdenzi C**, Richard Ortégón S, Delplanque S, Baldovini N, Bensafi M (2020). Interdisciplinary challenges for elucidating human olfactory attractiveness. *Philosophical Transactions of the Royal Society of London B*, 375, 20190268.
- Manesse C, Fournel A, Bensafi M, **Ferdenzi C** (2020). Visual priming influences olfactomotor response and perceptual experience of smells. *Chemical Senses*, 45, 211–8.
- Pierron D, Pereda-Loth V, Mantel M, Moranges M, Bignon E, Alva O, Kabous J, Heiske M, Pacalon J, David R, Dinnella C, Spinelli S, Monteleone E, Farruggia MC, Cooper KW, Sell EA, Thomas-Danguin T, Bakke AJ, Parma V, Hayes JE, Letellier T, **Ferdenzi C***, Golebiowski J*, Bensafi M* (*co-last authors) (2020). Smell and taste changes are early indicators of the COVID-19 pandemic and political decision effectiveness. *Nature Communications*, 11, 5152.
- Fournel A, Iannilli E, **Ferdenzi C**, Werner A, Hummel T, Bensafi M (2020). A methodological investigation of a dental MRI coil to obtain functional signals from the human olfactory bulb. *Journal of Neuroscience Methods*, 335, 108624.
- Parma V, [...], **Ferdenzi C**, [...], Hayes JE (94 authors) (2020). More than smell – COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. *Chemical Senses*, 45, 609-22.
- Iravani B, Arshamian A, Ravia A, Mishor E, Snitz K, Shushan S, Roth Y, Perl O, Honigstein D, Weissgros R, Karagach S, Ernst G, Okamoto M, Mainen Z, Monteleone E, Dinnella C, Spinelli S, Mariño-Sánchez F, **Ferdenzi C**, Smeets M, Touhara K, Bensafi M, Hummel T, Sobel N, Lundström JN (2020). Relationship between odor intensity estimates and COVID-19 prevalence prediction in a Swedish population. *Chemical Senses*, 45, 449-56.
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- Ferdenzi C**, Razafindrazaka H, Baldovini N, Poupon D, Pierron D, Bensafi M (2019). Influence of gender and culture on the perception of acidic compounds of human body odor. *Physiology & Behavior*, 112561.
- Mantel M, **Ferdenzi C**, Roy JM, Bensafi M (2019). 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. *Brain Topography*, 32, 977-86.
- Becker S, Bräscher A-K, Bannister S, Bensafi M, Calma-Birlinge D, Chan RCK, Eerola T, Ellingsen D-M, **Ferdenzi C**, Hanson JL, Joffily M, Lidhar NK, Lowe LJ, Martin LJ, Musser ED, Noll-Hussong M, Olino TM, Pintos Lobor R, Wang Y (2019). The role of hedonics in the human affectome. *Neuroscience & Biobehavioral Reviews*, 102, 221-41.
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- Ferdenzi C**, Jossain P, Digard B, Luneau L, Djordjevic J, Bensafi M (2017). Individual differences in verbal and non-verbal affective responses to smells: influence of odor label across cultures. *Chemical Senses*, 42, 37-46.
- Manesse C, **Ferdenzi C**, Sabri M, Bessy M, Rouby C, Faure F, Bellil D, Jomain S, Landis BN, Hugentobler M, Cuevas M, Hummel T & Bensafi M (2017) Dysosmia-associated changes in eating behavior. *Chemosensory Perception*, 10, 104-13.
- Jossain P, **Ferdenzi C**, Djordjevic J, Bensafi M. (2017) Relationship between psychophysiological responses to aversive odors and nutritional status during normal aging. *Chemical Senses*, 42, 465–72.
- Fournel A, Sezille C, Licon C, Sinding C, Gerber J, **Ferdenzi C**, Hummel T & Bensafi M (2017) Learning to name smells increases activity in heteromodal semantic areas. *Human Brain Mapping*, 38, 5958-69.
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- Ferdenzi C**, Delplanque S, Atanassova R, Sander D (2016). Androstadienone's influence on the perception of facial and vocal attractiveness is not sex specific. *Psychoneuroendocrinology*, 66, 166-75.

- Fournel A, **Ferdenzi C**, Sezille C, Rouby C, Bensafi M (2016). Multidimensional representation of odors in the human olfactory cortex. *Human Brain Mapping*, 37, 2161-72.
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- Ferdenzi C**, Fournel A, Thévenet M, Coppin G & Bensafi M (2015). Viewing olfactory affective responses through the sniff prism: Effect of perceptual dimensions and age on olfactomotor responses to odors. *Frontiers in Psychology*, 6, 1776.
- Ferdenzi C**, Delplanque S, Mehu-Blantar I, Da Paz Cabral KM, Domingos Felicio M & Sander D (2015). The GENEVA Faces And Voices (GEFAV) database. *Behavior Research Methods*, 47, 1110-21.
- Ferdenzi C**, Delplanque S, Vorontsova-Wenger O, Pool E, Bianchi-Demicheli F & Sander D (2015). Perception of men's beauty and attractiveness by women with low sexual desire. *Journal of Sexual Medicine*, 12, 946-55.
- Joussain P, Bessy M, Fournel A, **Ferdenzi C**, Rouby C, Krolak-Salmon P & Bensafi M (2015). Altered affective evaluations of smells in Alzheimer's disease. *Journal of Alzheimer's Disease*, 49, 433-41.
- Luisier A-C, Petitpierre G, **Ferdenzi C**, Clerc-Berod A, Giboreau A, Rouby C & Bensafi M (2015). Odor perception in children with autism spectrum disorder and its relationship to food neophobia. *Frontiers in Psychology*, 6, 1830.
- Sezille C, **Ferdenzi C**, Chakirian A, Fournel A, Thevenet M, Gerber J, Hummel T & Bensafi M (2015). Dissociated neural representations induced by complex and simple odorant molecules. *Neuroscience*, 287, 23-31.
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- Ferdenzi C**, Poncelet J, Rouby C, Bensafi M (2014). Repeated exposure to odors induces affective habituation of perception and sniffing. *Frontiers in Behavioral Neuroscience*, 8:119.
-
- Ferdenzi C**, Delplanque S, Barbosa P, Court K, Guinard JX, Guo T, Roberts SC, Schirmer A, Porcherot C, Cayeux I, Sander D & Grandjean D (2013). Affective semantic space of scents. Towards a universal scale to measure self-reported odor-related feelings. *Food Quality and Preference*, 30, 128-38.
- Ferdenzi C**, Patel S, Mehu-Blantar I, Khidasheli M, Sander D & Delplanque S (2013). Voice attractiveness: Influence of stimulus duration and type. *Behavior Research Methods*, 45, 405-13.
- Ferdenzi C**, Roberts SC, Schirmer A, Delplanque S, Cekic S, Porcherot C, Cayeux I, Sander D & Grandjean D (2013). Variability of affective responses to odors: Culture, gender and olfactory knowledge. *Chemical Senses*, 38, 175-86.
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- Delplanque S, Chrea C, Grandjean D, **Ferdenzi C**, Cayeux I, Porcherot C, Le Calvé B, Sander D & Scherer KR (2012). How to map the affective semantic space of scents? *Cognition and Emotion*, 26, 885-98.
-
- Ferdenzi C**, Schirmer A, Roberts SC, Delplanque S, Porcherot C, Cayeux I, Velazco M-I, Sander D, Scherer KR & Grandjean D (2011). Affective dimensions of odor perception: A comparison between Swiss, British, and Singaporean populations. *Emotion*, 11, 1168-81.
- Ferdenzi C**, Lemaître J-F, Leongomez JD & Roberts SC (2011). Digit ratio (2D:4D) predicts facial, but not voice or body odour, attractiveness in men. *Proceedings of the Royal Society of London B*, 278, 3551-7.
- Roberts SC, Kravich A, **Ferdenzi C**, Saxton TK, Jones BC, DeBruine LM, Little AC & Havlicek J (2011). Body odor quality predicts behavioral attractiveness in humans. *Archives of Sexual Behavior*, 40, 1111-7.
-
- Ferdenzi C**, Schaal B & Roberts SC (2010). Family scents: Developmental changes in the perception of kin body odor? *Journal of Chemical Ecology*, 36, 847-54.

Ferdenzi C, Coureaud G, Camos V & Schaal B (2010). Attitudes toward everyday odors for children with visual impairments: A pilot study. *Journal of Visual Impairment and Blindness*, 104, 55-9.

Ferdenzi C, Schaal B & Roberts SC (2009). Human axillary odor: Are there side-related perceptual differences? *Chemical Senses*, 34, 565–71.

Ferdenzi C, Mustonen S, Tuorila H & Schaal B (2008). Children's awareness and uses of odor cues in everyday life: A Finland-France comparison. *Chemosensory Perception*, 1, 190-8.

Ferdenzi C, Coureaud G, Camos V & Schaal B (2008). Human awareness and uses of odor cues in everyday life: Results from a questionnaire study in children. *International Journal of Behavioral Development*, 32, 422-31.

Chr  a C, **Ferdenzi C**, Valentin D & Abdi H (2007). Revisiting the relation between language and cognition: A cross-cultural study with odors. *Current Psychology Letters: Behavior, Brain & Cognition*, 22.

Invited commentaries (2)

Ferdenzi C, Licon C, Bensafi M (2017). Detection of sickness in conspecifics using olfactory and visual cues. *Proceedings of the National Academy of Sciences of the United States of America*, 114, 6157-9.

Ferdenzi C, Rouby C, Bensafi M (2016). The social nose: Importance of olfactory perception in group dynamics and relationships. *Psychological Inquiry*, 27, 299-305.

Other articles (5)

Ferdenzi C, Bensafi M (2020). COVID-19 et olfaction. *La Lettre des Neurosciences*, 59, 33-5.

Bensafi M, **Ferdenzi C** & Rouby C (2016). Olfaction et culture. *La Lettre des Neurosciences*, 51, 26-27.

Razafindrazaka H, Pereda V, **Ferdenzi C**, Ricaut F-X, Letellier T, Bensafi M & Pierron D (2016). Neuro-anthropologie de l'olfaction : une approche   volutive. *La Lettre des Neurosciences*, 50, 18-20.

Ferdenzi C & Wathelet O (2008). Une interdisciplinarit   tr  s scientifique : odeurs d'adolescentes, enjeux des liens d'attachement. *Cultures et Soci  t  s*, 8, 99-104.

Ferdenzi C, Holley A & Schaal B (2004). Impacts de la d  fici  nce visuelle sur le traitement des odeurs. *Voir (barr  )*, *Journal de la Ligue Braille*, 28-29, 126-43. Traduit en Espagnol dans : *Entre Dos Mundos, Revista de traducci  n sobre discapacidad visual*, 26, 19-35.

Conference proceedings (2)

Ferdenzi C (2019). Cross-cultural approaches to better understand chemical communication in humans. In: *Chemical Signals in Vertebrates 14*, Buesching CD (Ed), Springer Nature, Switzerland, 139-52.

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Book (1)

Schaal B, **Ferdenzi C** & Wathelet O (2013). Odeurs et émotions. Le nez a ses raisons... Editions Universitaires de Dijon.

Invited talks

- 2021 "Olfactory communication in humans" (in French) GDR MediatEC, 27 Oct, Toulouse, France.
- 2021 "Olfaction and Covid" (in French) Annual ENT meeting of Beaujolais, 14 Oct, Villefranche sur Saône, France.
- 2021 "Perception, processing and behavioral effects of sexually dimorphic body odor compounds" Interdisciplinary Erlangen Colloquium on Body Odours, 28-29 April, Erlangen, Germany (online).
- 2021 "Using virtual reality to induce positive emotions and to study chemical communication in humans" Naturalistic Neurosciences Webinar, 25 March, Lyon, France (online).
- 2019 "Communication of individual characteristics through human body odor" Women In Olfactory Science, 24-25 May, Wageningen, The Netherlands.
- 2019 "Individual differences in emission and perception of human body odours" Chemical communication in humans, 1-2 April, Royal Society Center at Chicheley Hall, United Kingdom.
- 2017 "Cross-cultural approaches to chemical communication in humans: new perspectives" Human olfaction at the intersection of language, culture and biology, 22-23 June, Max Planck Institute for Psycholinguistics, Nijmegen, The Netherlands.
- 2016 "Body odors and emotions: A psychological and neuroscientific approach of human attractiveness" (in French) Centre Européen de Dermocosmétologie, 8 Nov, Ecully, France.
- 2016 "Odors and social interactions in humans" (in French) GDR O3 Odorant Odeur Olfaction, 7 Oct, Lyon, France.
- 2016 "Human body odors and social interactions" Olfaction and Emotion workshop, 6 Oct, University of Geneva, Switzerland.
- 2014 "Olfactory affects: Cultural variations and invariants » (in French) A Nose or Noses? A transdisciplinary vision of olfactory diversity in deficits, expertise and across cultures, 7 Oct, Lyon, France.
- 2014 "Human olfactory perception: gender differences and implications for attractiveness?" (in French) Sex and Evolution, 14 April, Lyon, France.
- 2010 "Olfactory perception: Why gender matters" Perceptnet, 2 July, Barcelona, Spain.

Academic service

Reviewer for journals (* repeatedly)

Chemical senses: Appetite, Chemical Senses*, Chemosensory Perception*, Food Quality and Preference*

Psychology: Aging Neuropsychology and Cognition, American Journal of Psychology, Cognition & Emotion, Cognitive Science, Emotion*, Emotion Space and Society, Frontiers in Psychology, Journal of Psychosomatic Research, Memory, Perception, Personality and Individual Differences*, Psychological Research, Psychoneuroendocrinology, Trends in Cognitive Sciences

Neurosciences: Behavioral Brain Research, Human Brain Mapping, Neuroimage*

Multidisciplinary: PloS One*, Scientific Reports*

Other: Animal Behavior, Developmental Science, Frontiers in Ecology and Evolution, Human Ethology Bulletin, Journal of Nonverbal Behavior, Lung Cancer, Natural Product Communications, ORL, Philosophical Transactions of the Royal Society B, Physiology & Behavior*

Project evaluation

2021 PhD project for the CIFRE Doctoral Program, France
2020 Research project for the “Emergence en Recherche” call of the IDEX Université de Paris, France
2018 PhD project for the Doctoral Program of Excellence at the Université Côte d'Azur, France

Organization of symposia

2021 Symposium « Chemical communication of humans’ physiological and psychological states” at the 15th International Conference on Chemical Signals in Vertebrates, Dijon, France (speakers: Jitka Fialová, Hélène Loos, Mats Olsson, Valentina Parma, S. Craig Roberts, Dagmar Schwambergova)
2019 Session « Human odors and chemical communication » at the GDR O3, Toulouse, France (speakers: Valentina Parma, Arnaud Tognetti, Stéphane Richard Ortegón, Laurent Dormont)

Additional professional training

2019 First aid training (Inserm, Bron, France, 10 hrs)
2018 Biostatistics in R (VetAgro Sup, Lyon, France, 21 hrs)
2017 Good Clinical Practices (Formedea e-learning, 5 hrs)
2009 Summer School in Affective Sciences (University of Geneva, Switzerland, 60 hrs)
2003 Summer School on Human Olfaction (University of Dresden, Germany, 40 hrs)
2003 Developmental Psychology course (Bachelor level, University of Burgundy, France, 20 hrs)

Outreach and media coverage

Conferences

2021 « Functions of human body odors » and « Olfactory disorders » (in French), Rencontres Art et Sciences, St Malo, France
2021 « Covid-19 and smell » (in French), Semaine du cerveau, Orléans, France
2020 « Olfactory communication. What sweat tells about us » (in French), Musée de la Main, Lausanne, Switzerland

Articles

2020 Opinion piece for the journal Libération, with M. Bensafi and C. Rouby (smell and Covid-19)
2019 Three small articles in a special issue “Sentir, Ressentir” of the magazine Nez (odors and emotions, memory, social interactions)
2013 Article for the magazine Biofutur (odors and emotions)

Exhibition

2019-2020 Contribution to "What a nose! Scents and feelings" (in French), Musée de la Main, Lausanne, Switzerland

Television

2021 Participation in France 2 program "Les pouvoirs extraordinaires du corps humain" (chemical communication)
2020 Interviews for France 3 Région and BFM TV (olfaction and Covid-19)
2007 Participation in TV news of France Bleu Bourgogne (children’s olfaction)

Radio

- 2021 CNRS podcast (olfaction and Covid-19)
- 2020 Participation in radio program « CQFD » of RTS (chemical communication)
- 2019 Participation in radio program "La méthode scientifique" of France Culture (chemical communication)
- 2007 Participation in radio program « Le microscope et la blouse » of Radio Campus (children's olfaction)
- 2006 Participation in radio news of Fréquence Plus (children's olfaction)

Written press

- 2021 Interview for La Presse Canada (olfaction)
- 2020 Interviews for Le Figaro, Madame Figaro (twice), La tribune de Lyon, Que Choisir, L'Obs Rue89, Cortex Mag (olfaction and Covid-19), Popsciences Mag (olfaction)
- 2019 Interview for New Scientist, Stylist, Femina, L'Express Dix (chemical communication)
- 2017 Interview for L'Express and Okapi (chemical communication)
- 2006 Interview for Le Bien Public (children's olfaction)

Workshops

- 2021 Olfactory workshops at the public event Fête de la Science, Lyon, France
- 2015 Olfactory workshops at the public event Semaine du Cerveau, Lyon, France
- 2010 Olfactory workshops at the public event Nuit de la Science, Geneva, Switzerland
- 2008 Olfactory workshops at Ness Botanic Garden and World Museum, Liverpool, UK
- 2006 Olfactory workshops at the European Research and Innovation Exhibition, Paris, France
- 2004-2005 Olfactory workshops in primary schools, Dijon, France
- 2002-2007 Olfactory workshops for the outreach program Experimentarium, Dijon, France
- 2002 Cheese tasting workshops at the World Dairy Congress Congrilaît, Paris, France

9. Appendices

Appendix A - Submitted manuscript Richard Ortegón et al.

Richard Ortegón, S., et al. And I'm feeling good: relationships between emotional sweat, perfume, and others' creativity.

And I'm feeling good: relationships between emotional sweat, perfume, and others' creativity.

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Abstract

Emotions can be communicated in social contexts through chemosignals contained in human body odors. The transmission of positive emotions via these signals has received little interest in past research focused mainly on negative emotional transmission. Furthermore, many individuals use perfumed hygiene products that might interfere or modulate this transmission. To investigate human positive chemical communication we explored the autonomic, verbal, and behavioral responses of female receivers exposed to body odors of male donors who took part in a positive or neutral mood induction procedure. These responses were compared with those obtained after exposure to the same body odors with added fragrance. Our findings suggest that positive emotions can be transmitted through body odor. They not only induced modifications at the physiological (heart rate, skin conductance) and verbal levels (perceived intensity) but also at the behavioral level, with an improved performance on creativity tasks. This transmission was either unaffected or enhanced by perfume, depending on the response type.

Keywords

Chemical communication, positive emotions, body odor, perfume, emotional contagion

Introduction

A growing body of evidence suggests that there is a communication of social information in humans via cues contained in their biological odors (i.e., chemical communication). This has been observed for information such as gender (Penn et al., 2007), age (Mitro et al., 2012), health (Olsson et al., 2014), or even sexual arousal (Wisman and Shrira, 2020). It has been suggested that information about emotional states could also be transmitted via this medium. For example, presenting the odor of stress collected on “donors” during first-time skydiving (Mujica-Parodi et al., 2009) and during academic examinations (Pause, 2004) to “receivers” elicits stress-related responses in the latter (e.g., amygdalian activation, facilitated subliminal perception of angry facial expressions).

However, the question whether the transmission of positive emotional states is also possible has rarely been explored. Indeed positive affect has traditionally been neglected in psychological studies (Seligman and Csikszentmihalyi, 2000), perhaps because positive emotions are believed to be less differentiated than negative ones: scientific taxonomies of emotions (Ekman, 1992; Izard, 2013) only identify one positive emotion for every three or four negative ones. In addition, positive emotions are more idiosyncratic, hence more difficult to elicit in laboratory settings. This tendency could also be explained in the light of an evolutionary perspective: negative emotions are our answer to threats and failing to respond to them could be lethal, while failing to respond appropriately to positive emotions is not likely to have such life-threatening consequences (Pratto and John, 1991). The field of human chemical communication is no exception to this general trend : the most studied emotion is fear, which is as of today the only one eliciting a sufficient number of studies to be the target of a meta-analysis (de Groot and Smeets, 2017). And still, positive emotions have a major impact on our lives and are crucial for us as living organisms. Happier people have more stable marriages, stronger immune systems and are more creative (Lyubomirsky et al., 2005). This is not only a correlate but might rather be a cause as suggested by longitudinal studies (Lyubomirsky et al., 2005).

Only very few studies have explored “happy” sweat. In the first study, Chen & Haviland-Jones (2000) found that participants could discriminate this odor at an above-chance rate. Zhou & Chen (2009) found that fear sweat – but not happy sweat – affected the labeling of an ambiguous expression (morphed faces between happy and fearful) by increasing its perception as a fearful face. They also showed, (2011) that receivers could discriminate happy sweat from neutral control sweat, but they were less accurate at doing so than they were when discriminating fear sweat from the control. The last study performed by de Groot and colleagues (2015) found that exposure to happy sweat elicited happier facial expressions and a more global processing style, when compared with fearful sweat. This was the first study investigating not only the transmission of positive emotional information to receivers, but also the partial replication of the state of the donors in them (i.e., emotional contagion; Hatfield et al., 1993). Indeed, more global processing style has been robustly linked with positive affect (Ashby et al., 1999; Bolte et al., 2003; Isen et al., 1987, 1985). Because of the scarce evidence, and of the discrepancy between findings, we aimed at exploring this question further: not only by testing the hypothesis

that the receivers may respond to olfactory emotional cues, but also that emotional contagion could happen, allowing internal state synchronization and therefore communication (Semin, 2007).

Furthermore, the fact that in ecological situations body odors are rarely found alone (Allen et al., 2019) has never been taken into consideration in emotional chemical communication studies before. Body odors are an integral part of the sensory image we send to the world, impacting our social interactions including the evolutionarily most relevant ones such as mate choice (Franzoi and Herzog, 1987; Sergeant et al., 2005). Trying to “control” these endogenous odors with exogenous ones has taken place almost universally since antiquity, with the use of fragrances, deodorant, or soaps. Fragrances could be chosen to complement our natural body odor and genetics (Lenochová et al., 2012; Milinski and Wedekind, 2001), and our individual preferences could be the result of a culture-gene coevolution (Havlíček and Roberts, 2013). This is particularly relevant for the studies of positive emotions because cosmetic odors are chosen by their wearers to generate positive feelings in themselves and in surrounding people. Perfumes could then act in synergy with endogenous odors to produce such positive emotional states. However, some studies have also found that perfume addition alters (although does not suppress) discrimination between individuals (Allen et al., 2015). Because humans usually emit a combination of biological and artificial odors, close attention should be paid to their interaction to fully understand chemical communication.

In this study, we aimed at testing whether positive emotions can be communicated through body odor, and to determine to what extent the addition of perfume can modulate this. We collected sweat from male donors during a positive and a neutral Mood Induction Procedure (MIP) and presented them to female receivers. Receivers’ responses were monitored at three levels: verbal descriptions, peripheral nervous systems’ responses, and performances in behavioral tasks. Indeed, we hypothesized that the influence of emotional body odors is more likely to remain below the level of consciousness, and should be measurable on physiological and/or behavioral responses as shown in previous studies (Ferdenzi et al., 2016; Li et al., 2007). Especially, we used creative problem-solving and divergent thinking tasks, based on the “broaden-and-build” theory (Fredrickson, 1998), which proposes that positive emotions increase attentional scope and allow more flexibility in the thoughts. We hypothesized first that receivers’ autonomic nervous system responses should differ in response to the positive versus the neutral odor. Predicting the direction of the changes is difficult but higher arousal in response to the positive body odor compared to the neutral one should occur and be reflected by increased skin conductance. Second, we hypothesized that if an emotional contagion occurred, receivers should be more efficient in creative tasks after smelling the positive body odor. Third, we expected that these odors might elicit higher positive verbal ratings (pleasantness, well-being), although it may very well not be the case because being produced in pleasant circumstances does not necessarily imply that a stimulus yields pleasant qualities in itself (see also de Groot et al., 2015, for a lack of pleasantness difference across sweat conditions). Lastly, the lack of studies renders prediction of the effect of perfume uncertain: perfume could either have no effect on chemical communication, erase it (by masking chemical cues), or enhance it due to a synergy between two emotionally positive messages.

Materials and Methods

Body odor donors

Donors were 21 males (Mean $\pm$ Standard Deviation: 21.5 ± 2.7 years of age), who declared being heterosexual, of European descent, and non-smokers. Males were recruited because they have larger apocrine glands (Doty et al., 1978). Sexual orientation and ethnicity were controlled because these parameters have been shown to influence body odor perception (Martin et al., 2010; Martins et al., 2005; Prokop-Prigge et al., 2016). All participants (donors and receivers below) provided written informed consent prior to participation and received monetary compensation. This research was conducted in accordance with the Declaration of Helsinki and was approved by the local Lyon Sud-Est II ethical review board (March 6, 2014).

Mood Induction Procedure

Donors attended two emotion induction sessions, a positive and a neutral one in random order, one day apart. During each induction session, after having been equipped for body odor collection, donors entered a separate room where the experiment was conducted. Induction was performed using short film clips assembled to provide a 30-minute sequence for each condition (for further details, see Supplementary Methods). Donors seated and watched the videos after the experimenters left the room. For the positive condition, donors were seated in groups of 3 which is believed to increase positive emotions thanks to the interaction and sharing of the feelings (as seen in de Groot et al., 2015). They were also given a personalized present (perfume and chocolates) before the induction started (Isen et al., 1987). In the neutral condition, donors were seated alone in the room and did not receive any present. To measure the emotional response of the donors during the MIP, we asked them after each excerpt to rate how amused, afraid, happy, sad, surprised, disgusted, angry, neutral and calm they felt during the clips using a paper-and-pencil 10-cm continuous scale from 0 (not at all) to 10 (extremely). Ratings were recorded in centimeters to the nearest 0.1 cm.

Body odor collection

From two days before the first odor collection, donors followed a protocol to prevent odor contamination (details can be found in Supplementary Methods). On collection days, donors had to take a shower just before coming to the laboratory. Experimenters used odorless tape (Urgopore microporousTM, Urgo) to attach 10x10cm sterile cotton gauze pads (Sylamed) under each donor's armpit, while wearing nitrile gloves. Donors were then asked to put on a cotton t-shirt (Decathlon, previously washed with a non-perfumed detergent) instead of their personal clothes to prevent odor contamination. At the end of the emotion induction procedure, pads were removed, cut into 1x3cm strips taken from the central area of the pads, placed in aluminum foil and then in one ziplock bag per donor and per emotion condition (positive/neutral), before being stored at -32°C.

Sample selection for odor presentation

Selection of the samples to be presented to the receivers was carried on based on the emotional ratings provided by the donors after the video clips (see Mood Induction Procedure). As we noticed that emotional induction was not equally efficient in all donors (i.e., average happiness ratings collected during the positive MIP ranged from 2.7 to 9.4 on a scale from 1 to 10), we selected only the body odor samples of the donors who were best responsive to the MIP. Among those who gave i) average happiness ratings > 5 in the positive MIP and ii) average happiness ratings ≤ 5 in the neutral MIP, the 8 individuals with the highest happiness ratings were kept.

Female receivers

Receivers were 60 females (mean age ± SD: 20.8 ± 2.2 years old), who declared being heterosexual, of European descent, non-smokers, and used hormonal contraception. They reported not suffering from any psychological, cardiac, respiratory or olfactory diseases. Females were recruited as receivers because they have a better sense of smell and greater sensitivity to emotional chemosignals (Brand and Millot, 2001; de Groot et al., 2014). Sexual orientation and ethnicity were controlled for the same reasons as in donors, and hormonal contraception was also added to limit olfactory variations due to menstrual cycle in spontaneously ovulating women (Navarrete-Palacios et al., 2003). Sixteen of the receivers took part in a physiological recording session, and all 60 receivers performed odor verbal ratings and creativity tasks.

Olfactory stimuli

In the physiological recording session, all receivers were presented with 6 stimuli: clean air, body odors sampled during the positive and neutral MIP added or not with perfume, and perfume alone. The stimuli were presented 3 times each, in three blocks comprising the 6 stimuli in a pseudo-randomized order (clean air never in first or last position). In the behavioral tasks, receivers were exposed either to positive body odor samples, neutral body odor samples or to one of the control conditions, i.e. a control odor (Leather, Firmenich SA) or clean air.

Preparation of the body odor samples was performed by putting the frozen 1×3cm sweat pad strips obtained in donors at room temperature one hour before the start of the receivers' session. To reduce the effects of interindividual variability, four strips from four different donors, combining left or right armpits chosen randomly (see Ferdenzi et al., 2009), were placed into a U-shaped Pyrex® tube (VS technologies, France; volume: 10 ml; length: 50 mm; external diameter: 14 mm). Each positive body odor and neutral body odor was prepared twice, to allow the addition of 2 drops of a male perfume in one of the two samples. The perfume (concentrate of commercially available fine fragrance diluted in Dipropylene-glycol, 10% concentration) was chosen among other perfumes because it received the highest scores of pleasantness in a preliminary test (N=24, 16 women). The “perfume alone” stimulus was obtained by putting 2 drops of the same perfume in a U-tube containing 4 clean 1×3cm strips of gaze. The control stimuli (Leather and clean air) were obtained by placing 2 mL solution (leather diluted in Dipropylene-glycol, 20% concentration, or Dipropylene-glycol alone from Sigma–Aldrich for the clean air condition) in U-tubes containing scentless polypropylene fabric (twice 1×6 cm;

3M®, Valley, NE, USA). Olfactory stimuli were diffused at an airflow of 1.5 L/min using a computer-controlled olfactometer with time-controlled stimulus onset.

Physiological recordings

Heart rate and skin conductance of the receivers were measured with Equivital EQ02+ Lifemonitor system (Equivital, Cambridge, UK), and amplified by a Dual Bio Amp from AD instruments (Dunedin, New Zealand). The acquisition software was Labchart v8.1.5 (AD instruments, Dunedin, New Zealand). Signals were analyzed in a range of 10-seconds pre- and 10 seconds post-stimulus for the heart rate and 10-second post stimulus for the skin conductance. High-pass, low-pass filters were added along with smoothing algorithms to eliminate artifacts. A local mean of the points during these 10-second windows was calculated using python scripts developed in house. For *heart rate*, the mean values of the frequency were computed. For *skin conductance*, we calculated the number of responses found in the 10s-post-stimulus window and the basic peak (maximal value of the signal during the very same window). Sniffing behavior of the receivers was also recorded. This was performed by means of a nasal cannula positioned in both nostrils and connected to an airflow sensor (AWM720, Honeywell, France). This system was developed in house to allow us i) to synchronize odor delivery with the participants' respiration, and ii) to record sniffing behavior. The sniffing signal was amplified and digitally recorded at 256 Hz using LabVIEW software®. The maximum airflow (highest point), the area under the airflow curve (volume inspired) and the duration of the sniff (time between the inhalation starting point and the point where the flow returned to zero) were computed for the first sniff following odor presentation.

Behavioral tests: creativity and problem-solving

The receivers took part in two behavioral tasks. The first task was the *Guilford's Alternate Uses Task* (Guilford, 1967). In this test, the participants are asked to list as many non-obvious uses as possible for common objects in a limited time and their answers are given scores in terms of fluency, originality, elaboration, and flexibility (for details about scoring and examples, see Supplementary Method). Here, receivers were given 2 minutes per object, which were: *brick, barrel, pencil, shoe, car tire, hanger*.

The second task was *Duncker's Candle Problem* (Duncker, 1945). The receivers were brought in front of a table where they could find a box of tacks, a candle, and a box of matches. They were asked to find a way, with the available objects, to affix the candle to the wall (on a corkboard) in such a way that it will burn without dripping wax on the table or on the floor. The analyzed variable was solving time. The problem was considered as solved if the receivers emptied the book of matches, used the tacks to nail the box to the corkboard and made the candle stand inside the empty box. They were given 10 minutes to solve this problem and the time they spent to find the solution was scored in seconds. The participants who did not find the solution in the maximum allocated time were discarded.

Verbal measures

At the end of the physiological recording session (or of the behavioral tasks for those who took part in these tasks), the odors were presented in random order and receivers were asked to

evaluate them on 9-point Likert scales (1 = not at all, 9 = extremely) for the following characteristics: how intense, pleasant and familiar the odors were, and to what extent they caused well-being.

Odor presentation procedure

For the physiological recording session, the receivers were equipped with the measurement sensors and seated in a comfortable chair in a quiet and well-ventilated room with standardized conditions of light (no windows) and temperature. They were also given white noise, sound-cancelling headphones. The experiment started with 2 minutes of rest to assure a baseline, then the first odor was sent with the olfactometer for 5 seconds, on an expiration to ensure that it would enter the nostrils at the beginning of the next inspiration. The next 60 seconds were odorless to return to the baseline and to avoid olfactory adaptation. Then the next odor was sent and so on (in a pseudo-randomized order) until all odors were sent (first block out of three).

After a 5-minute break, the behavioral tasks started. The odor condition was attributed randomly, the receivers being blind with regards to the nature of the odor. During the whole duration of the behavioral session, the odor was sent to receivers' noses through the olfactometer, for 5 seconds every 30 seconds. Finally, the receivers rated the odors on verbal scales and were thanked for their participation after a small brief about the purpose of the experiment.

Preparation of the data

The receivers' physiological variables that we analyzed were: i) Mean heart rate difference between the 10-second post-stimulus and the 10-second pre-stimulus windows (beats per minute, post- minus pre-), ii) Log-transformed characteristics of the first sniff during odor presentation, namely sniff volume (area under the curve AUC, arbitrary unit) and sniff duration in seconds (between inhalation starting point and the point where the sniff's flow returned to zero), iii) Characteristics of the skin conductance response, namely the log-transformed SC basic peak (in μS , maximum value of the signal during the 10-s post-stimulus window minus value of the signal at stimulus onset), and number of SC responses (during the 10-s post-stimulus window). The odor ratings of intensity, pleasantness, familiarity and well-being collected after stimulus presentation were used as such. Finally, we analyzed the receivers' performances in the creativity tasks, represented by Alternate Uses Task (AUT) scores of fluency, originality, elaboration and flexibility (see Behavioral tests) and time to solve the Candle Problem (in sec). The AUT scores were attributed in a double-blind fashion by two independent judges (SRO, CF). Scores of both judges on each variable were highly correlated ($r = 0.70$ to 0.98), and thus averaged.

There were missing data described as follows. Because of technical saving issues, 1 block (repetition) out of 3 was lost for 2 receivers (2 out of 48 blocks in total, 0.04%) for the physiological recordings. During data analysis, several outliers were deleterious for the quality of some of the statistical models detailed in Tables 1 and 3: after being identified by visual inspection of the graphs of residuals and of Cook's distances, they were removed before recomputing the final model.

Statistical analyses

The continuous variables (physiology, ratings) have been analyzed with linear mixed-effects models, using the *lme4* package (Bates et al., 2015) in R (R Core Team 2019, RStudio version 3.6.1). Fixed factors were Condition (Positive/Neutral body odor) and Perfume (With/Without). Subject was used as a random factor. Model selection was used to select the best models, using the *anova* function. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality, and when it did, outliers were removed to improve the quality of the model. P-values were obtained using Kenward–Roger approximation in the *anova* function of *lmerTest* package in R (Kuznetsova et al., 2017) and non-significant interactions were removed to keep only the best model including the main effects. Post-hoc contrasts were performed using the *multcomp* function of the *emmeans* package in R (Lenth et al., 2020).

The number of SC responses was analyzed with three Chi-square tests to evaluate the effect of Condition and Perfume (for all trials together, and for trials with and without Perfume separately). Because the size of some cells of the contingency tables was < 5 , a Yates' correction was applied. In addition, responses were divided in two groups: 0-1 responses versus 2-3 responses.

For both creativity tasks, we conducted one-tailed t-tests because a clear *a priori* hypothesis was postulated before data collection: smelling positive body odors is expected to increase positive affect and thereby creativity (Isen et al., 1987). A preliminary analysis comparing performances in presence of the neutral body odor with those in the control conditions revealed no significant differences: neither between neutral body odor and clean air (AUT Fluency: $p=0.328$; AUT Originality: $p=0.412$; AUT Elaboration: $p=0.910$; AUT Flexibility: $p=0.439$; Candle Problem: $p=0.144$) nor between neutral body odor and leather (AUT Fluency: $p=0.580$; AUT Originality: $p=0.297$; AUT Elaboration: $p=0.510$; AUT Flexibility: $p=0.443$; Candle Problem: $p=0.117$). Consequently, in the results section we focus only on the comparison of interest between positive and neutral body odor.

Results

Positive male body odors induced physiological changes in women

When smelling the positive body odor, receivers had a decrease in mean heart rate (Mean $\pm$ Standard Deviation: -0.957 ± 2.85) which was not found after smelling the neutral body odor (-0.050 ± 2.81 ; Figure 1A), as shown by a significant effect of the Condition (Positive vs. Neutral: $p < 0.05$; Table 1). Skin conductance (SC) was also modulated by Condition. Indeed, positive body odors were associated with a higher number of SC responses than the neutral stimulus (0/1 responses: $N=88$ in the Neutral vs. 78 in the Positive condition; 2/3 responses: $N=4$ in the Neutral vs. 14 in the Positive condition; $\chi^2(1)=4.988$, $p=0.026$; Figure 1B). No effects were found for the other examined component of SC, i.e., log-transformed SC basic peak ($p > 0.05$, Table 1). When the same analysis was conducted on the trials with and without perfume separately there was no effect of Condition on the number of SC responses ($\chi^2(1)=1.971$, $p=0.160$, for both tests) and the Condition $\times$ Perfume interaction did not modulate any of the other physiological variables (Table 1).

Women were more creative when smelling positive body odors

Receivers' responses in both behavioral tasks revealed consistent results. In the first task, the Alternate Uses Task, the group exposed to positive body odors found significantly more alternative uses (higher Fluency) than the group receiving the neutral body odor (Positive: 24.37 ± 10.87 words, Neutral: 16.50 ± 5.83 , $t(30) = 2.553$, $p = 0.005$; Figure 2A). They also displayed higher Flexibility, i.e. they used more varied categories of uses (Positive: 3.33 ± 1.23 categories, Neutral: 2.54 ± 0.78 , $t(30) = 2.152$, $p = 0.013$; Figure 2B). Both groups did not differ on the Originality ($t(30) = 1.290$, $p = 0.09$) or Elaboration ($t(30) = 0.651$, $p = 0.265$) of their responses. In the second task, participants had to solve The Candle Problem in a limited time. Those who were exposed to the positive body odor found the solution faster than those who smelled the neutral one (Positive: 230.43 ± 144.75 seconds, Neutral: 389.67 ± 177.22 ; $t(13.94) = 1.978$, $p = 0.034$; Figure 2C). The effect of perfume was not investigated in these tasks.

Perfume and body odor emotional content: a synergy

When asked to explicitly evaluate the stimuli used in the experiment, the participants rated the perfumed stimuli as more pleasant (With perfume: 5.41 ± 1.87 ; Without perfume: 3.89 ± 2.09 ; $p < 0.001$; Table 2) and felt more well-being (With: 4.56 ± 1.66 ; Without: 3.87 ± 2.13 ; $p < 0.05$; Table 2). Examination of the olfactomotor responses are consistent with these results. Larger sniff volumes and longer sniff durations were found when body odors were presented with perfume (log-transformed Volume: With perfume -0.35 ± 0.33 and Without -0.44 ± 0.30 ; log-transformed Duration: With 0.27 ± 0.20 and Without 0.20 ± 0.14 ; Table 3), which is usually observed with more pleasant odors. Perfumed body odors were also rated as more intense (With perfume: 5.74 ± 1.90 ; Without: 1.94 ± 1.25 ; Table 2) and more familiar (With perfume: 5.30 ± 2.03 ; Without: 3.15 ± 2.10) ($ps < 0.001$, Table 2). For these two variables the Condition $\times$ Perfume interaction was significant (Intensity: $p < 0.05$) or close to significance (Familiarity: $p = 0.06$) (Table 2). In both cases, perfumed positive body odors received higher ratings than perfumed neutral body odors (Intensity: Positive 6.41 ± 1.57 , Neutral 5.07 ± 1.98 , Familiarity: Positive 5.89 ± 1.99 , Neutral: 4.70 ± 1.94 ; post-hoc contrasts $ps < 0.05$), while positive and neutral body odors did not differ when presented unperfumed (Figure 3).

Discussion

The aim of this research was to explore whether positive emotions could be communicated between humans through body odors and if this transmission could take the form of an emotional contagion between an emitter and a receiver. We also explored for the first time whether a perfume could modulate this potential emotional contagion, which appears to be highly ecological since body odors are uncommonly found alone. We showed that exposure to chemosignals denoting positive affect collected on donors impacted receivers' responses, in line with our hypotheses and previous work (Chen and Haviland-Jones, 2000; de Groot et al., 2015). Moreover, there was concordant evidence that positive affect may transfer from one individual to another through this route (emotional contagion, Hatfield et al., 1993), since we recorded increased performances in two different creativity tasks in presence of the positive body odor. Indeed, it has been extensively documented that performance on those tasks is

affect-dependent, and facilitated if one is experiencing positive affect (Isen et al., 1987, 1985). Finally, perfume increased stimuli pleasantness and had a synergic effect by revealing differences in perceived intensity and familiarity between positive and neutral body odors that did not reach conscious perception in absence of perfume.

At a physiological level, heart rate and skin conductance were modulated by the presentation of a positive body odor compared with a neutral body odor. There was a deceleration of the mean heart rate after participants smelled the positive body odor: such a decrease has been reported before with odors considered as pleasant (Alaoui-Ismaili et al., 1997; Bensafi, 2002). This may be related to the positive valence of the odor, even though this did not reach consciousness since they did not receive higher pleasantness ratings. Receivers also displayed a higher number of skin conductance responses after smelling the positive body odor when compared to the neutral one, which is considered as a marker of emotional arousal, independently of the valence of the emotion (Bensafi, 2002). This emotional arousal may show through intensity ratings, which were higher for positive body odors than for neutral ones (although only when perfume was added). The fact that most participants (97%) reported not to smell anything when presented with body odors alone and that no perceived differences were found in the “without perfume” condition (they were forced to provide ratings anyway) suggests that chemosignals of positive affect may alter physiology and cognition at a subliminal level. This is consistent with previous studies in the field of olfactory chemical communication in humans, where body odors are consistently rated as very low in intensity, if not perceived at all (Mujica-Parodi et al., 2009) and have subliminal effects on perception and behavior (Ferdenzi et al., 2016; Li et al., 2007).

Most importantly, when using creativity-related tasks as an indirect measure of a transfer of positive emotional affect, we showed that the group smelling the positive body odor was significantly more efficient in these tasks than the group exposed to the neutral body odor. They had higher fluency and higher flexibility scores at the AUT, and found the solution to the Candle problem more quickly. Note that for the AUT, the scores of originality and elaboration remained unaffected by Condition, probably due to the time constraints which can have detrimental effects on creativity (Amabile, 1979). As a whole, the results observed at the physiological and the behavioral level are in agreement and constitute indirect evidence suggesting that emotional contagion may have occurred at two levels in the experimental setting, even though the design only provides indirect evidence of it. Respectively at physiological and behavioral levels, low heart rate (Ekman et al., 1983) and better performances at creative problem-solving tasks (Isen et al., 1987) have been linked with experiencing happiness or positive affect. This is the first time an effect on creativity has been shown in receivers exposed to emotional body odors of donors.

Regarding the role of fragrance in the chemical communication of emotions, we found that adding perfume to body odors either did not interfere with chemical communication, or in some cases had a synergic effect with the positive emotion. Indeed, perfume increased positive body odor intensity and familiarity compared to the neutral body odor, while both odors were perceptually similar (and mostly not consciously perceived at all) when presented unperfumed.

This suggests that fragrance use may not be detrimental to chemical communication within human social networks, and that in some cases it could even facilitate it (at least with the particular perfume and concentration we used). It can be assumed that this facilitating effect could be specific to the communication of positive states. Here, body odors received positive ratings (pleasantness, well-being) when mixed with perfume, which was corroborated by a more intense sniffing behavior (sniff duration and volume) than without perfume: therefore, the synergic effect we found might only take place if the intrinsic qualities of the exogenous (perfume) and endogenous (body) odors are consistent, allowing an easier discrimination by repetition of coherent information without redundancy.

To conclude, the study presented here constitutes a step forward in understanding the chemical communication of emotions in humans, by focusing on positive affect and on its modulation by exogenous fragrances. Here we provided evidence in favor of the presence of chemosignals of positive emotions in human body odor, of the modulation of receivers' physiology and behavior in response to these chemosignals and of a likely replication of the positive emotional state in the receivers. Future research would be appropriate both to confirm these conclusions and to go further in our understanding of chemical communication. For example, because of technical constraints our study had to be conducted in a single-blind fashion (participant unaware of the odor conditions): although maximum precautions were taken to prevent observer-expectancy, a double-blind design should be favored in the future when possible. In addition, as an initial approach of the question, we limited our study to female receivers responding to male odors of about the same age. However, investigating other combinations of sex (and age) characteristics would provide a more ecologically valid picture of chemical communication between humans. Regarding perfume, investigating its effects on negative emotion communication could be useful, especially in situations where disruption of such a communication could be beneficial (e.g., stress contagion during exams or in confined situations, etc.). Finally, future research could extend the investigation in social situations closer to real contexts, in which olfactory signals co-occur with visual, auditive and other signals and in which multisensorial integration takes place. While negative emotional contagion serves an adaptive function of alerting conspecifics about dangerous situations, positive emotional contagion also has adaptive advantages: it allows communities to build social interaction, inciting them to explore new approaches about situations and ideas, and promoting global communication. Sharing positive emotions helps us build resources and contributes to defining us as a social species.

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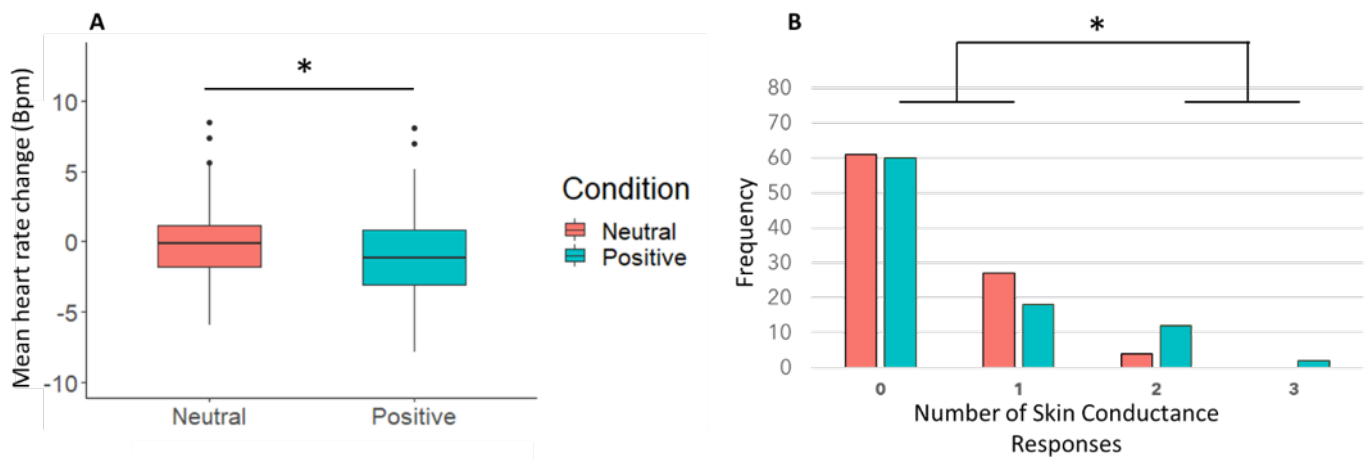


Fig. 1: Female receivers' autonomic responses during the presentation of male body odors collected during Positive and Negative mood induction. A) Boxplot of mean heart rate change between the 10 second post-stimulus and the 10 second pre-stimulus window, in beats per minute (Bpm) for the neutral and positive condition (*: $p < 0.05$, see statistics in Table 1). **B)** Frequency of the skin conductance SC responses, i.e., number of trials where either 0, 1, 2 or 3 SC responses were recorded after exposure to neutral and positive body odors, during a 10-second post-stimulus window (*: $p < 0.05$, result of a Chi-square test comparing 0-1 to 2-3 responses).

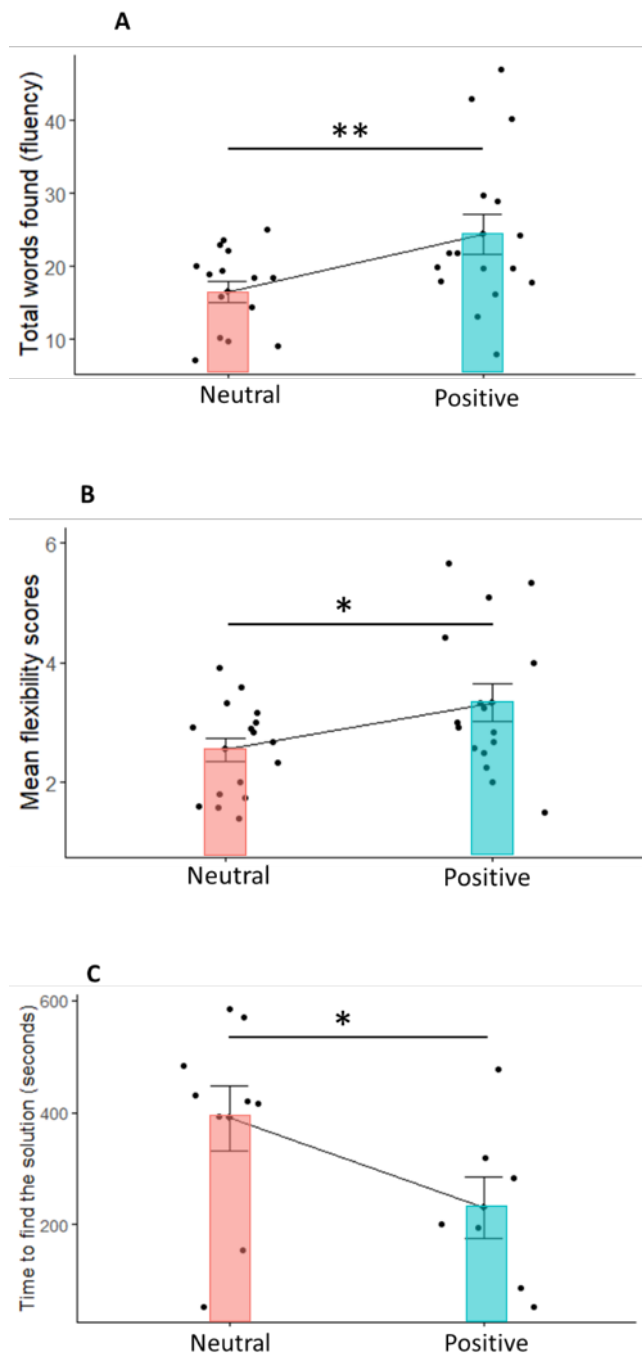


Fig. 2: Female receivers' behavioral responses in creativity tasks during the presentation of male body odors collected during either a Positive or a Neutral mood induction. A) Total number of words found per participant in the Alternate Uses Test in the presence of the positive and neutral body odors. **B)** Mean flexibility scores for the AUT in the presence of the positive and neutral body odors. **C)** Mean time to find the solution to the Candle problem, in seconds. Means $\pm$ Standard Error of the Mean in all graphs.

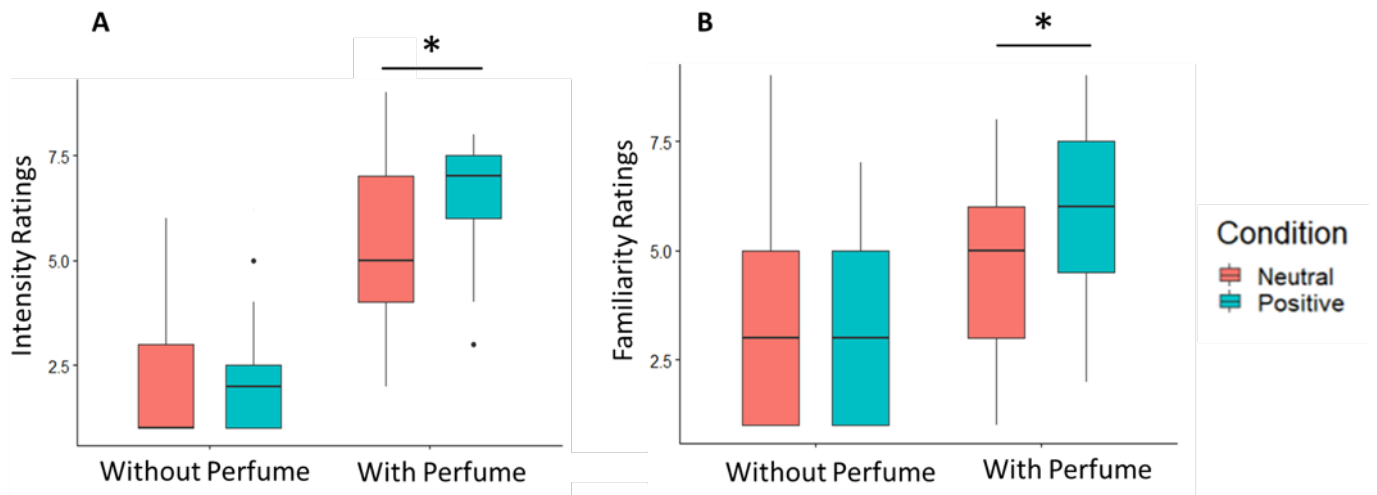


Fig. 3: Female receivers' verbal responses during the presentation of male body odors collected during Positive and Negative mood induction. A) Boxplot of the intensity ratings (1-9) for neutral and positive body odors, without and with perfume (Condition×Perfume interaction: $p<0.05$, see statistics in Table 1). **B)** Boxplot of the familiarity ratings for neutral and positive body odors, with and without perfume (Condition×Perfume interaction: $p=0.06$). *: $p<0.05$, results of post-hoc contrasts between Positive and Negative Conditions.

Table 1. Physiological responses as a function of Condition (Positive vs. Neutral body odor) and Perfume (With vs. Without). Results of the linear mixed models with Condition and Perfume as fixed factors and Subject as random factor (intercept). For all variables, the best model was $Variable \sim Condition + Perfume + (1|Subject)$, therefore the effect of the interaction was not tested (see Methods). P -values < 0.05 are in bold.

Variable	Main effects and interactions	Statistics	
Heart Rate	Condition	F(1,166.03)=5.496	p=0.020
	Perfume	F(1,166.03)=0.334	p=0.564
	Condition×Perfume	-	-
Skin Conductance basic peak	Condition	F(1,61.237)=0.044	P=0.835
	Perfume	F(1,60.352)=1.360	P=0.248
	Condition×Perfume	-	-

Table 2. Odor ratings as a function of Condition (Positive vs. Neutral body odor) and Perfume (With vs. Without). Results of the linear mixed models with Condition and Perfume as fixed factors and Subject as random factor (intercept). The effect of the interaction was tested only when the interaction was present in the best model (see Methods). *P*-values < 0.05 are in bold.

Variable	Main effects and interactions	Statistics	
Pleasantness ¹	Condition	F(1,79)=0.013	P=0.909
	Perfume	F(1,79)=22.135	P<0.001
	Condition×Perfume	-	-
Well-being ¹	Condition	F(1,79)=0.732	P=0.395
	Perfume	F(1,79)=4.451	P=0.038
	Condition×Perfume	-	-
Intensity ²	Condition	F(1,78)=9.547	P=0.003
	Perfume	F(1,78)=238.674	P<0.001
	Condition×Perfume	F(1,78)=5.458	P=0.022
Familiarity ²	Condition	F(1,78)=2.671	P=0.106
	Perfume	F(1,78)=39.932	P<0.001
	Condition×Perfume	F(1,78)=3.431	P=0.068

¹ Best model: *Variable ~ Condition + Perfume + (1|Subject)*

² Best model: *Variable ~ Condition + Perfume + Condition×Perfume + (1|Subject)*

Table 3. Olfactomotor responses as a function of Condition (Positive vs. Neutral body odor) and Perfume (With vs. Without). Results of the linear mixed models with Condition and Perfume as fixed factors and Subject as random factor (intercept). For all variables, the best model was $Variable \sim Condition + Perfume + (1|Subject)$, therefore the effect of the interaction was not tested (see Methods). *P*-values < 0.05 are in bold.

Variable	Main effects and interactions	Statistics	
Sniff volume	Condition	F(1,166)=0.0004	P=0.984
	Perfume	F(1,166)=9.788	P=0.002
	Condition×Perfume	-	-
Sniff duration	Condition	F(1,166)=0.028	P=0.866
	Perfume	F(1,166)=21.090	P<0.001
	Condition×Perfume	-	-

Appendix B – Manuscript in revision Ferdenzi et al. (in French)

Ferdenzi, C., Bellil, D., Boudrahem, S., Bousquet, C., Daudé, C., Degraix, J.-L., Denoix, L., Faure, F., Fieux, M., Fournel, A., et al. in revision. La rééducation olfactive : bénéfices d'une prise en soins pluri-professionnelle.

La rééducation olfactive : bénéfices d'une prise en soins pluri-professionnelle

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Résumé

Près d'un français sur cinq souffre de troubles de l'odorat (TO), ou dysosmie. Cette prévalence a augmenté depuis l'apparition de la COVID-19 dont la dysosmie est un symptôme très fréquent et possiblement persistant. Pourtant, la prise en soin des personnes dysosmiques reste insuffisante. Cet article ouvre des pistes pour développer les rééducations olfactives (RO) sur la base de protocoles déjà éprouvés, mais aussi pour améliorer l'accompagnement des patients dysosmiques. Pour cela, une stratégie de prise en charge pluri-professionnelle est préconisée, alliant l'intervention de scientifiques, de médecins (généralistes, ORL) et de professions paramédicales.

Mots-clé

Troubles olfactifs, rééducation, prise en charge, COVID-19, dysosmie, qualité de vie.

Summary

Nearly one in five French people suffer from olfactory disorders (TO), or dysosmia. This prevalence has increased since the onset of COVID-19, for which dysosmia is a very common and possibly persistent symptom. However, the care of people with dysosmia remains insufficient. This article opens up avenues for developing olfactory rehabilitation (OR) on the basis of existing protocols, but also for improving support for dysosmic patients. For this purpose, a multi-professional care strategy is recommended, combining the intervention of scientists, doctors (general practitioners, ENT) and paramedical professions.

Key-words

Olfactory disorders, rehabilitation, care, COVID-19, dysosmia, quality of life.

1. Les troubles olfactifs en France, avant et depuis la COVID-19

1.1. Définition, étiologie et prévalence

Les troubles olfactifs (TO), ou dysosmies, peuvent se manifester par des perturbations quantitatives ou qualitatives. Les premières se caractérisent par une perte des perceptions olfactives partielle (hyposmie, allant de légère à sévère) ou totale (anosmie), et plus rarement par un odorat décuplé (hyperosmie). Les perturbations qualitatives sont caractérisées quant à elles par des distorsions (parosmie) ou des hallucinations olfactives (fantosmie) [1]. Les TO ont des étiologies variées [2]: 1) origine traumatique (section des filets olfactifs traversant la lame criblée lors d'un traumatisme crânien) ; 2) maladies naso-sinusiennes telles que la polypose nasale, qui peuvent causer soit un obstacle au passage des molécules odorantes dans la cavité nasale soit perturber le processus de liaison des odorants aux neurones récepteurs olfactifs du fait des phénomènes inflammatoires ; 3) vieillissement normal caractérisé par une presbyosmie (par analogie avec la presbycousie ou la presbytie), et maladies neurodégénératives (maladies de Parkinson et d'Alzheimer) ; 4) infections des voies respiratoires supérieures par des bactéries ou des virus, qui perturbent l'odorat par simple congestion de la muqueuse empêchant les molécules odorantes d'atteindre l'épithélium olfactif ou par lésion directe de celui-ci. D'autres étiologies existent, telles que l'anosmie congénitale (par ex. dans le syndrome de Kallmann), l'exposition à des substances toxiques qui endommagent le neuroépithélium olfactif, ou encore les maladies psychiatriques et neurologiques, les tumeurs et certaines maladies systémiques. Enfin, dans près d'un cas sur cinq [3], la dysosmie est qualifiée d'idiopathique car les mécanismes en cause ne peuvent être identifiés. La prévalence des TO dans la population a été estimée à environ 20-25% dans les populations occidentales, ce qui est loin d'être négligeable. Il s'agit surtout d'hyposmies, le taux d'anosmie variant de 1 à 5% selon les études et les pays [1]. Une étude menée fin 2014 par le Centre de Recherches en Neurosciences de Lyon (CRNL) en collaboration avec l'Hôpital Nord-Ouest de Villefranche, l'Infirmierie Protestante de Caluire et les Hospices Civils de Lyon, a permis de tester les capacités olfactives de 3685 participants en France, à l'aide de 8 odeurs sous forme de cartes à gratter [4]. Cette étude met en évidence une incidence des dysosmies de 17% en moyenne tous âges confondus, et de presque 30% chez les plus de 60 ans.

1.2. Les dysosmies liées à la COVID-19

La prévalence des TO a certainement augmenté depuis la survenue du nouveau virus SARS-CoV-2 à la fin de l'année 2019. En effet, la perte du goût et de l'odorat a rapidement été identifiée comme un des symptômes les plus spécifiques de la COVID-19. En France, plus de 2 millions de cas de COVID-19 ont été recensés à ce jour, et 46 à 86% des patients ont été atteints de TO [5,6]. Avant la pandémie, les TO post-infectieux étaient connus pour avoir des durées variables, de quelques jours pour les uns à des durées plus longues pour d'autres, allant même jusqu'à être permanents chez certaines personnes, ce qui suggère une diversité de mécanismes d'action des virus [7]. Plusieurs études, dont une menée par le CRNL³, confirment cette variabilité dans le cas de la COVID-19. Si au début de la crise sanitaire, on annonçait une durée de perte olfactive de 9 jours en moyenne [8], on a bien vite constaté qu'un nombre

³ Questionnaire en ligne : https://frama.link/covid_odorat

croissant de patients se plaignaient de pertes olfactives persistantes [9]. En fait, il semble exister deux formes cliniques : celle des TO inauguraux qui récupèrent totalement en une dizaine de jours et celle des TO différés qui laissent un déficit important et des parosmies dont les patients parlent beaucoup. Dans l'étude du CRNL, sur la période du 8 avril au 13 janvier 2021, sur 2502 patients COVID-19 n'ayant pas encore récupéré de leurs pertes olfactives plus de deux tiers avaient des durées de troubles olfactifs supérieures à la normale (1 mois) et allant jusqu'à 10 mois [10]. Parmi ces patients décrivant des troubles persistants, 329 en souffraient depuis la première vague, soit depuis plus de 200 jours. Par ailleurs, la probabilité de développer un trouble olfactif persistant suite à la COVID-19 est plus importante chez les femmes et augmente avec l'âge. Ces chiffres sont préoccupants et laissent présager dans un futur proche une augmentation du nombre de patients en demande d'un accompagnement médical et rééducatif pour la récupération de l'odorat.

1.3. Impact des troubles olfactifs sur la qualité de vie

Que la perte olfactive soit liée ou non à la COVID-19, une aide à la récupération semble indispensable au vu de ses conséquences sur le quotidien des patients. En effet, le handicap dans la vie quotidienne est important et il peut même avoir des conséquences graves sur la santé mentale et physique [11,12]. Les personnes dysosmiques sont plus susceptibles de subir des accidents domestiques car elles détectent moins les odeurs de feu, de gaz ou d'aliments avariés. Un manque de confiance en soi lié à l'absence du contrôle de sa propre odeur corporelle (sueur, haleine) peut apparaître, débouchant parfois sur des comportements hygiéniques compulsifs. Une déstabilisation des interactions sociales peut survenir notamment dans la sphère intime (relations parent-enfant, ou entre partenaires sexuels). Des problèmes importants dans le domaine alimentaire et nutritionnel sont souvent observés car la plupart des patients modifient leur comportement alimentaire. En effet, la richesse perceptive des aliments est drastiquement réduite⁴ ce qui conduit à une diminution du plaisir de manger puis, à plus long terme, à une diminution de l'appétit. Dans le même temps, on a constaté une augmentation de l'utilisation de condiments salés et gras afin de rendre les aliments plus savoureux [12]. A cela s'ajoute le manque de motivation pour la préparation des repas, qui peut devenir un problème pour certains patients ainsi que pour leurs proches. Enfin, si la personne exerce un métier où les odeurs ont une importance, comme les arts culinaires ou la parfumerie, la soudaine inadéquation professionnelle pourra s'avérer très problématique. Dans l'ensemble, la perte de l'odorat peut engendrer de réelles difficultés dans la vie sociale, une tendance à l'isolement et des symptômes dépressifs chez un quart à un tiers des personnes dysosmiques [11]. Nous avons pu retrouver ces effets délétères des déficits olfactifs sur la qualité de vie chez nos patients COVID-19, et observé un lien entre la durée du déficit et son caractère délétère [10]. Une fois la menace vitale écartée, lutter contre le déficit olfactif est important d'une part pour la santé mentale des patients concernés – déjà mise à mal par la crise sanitaire actuelle [13] – et d'autre part pour le processus

⁴ Le « goût » d'un aliment au sens commun du terme est constitué des saveurs (sucré, salé, acide, amer et umami, dont les récepteurs sont sur la langue) associées à des sensations olfactives (dont les récepteurs se trouvent dans la cavité nasale). Une expérience toute simple permet de se rendre compte de la diminution de la richesse perceptive d'un aliment en l'absence d'odorat : 1) se pincer le nez puis mettre en bouche un aliment, le mastiquer et constater la sensation (saveurs uniquement) ; 2) puis déboucher le nez en continuant à mastiquer (aux saveurs s'ajoutent maintenant les perceptions olfactives).

de guérison qui peut être ralenti si l'état nutritionnel est affecté par la perte d'odorat. Reste à savoir si, et comment, ces TO peuvent être traités.

2. Prise en soin des patients dysosmiques à l'heure actuelle

Depuis plusieurs années, quelques médecins et scientifiques tentent de dénoncer le manque de considération accordée aux déficits olfactifs. Une enquête de 2009 [14] révèle l'insatisfaction des patients, qui se disent insuffisamment ou mal informés, que ce soit sur le diagnostic ou sur le pronostic de leur perte olfactive. Parmi les patients, la plupart consultent en premier lieu leur médecin généraliste, chez lequel on constate, d'une manière générale, une méconnaissance des troubles de l'olfaction et de leurs différentes étiologies ainsi que de leur traitement [14]. Bien que cette étude ait concerné la Suisse et l'Allemagne, la situation est comparable en France. On observe alors que les patients dysosmiques s'adressent souvent directement aux laboratoires de recherche plutôt qu'aux spécialistes ORL, eux aussi en retard sur le plan de l'évaluation médicale. Les tests olfactifs ne font pas partie de l'équipement habituel du cabinet. Seuls quelques centres universitaires proposent une évaluation olfactive à partir de tests reconnus et validés. La diffusion de ces tests rencontre une problématique multifactorielle liée : i) à la non-reconnaissance par la CPAM de l'acte médical d'évaluation olfactive (olfactométrie clinique) et de son coût, ii) au faible nombre de patients qui se manifeste auprès des praticiens ORL de ville (2 à 3 patients dysosmiques par an, hors période de COVID-19), et iii) à l'absence de proposition de prise en charge médicale par ces derniers. On peut illustrer cette situation en examinant les retours d'expérience des patients COVID-19 en 2020, dans l'étude du CRNL portant sur 3111 personnes [10]. C'est seulement chez à peine la moitié de ceux qui ont consulté pour leur perte d'odorat qu'un diagnostic de dysosmie a été posé. Seulement 19% ont consulté un spécialiste ORL. Dans la plupart des consultations, les TO n'ont été utilisés par le praticien que pour poser le diagnostic de COVID-19 sans le considérer comme un symptôme à traiter à part entière, et ce, malgré l'inquiétude des patients pour leur perte sensorielle. Attendre la guérison spontanée était la réponse la plus souvent apportée par le corps médical [10]. Or il existe des solutions dont certaines sont faciles à mettre en œuvre. Outre des solutions médicamenteuses visant à restaurer la circulation des odeurs dans la cavité nasale et/ou le bon équilibre de la muqueuse olfactive, ou encore à stimuler la régénération des neurones olfactifs, la rééducation olfactive (RO) basée sur la stimulation olfactive quotidienne peut être envisagée. Cette solution thérapeutique simple, efficace dans un certain nombre de cas (**Encadré 1**), reste largement méconnue des praticiens de santé. Dans l'étude du CRNL, les patients rapportaient que la RO était la solution la plus fréquemment prescrite, mais elle ne l'était que dans 4% des consultations (ceci, principalement par des ORL). Depuis plusieurs années, le CRNL et plusieurs équipes cliniques de la région lyonnaise ont mis en place un protocole de RO dont nous présentons les grandes lignes ci-après. La diffusion de cet outil de remédiation rencontre à ce jour les mêmes obstacles successifs que ceux décrits plus haut au volet diagnostique.

3. Vers une implication de la médecine générale et des professions paramédicales

3.1. *Trois défis sont à relever*

Afin de mieux accompagner les patients atteints de dysosmies, un 1^{er} défi est l'amélioration, chez le personnel soignant, de la connaissance de la sensorialité olfactive, de ses perturbations et des pistes de remédiation : nous voulons y contribuer grâce à cet article. Notons que la méconnaissance des patients est grande elle aussi (même si elle a tendance à se réduire du fait de la couverture médiatique sans précédent dont bénéficie la COVID-19). L'entrée tardive des patients dans le parcours de soin des dysosmies n'est déjà pas souhaitable en soi et joue en défaveur d'une possible récupération. Le 2^{ème} défi est la mise au point et la validation de méthodes de RO, par exemple des kits de stimulation olfactive utilisables par les patients, quotidiennement et à domicile, assorties d'un enregistrement des performances au cours de l'entraînement et de la possibilité pour le patient de visualiser sa progression. Sur la base des protocoles développés ces dernières années (**Figure 1**), le CRNL finalise actuellement des solutions de ce type, avec pour objectif que les médecins ORL puissent prochainement les proposer à leurs patients. En attendant leur validation, des conseils pour une RO avec des produits domestiques sont communiqués aux patients demandeurs (**Figure 2**) – ceux atteints de dysosmies post-COVID étant particulièrement nombreux actuellement. Enfin, le 3^{ème} défi réside dans l'accompagnement des patients pour assurer le maintien de la motivation et augmenter ainsi l'efficacité de la RO. En effet, dans une précédente étude du CRNL [15] (**Figure 1**), deux tiers seulement des patients avaient réalisé l'entraînement dans son intégralité, les autres s'étant retirés de l'étude avant la fin. La récupération de l'odorat est très lente et ne se produit pas de manière systématique chez tous les patients : il n'est donc pas surprenant que les patients aient des difficultés à persévérer dans leur pratique, surtout s'ils reçoivent peu de soutien. Par homologie, l'accompagnement par un praticien améliore significativement la récupération olfactive chez des patients laryngectomisés en comparaison avec une rééducation effectuée en autonomie à domicile [16]. C'est pour relever ce défi lié à l'observance, que nous proposons une stratégie de prise en soin pluri-professionnelle des TO.

3.2. *Des praticiens paramédicaux légitimes dans l'accompagnement des rééducations olfactives*

L'observance de la part des patients est un élément clé de l'efficacité d'une rééducation. L'implication de certaines professions paramédicales dans le parcours de soin des patients dysosmiques pourrait s'avérer vraiment pertinente. Notamment, l'aide des kinésithérapeutes et des orthophonistes dans les RO, qu'elles soient post-COVID ou non, pourraient être significative. Ces deux professions disposent des savoirs et savoir-faire pour lutter contre les conséquences potentielles des atteintes du système nerveux. Ils agissent sur les troubles moteurs, perceptifs et sensoriels, notamment de la sphère ORL, en contribuant aussi bien à la phase diagnostique que thérapeutique. Ils préviennent l'altération des capacités fonctionnelles, concourent à leur maintien et, lorsqu'elles sont altérées, œuvrent pour les rétablir ou les suppléer. Le masseur-kinésithérapeute intervient de façon manuelle ou instrumentale, par des actes de massage et de gymnastique médicale. L'orthophoniste intervient plus particulièrement sur la communication, le langage, les activités cognitives et les fonctions oro-myo-faciales. La fonction olfactive mobilise plusieurs systèmes appartenant au champ de compétences de ces

deux professions : respiration, posture, traitement cognitif, en interaction les uns avec les autres. Par exemple, le flairage, point de départ de la perception olfactive, est un acte moteur sur lequel le kinésithérapeute peut intervenir en matière d'intensité, de durée, de fréquence ; l'orthophoniste peut travailler sur les capacités mnésiques et langagières mobilisées par les odeurs mais aussi sur les mécanismes fonctionnels de la sphère orale (voir par exemple la technique du « bâillement poli » pour rétablir la circulation rétronasale des odeurs [16]). Au même titre que les autres canaux sensoriels (visuel, auditif, proprioceptif, vestibulaire), le canal olfactif est d'ores et déjà investi par les rééducateurs, comme un outil de stimulation : des fonctions cognitives en phase de réveil de coma chez des patients cérébrolésés par exemple ; mais aussi de la stimulation oro-faciale globale dans le cadre des troubles sensoriels ou de l'oralité alimentaire ; ou encore des capacités cognitives dans la prise en soin de patients atteints de pathologies neurodégénératives (Parkinson, Alzheimer etc.). Entre ces rééducations « par les odeurs » et les rééducations « de l'odorat », il n'y a qu'un pas qui peut être franchi aisément. Enfin, si la RO était retenue comme une option thérapeutique adaptée par leur médecin ORL, les patients trouveraient un excellent relais auprès des kinésithérapeutes et des orthophonistes pour mener à bien leur rééducation. La récupération d'une dysosmie est un processus long, qui peut prendre plusieurs semaines à plusieurs mois, comme beaucoup de rééducations neurologiques (voir l'exemple de la récupération post AVC [17]). Le cadre de soin que proposent les rééducateurs (kinésithérapeutes ou orthophonistes) en matière de fréquence et de durée des séances, de durée totale du traitement, et de relation duelle avec le patient, semble être tout à fait adapté à l'accompagnement des RO. Une rééducation intensive assistée par un professionnel de santé permet d'améliorer l'état psychologique et social des patients, et de développer la confiance que le patient accorde au thérapeute, ce qui concourt à maintenir une adhésion optimale au traitement.

3.3.Exemple d'un accompagnement de rééducation olfactive par un kinésithérapeute

Dans une étude pilote menée début 2020, 26 patients dysosmiques (18 femmes et 8 hommes, âgés de 23 à 77 ans, 49.6 ans en moyenne) ayant des étiologies variées (origines post-infectieuse, post-traumatique, tumorale, congénitale, idiopathique) ont pris part à un protocole de RO développé par le CRNL et mis en œuvre par un kinésithérapeute (AK). Cette étude a reçu l'avis favorable du Comité de Protection des Personnes Sud-Méditerranée III le 13 mai 2019. La dysosmie a été diagnostiquée à T0, soit avant le début de la rééducation, grâce à un test olfactif (ETOC [18]) dont les scores moyens ($\pm$ écart-type) de détection et d'identification pour le groupe étaient $8,6 \pm 4,8$ (sur 16) et $3,7 \pm 3,7$ (sur 16), respectivement. Concernant la RO, sept odorants étaient présentés, à raison d'une odeur par jour pendant 12 semaines. Les odeurs étaient perceptivement bien distinctes (herbe, agrume, citronnelle, moisi, clou de girofle, eucalyptus, rose). Chaque jour, trois flacons étaient sentis, l'un contenant l'une des 7 odeurs et les deux autres étant non odorisés. Les patients devaient d'abord indiquer quel était le flacon odorant (tâche de détection), puis ils devaient noter l'intensité de l'odeur perçue sur une échelle allant de 0 "pas d'odeur du tout" à 10 "odeur très intense" (tâche d'évaluation de l'intensité) après avoir senti le flacon odorant identifié par une pastille apposée sous le flacon. Certains participants ont reçu des instructions précises quant à la manière de flairer les odeurs et d'autres non mais comme aucune différence n'a été mise en évidence entre ces deux groupes, les résultats sont présentés ici pour l'ensemble des 26 patients. Un mode d'accompagnement inédit

et particulièrement intensif a été mis en place : chaque participant bénéficiait d'un rendez-vous hebdomadaire d'une quinzaine de minutes sous la forme d'un appel vidéo au cours duquel le patient effectuait son entraînement du jour et pouvait échanger librement avec le praticien à propos du déroulement de sa rééducation. Il est à noter que le critère d'évaluation de l'efficacité de la RO (score ETOC à T1, c'est-à-dire à l'issue de la 12^{ème} et dernière semaine d'entraînement) n'a pu être relevé du fait de l'arrêt des protocoles de recherche dès mars 2020 à cause de la crise sanitaire COVID-19. Ainsi, l'efficacité de la RO a été évaluée sur la base des scores aux tâches quotidiennes de détection et d'évaluation de l'intensité. Nous avons comparé les scores de détection et d'intensité perçue moyennés sur une semaine, à T1 versus T0. Si les capacités de détection sont restées identiques, en revanche l'intensité perçue a significativement augmenté (T0 : $2,66 \pm 1,96$; T1 : $3,88 \pm 2,57$; $t_{(22)}=2,76$ et $p=0,011$)⁵ (**Figure 3a**). Lorsqu'on examine les résultats individuels, cette amélioration de l'intensité perçue entre T0 et T1 concerne 71,4% des patients inclus. Du fait de l'absence de comparaison avec un groupe contrôle sans entraînement, il n'est pas possible d'affirmer de manière certaine que l'amélioration observée est due à la RO plutôt qu'à une récupération spontanée. Toutefois, plusieurs études montrent la supériorité de la RO par rapport à la récupération spontanée pour améliorer les capacités olfactives [19,20] : ainsi, nous avons de bonnes raisons de penser que les odeurs sont perçues comme plus intenses grâce à l'exposition olfactive répétée. Pour finir, le protocole de suivi intensif instauré par le kinésithérapeute a permis d'obtenir un taux d'observance très élevé : 23 personnes sur 26 (soit 88%) ont réalisé l'entraînement dans son intégralité, contre seulement 64% dans notre précédente étude où les patients avaient des contacts bien plus espacés avec l'expérimentateur [15] (**Figure 3b**). Ce résultat plaide en faveur d'un suivi intensif du type de ceux pratiqués en cabinets de kinésithérapie ou d'orthophonie.

4. Conclusion

Malgré une forte prévalence des dysosmies dans la population française, et leur augmentation récente liée à la maladie COVID-19, le traitement des TO demeure insatisfaisant en France. Ce défaut de prise en charge est lié à une méconnaissance, dans la population générale aussi bien que dans le corps médical, de la sensorialité olfactive, de ses perturbations et des solutions thérapeutiques. Nous présentons ici les rééducations olfactives, dont on reconnaît de plus en plus le bénéfice, et pour lesquels des protocoles sont actuellement en développement au CRNL. Outre la nécessité de rendre les outils diagnostiques aussi bien que les ressources thérapeutiques accessibles au plus grand nombre, grâce à leur reconnaissance par les instances gouvernementales, il paraît essentiel d'accompagner les patients dans leur rééducation : kinésithérapeutes et orthophonistes semblent être les professions les mieux préparées à cela, alors même qu'elles offrent un suivi particulièrement souhaitable tout au long de la récupération.

⁵ Test-t pour échantillons appariés. Suite à un problème lors de l'enregistrement des données, les scores moyens de 2 participants n'ont pu être calculés à T1 et ont été remplacés par la valeur moyenne du groupe, ce qui ne modifie pas le niveau moyen de performance à T1 tout en conservant le pouvoir statistique (NB : le résultat reste significatif à $p = 0,012$ si ces deux participants sont exclus). Résultats pour la détection des odeurs : $66,7\% \pm 32,5\%$ de détection correcte à T0 vs. $71,1\% \pm 35,4\%$ à T1 ; $t_{(22)}=0,89$ et $p=0,381$.

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Les auteurs déclarent ne pas avoir de liens d'intérêt.

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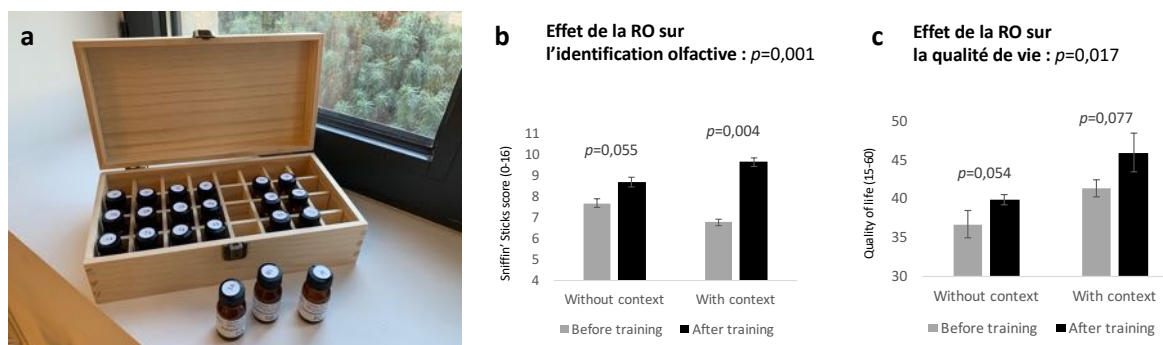


Figure 1 - Effet d'une rééducation olfactive RO sur la récupération des perceptions olfactives. Cette étude du CRNL, publiée en 2018 [15], a consisté à faire sentir 7 odeurs différentes, à raison d'une odeur par jour, pendant 12 semaines, à 22 patients dysosmiques. Une partie des patients effectuaient leur RO avec des flacons simples (a) ; pour les autres, des images illustrant les odeurs étaient présentes sur les étiquettes des flacons. L'accompagnement des patients consistait en un échange téléphonique mensuel avec l'expérimentateur. Les résultats ont montré : (b) une amélioration globale des capacités à identifier les odeurs (mesurée par le test des Sniffin' Sticks), qui était plus marquée pour le groupe avec contexte visuel, (c) une amélioration globale de la qualité de vie (mesurée par questionnaire). En revanche, seulement 14 patients (64%) ont réalisé l'entraînement dans son intégralité, 8 patients s'étant retirés de l'étude avant la fin. Illustrations (b) et (c) extraites de Manesse et al. [15], $N=6$ pour la condition sans contexte visuel et $N=8$ pour la condition avec contexte visuel.

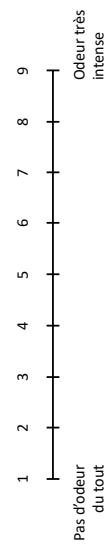
Rééducation olfactive

Conseils

Ce programme de rééducation olfactive a été conçu par l'équipe Neuropop du Centre de Recherche en Neurosciences de Lyon. Il a pour objectif d'aider des personnes atteintes de troubles de l'odorat à récupérer leurs perceptions.

Le principe de ce programme est le suivant.

- Il dure 12 semaines (3 mois) et nous vous proposons tout simplement d'utiliser des produits odorants que vous avez chez vous.
- Pendant ces 12 semaines, chaque jour à peu près à la même heure et de préférence à distance des repas, vous sentirez chacune des odeurs (au minimum 5) que vous aurez sélectionnées au préalable parmi les produits disponibles dans vos placards. Vous trouverez une fiche d'aide au choix des odeurs dans la suite de ce document.
- Sentez les odeurs une par une, en essayant d'observer un intervalle d'environ 1 minute entre chaque. Flairez l'odeur plusieurs fois de suite, en vous concentrant sur elle et en essayant de réactiver le souvenir que vous avez de cette odeur. Ensuite, vous pouvez évaluer l'intensité de l'odeur sentie à l'aide d'une échelle allant de 1 « pas d'odeur du tout » à 9 « odeur très intense » :



Si vous détectez une odeur, vous pouvez aussi noter quelle émotion elle suscite chez vous et tenter de la décrire. Nous vous conseillons d'utiliser un carnet pour y noter quotidiennement vos perceptions / vos ressentis.

- Cette séance quotidienne ne devrait pas vous prendre plus de 5 minutes.
- N'hésitez pas à doubler le nombre de séances quotidiennes (par ex. une séance le matin et une séance le soir) et à prolonger la rééducation au-delà de 12 semaines, si vous vous sentez motivé(e).

Fiche d'aide au choix des odeurs

Pour cette rééducation olfactive, vous allez utiliser des produits que vous avez chez vous, dans vos placards. Voici quelques consignes pour le choix de ces produits :

- Choisissez des odeurs variées, bien différentes les unes des autres (par exemple, ne prenez pas uniquement des odeurs fruitées). Une liste vous est proposée ci-dessous à titre indicatif, pour vous aider dans vos choix.
- Choisissez des produits qui sont stables dans le temps, c'est-à-dire qui seront toujours les mêmes au cours des 12 semaines de rééducation (par exemple, le café moulu de votre marque habituelle). Cela vous permettra d'observer votre progression de manière plus fiable. Favorisez des produits peu périssables.
- Choisissez des odeurs qui sont fortes (vous pouvez vous faire aider d'un proche pour cela). Utilisez les produits sous la forme la plus concentrée possible, et à température ambiante (ne faites pas votre rééducation avec des produits tout juste sortis du réfrigérateur).
- Pensez à renouveler régulièrement les produits que vous avez choisis pour votre rééducation. Ici encore, n'hésitez pas à vous faire aider d'un proche pour vérifier la qualité des produits.

Exemples de produits que vous pouvez sélectionner

Cette liste par catégories d'odeurs est indicative. Adaptez vos choix en fonction des conseils ci-dessus et de ce que vous avez à disposition.

Fruité, sucré Une confiture (fraise, abricot, orange, framboise...) Un jus de fruit (orange, pomme, pamplemousse, ananas...) Extrait de vanille Pâte à tartiner Miel, Sirop d'érable	Cosmétiques, produits ménagers Dentifrice Savon pour les mains, gel douche Shampoing, après-shampoing, soin pour les cheveux Crème pour les mains, lait pour le corps, crème solaire Parfums Huile de massage Lessive
Épices, herbes, autres Une épice (clou de girofle, cardamome, cannelle, coriandre, cumin...) Une herbe aromatique (thym, laurier, romarin, basilic, origan...) Une sauce (soja, tomate, ketchup, pesto, barbecue...) Une huile (d'olive, de sésame, de noix de coco...)	Divers Café (moulu, instantané), thé ou infusion Conserves de poisson (thon...) Chips, biscuits Nourriture pour chat/chien/poissons Mégot de cigarette ou cendrier, allumettes brûlées Grage Encens
Produits piquants Un condiment piquant (moutarde, vinaigre, poivre moulu...) Un alcool fort (vodka, rhum...) Vicks VapoRub ou Baume du Tigre	



IMPORTANT : n'utilisez pas de produits nocifs possédant un pictogramme du type A (produits ménagers, produits de bricolage...). Par ailleurs, évitez les huiles essentielles car elles sont déconseillées dans certains cas (femmes enceintes, enfants, personnes sous traitement médicamenteux ou souffrant d'affections particulières...).

Figure 2 - Fiche conseil du CRNL pour la rééducation olfactive en autonomie basée sur des produits domestiques.

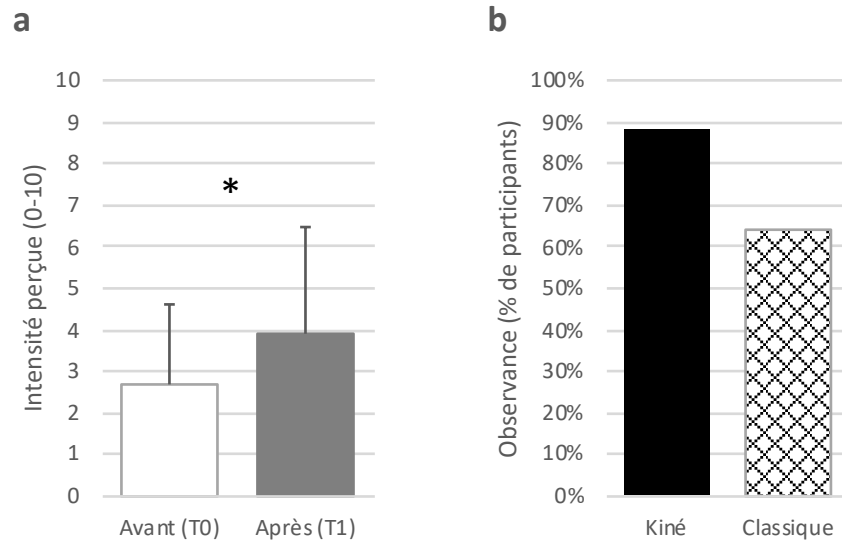


Figure 3. (a) Évolution de l'intensité perçue des odeurs entre la semaine 1 (T0) et la semaine 12 (T1) de rééducation olfactive RO (moyenne sur 7 odeurs, écart-type ; * : $p < 0,05$, t-test apparié). (b) Taux d'observance en pourcentage de participants ayant réalisé la RO dans sa totalité : avec un suivi intensif par un kinésithérapeute (appel vidéo hebdomadaire) et avec un suivi classique (appel téléphonique mensuel).

Encadré 1 - Efficacité des rééducations olfactives

Si une récupération spontanée se produit chez une partie des patients ayant perdu l'odorat (7 à 27% en fonction de l'étiologie et du niveau de perte sensorielle) [21], pour les autres la rééducation olfactive (RO) s'avère une approche prometteuse. Développée en clinique dès 2009 [22], elle consiste à sentir quotidiennement des stimulations odorantes différentes, pendant plusieurs semaines. La fréquence des sessions, la durée totale ainsi que le nombre et l'identité des odeurs varient d'une étude à l'autre. Malgré ces disparités méthodologiques, des effets positifs de la RO ont été mis en évidence sur la sensibilité, la discrimination et l'identification olfactive, selon une méta-analyse [20]. Les patients qui bénéficient le plus de cette RO sont ceux ayant une perte olfactive post-infectieuse, post-traumatique ou idiopathique [20]. Le bénéfice est d'autant plus important que la durée de la RO augmente, jusqu'à 1 an [23]. Changer périodiquement l'identité des odeurs senties permet d'augmenter l'efficacité de la RO [24], tout comme le fait de commencer la RO rapidement après l'apparition de la perte d'odorat et avec des concentrations d'odeurs élevées [19]. Pour expliquer la récupération olfactive, il a été avancé que la RO pourrait avoir une action i) au niveau périphérique (plasticité des neurones olfactifs illustrée par une augmentation des réponses électrophysiologiques aux odeurs au niveau de l'épithélium olfactif [25]) mais aussi ii) au niveau central (augmentation du volume de matière grise dans l'hippocampe et le thalamus, possiblement en lien avec une plus grande attention et mémoire des odeurs [26]). Nous manquons toutefois d'études confirmatoires en double aveugle avec des groupes contrôles adéquats pour conforter ces nombreux éléments prometteurs [27].
