Brain Topography (2019) 32:977–986
https://doi.org/10.1007/s10548-019-00733-9

REVIEW

Individual Differences as a Key Factor to Uncover the Neural Underpinnings of Hedonic and Social Functions of Human Olfaction: Current Findings from PET and fMRI Studies and Future Considerations

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Received: 1 July 2019 / Accepted: 18 September 2019 / Published online: 28 September 2019

Abstract
The hedonic and social dimensions of olfactory perception are characterized by a great diversity across people. Whereas the cerebral processing underlying these aspects of odor perception have been widely explored in the last decades, very few brain imaging studies considered individual differences. This lack of consideration weakens the current models in the field, where the paradigm of universality is the norm. The present review is aimed at examining this issue. Through a synthetic summary, we will first present past studies suggesting that (1) hedonics are represented consistently throughout the olfactory system from primary to secondary areas, with a progressive cognitive modulation and integration with other senses, (2) social dimension of odors may be represented in a distinct pathway involving social and attentional networks. In a second, and more critical part, we will highlight the importance of individual differences for the cerebral study of human olfaction.

Keywords Olfaction · Hedonics · Social · fMRI · PET · Representation · Perception · Variability

Introduction

Do humans still need their sense of smell? Psychological and philosophical researchers from the last centuries (see Carterette 2012 for a review) considered olfaction as a secondary sense that could not be abstracted or theorized, a mere remainder of the mammals' ability to track down items on the ground, to spot predators and to seduce sexual partners. This led scientific personalities like Broca and Freud to categorize humans as a "microsmatic" species, reflected by the smaller relative size of the olfactory bulb compared to other mammals at the expense of the enlargement of the frontal lobe throughout evolution. Thus, olfaction has been negatively associated to animality (Le Guérer 2002) and out of scientific interest in humans for a long time. However, modern research has shown that humans have a similar number of olfactory neurons than other mammals such as mice and dogs, and are actually able to discriminate around a trillion of odorants (McGann 2017). In fact, it is now clear that the olfactory system significantly influences human behavior, through two main functions (Stevenson 2010): 1—a hedonic/defense function (approach of rewarding objects/defense against environmental hazards), 2—a social function (chemical communication with others). For instance, psychological and anthropological studies showed that in eating behavior, smells play a prominent role in hedonic pleasure and help us to recognize food. The defense function enables us to be wary and move away from some potentially dangerous odor sources: spoiled foods, smoke, gases or unfamiliar chemicals—through the emotions and hedonic feelings such as disgust and fear. Consequently, individuals with an impaired sense of smell report social difficulties, increased domestic risks and are more prone to depressive mood (Croy et al. 2012). The social

Handling Editor: Christoph M. Michel.

This is one of several papers published together in Brain Topography on the "Special Issue: Current Opinions in Brain Imaging Methods and Applications".

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function is less well known; at the cultural level, it is notable that we spend a lot of money to control odors by deodorizing and perfuming our body and our living environment. Beyond these cultural habits, research in the last two decades showed that our social life is still regulated by odors, very often without our awareness; we can thus detect through the smell of a human body the genetic proximity between different individuals (Havlicek and Roberts 2009), the state of health/sickness (Olsson et al. 2014) and also the emotional state of others (Albrecht et al. 2011); smells help the newborn to find the mother's breast and contributes to mother–child attachment (Porter and Winberg 1999), as in other mammals .

In the last 25 years, beside these behavioral approaches, researchers in the field of neuroscience have set out to examine the neural underpinnings of these hedonic and social functions of human olfaction. However, an important parameter that has been neglected is the inter-individual variability in how these aspects are processed. The aim of the present review is to emphasize this issue for the scientific community to consider it in their future investigations. To this end, we will first present a synthesis of scientific findings on the way odor hedonics (Sect. "Neural underpinnings of the hedonic dimension of the olfactory experience") and social body odors (Sect. "Neural underpinnings of the olfactory experience of social odors") are processed in the human brain. Here, we selected studies that were able to investigate the neural networks and areas involved in such processing, by using imaging techniques such as fMRI and PET. Although some work has been done with EEG (Kline et al. 2000; Kim and Watanuki 2003), it was not included in this review, as source localization algorithms used in these studies do not allow for fine-grained differences in hedonic/social representations. Then, in Sect. "Toward a deeper understanding of hedonic and social processing: individual variability as a key factor" we will discuss these findings and draw perspectives for future studies, by pointing the current potential issues in the field and by highlighting the necessity for future work to consider inter-individual variability for a better understanding of odor processing in the human brain.

Neural Underpinnings of the Hedonic Dimension of the Olfactory Experience

Hedonics is a prominent dimension in olfaction and several brain imaging studies have examined how the olfactory system responds to changes in this perceptual attribute (see Bensafi

Table 1 Main structures of the anatomical pathway involved in human olfactory hedonic processing

Structure	Main Findings	Studies
Olfactory epithelium	Mapping of pleasantness	Epithelium-evoked response: Lapid et al. (2011)
Piriform cortex	Activation for aversive odors but not for pleasant odors	PET: Zald and Pardo (1997)
	Higher activation for unpleasant vs pleasant odors	fMRI: Royet et al. (2003)
	Higher difference between unpleasant vs pleasant odors in the ventral compared to temporal PC	fMRI: Zelano et al. (2007), Gottfried et al. (2002a, b) and Gottfried and Dolan (2003)
	Higher difference between imagined unpleasant vs pleasant odors in the ventral compared to temporal PC	fMRI: Bensafi et al. (2007)
	Higher activity for intense odors in temporal PC	fMRI: Anderson et al. (2003) and Rolls et al. (2003)
	Odor hedonics modulate frontal PC habituation	fMRI: Gottfried et al. (2002a, b)
Amygdala	Higher activation for unpleasant versus pleasant odors	fMRI: Royet et al. (2003) PET: Zald and Pardo (1997)
	Higher activity for intense odors	fMRI: Anderson et al. (2003)
	Higher activity for odors with high emotional value	fMRI: Winston et al. (2005)
	Processing of the complete spectrum of valence	fMRI: Jin et al. 2015)
	Processing of trigeminal aspects	fMRI: Fournel et al. (2016)
Orbitofrontal cortex	Differential activity for unpleasant smells in medial part and pleasant smells in lateral part	fMRI: Anderson et al. (2003), Rolls et al. (2003), de Araujo et al. (2005) and Grabenhorst et al. (2007)
	Integration of sensory modalities for hedonics	fMRI: O'Doherty et al. (2000), Kringelbach (2005) and Schoenbaum and Esber (2010)
Insula	Differential activity for unpleasant smells in anterior part and pleasant smells in posterior part	fMRI: Fulbright et al. (1998), Royet et al. (2003) and Wicker et al. (2003)
	Higher activation in left anterior and posterior insula for unpleasant vs pleasant imagined odors	fMRI: Bensafi et al. (2007)
Anterior cingulate cortex	Higher activation for pleasant vs unpleasant odors	fMRI: Rolls et al. (2003) and Bensafi et al. (2012)
Ventral Tegmental Area	Activation for pleasant but not for unpleasant odors	fMRI: Bensafi et al. (2012)

The first column depicts the different brain structures, the second the main findings about their role in hedonic processing with the corresponding references in the third one

et al. 2012; Zou et al. 2016 for reviews). In this section, we review how hedonics is processed throughout the olfactory system (cf. Table 1 for a summary). Before evoking each region, let us briefly expose its general anatomy. When the odorant molecules enter the nasal cavity, they bind with the olfactory receptors and the signal is then passed onto the olfactory bulb. Next, there are projections to what we call the primary olfactory cortex, an assembly of regions comprising the piriform cortex, as well as the amygdala and the entorhinal cortex. Then, the information is distributed to other regions such as the orbitofrontal cortex, the insula, and the perirhinal and the cingulate cortices. Here, we will focus on the most studied olfactory areas, which are the piriform cortex, the amygdala, the orbitofrontal cortex and the insula (cf. Fig. 1 for the anatomical location of the subsequently mentioned brain areas).

Even at the very first steps of olfactory processing, some traces of hedonics are found. In humans, Lapid et al. (2011) showed that the topographical organization of the olfactory receptors in the epithelium reflected the pleasantness of the smell (see Table 1). In the olfactory bulb (OB), the first cerebral relay of olfactory processing, it has been shown that hedonics are topographically mapped in the ventral region of the bulb in non-human animals (Kermen et al. 2016). However, the existence of such hedonic trace within the OB is not very well understood yet in humans as this area is prone to disturbances of the in vivo brain activity recordings due to the orbital proximity. That being said, Iravani et al. (2019) recently demonstrated that accurate non-invasive recording of the activity of the olfactory bulb can be performed, by using electrodes at the base of the nose. Another pilot study involving fMRI acquisition through a magnifying antenna has also been conducted (Fournel et al. 2015). With these promising techniques, we can expect in the following years to have a better understanding of whether pleasantness is processed in the OB in humans as well.

In the primary olfactory cortex, the principal region of interest for researchers in olfaction is the piriform cortex. One of the first brain imaging study that explored how hedonics influences its activity is that of Zald and Pardo (1997) who used positron emission tomography (PET) imaging in response to both pleasant and aversive odors. They observed that aversive odors tended to induce greater regional cerebral blood flow (rCBF) in piriform cortex, although not significantly after correction for multiple comparisons, while on the contrary pleasant odors showed no such trend. Using functional magnetic resonance imaging (fMRI) 1 year later, Fulbright et al. (1998) were unable to show any piriform activation by comparing a pleasant (tangerine) vs unpleasant (butyric acid) odor. However, Royet et al. (2003) revealed that unpleasant odors induced greater

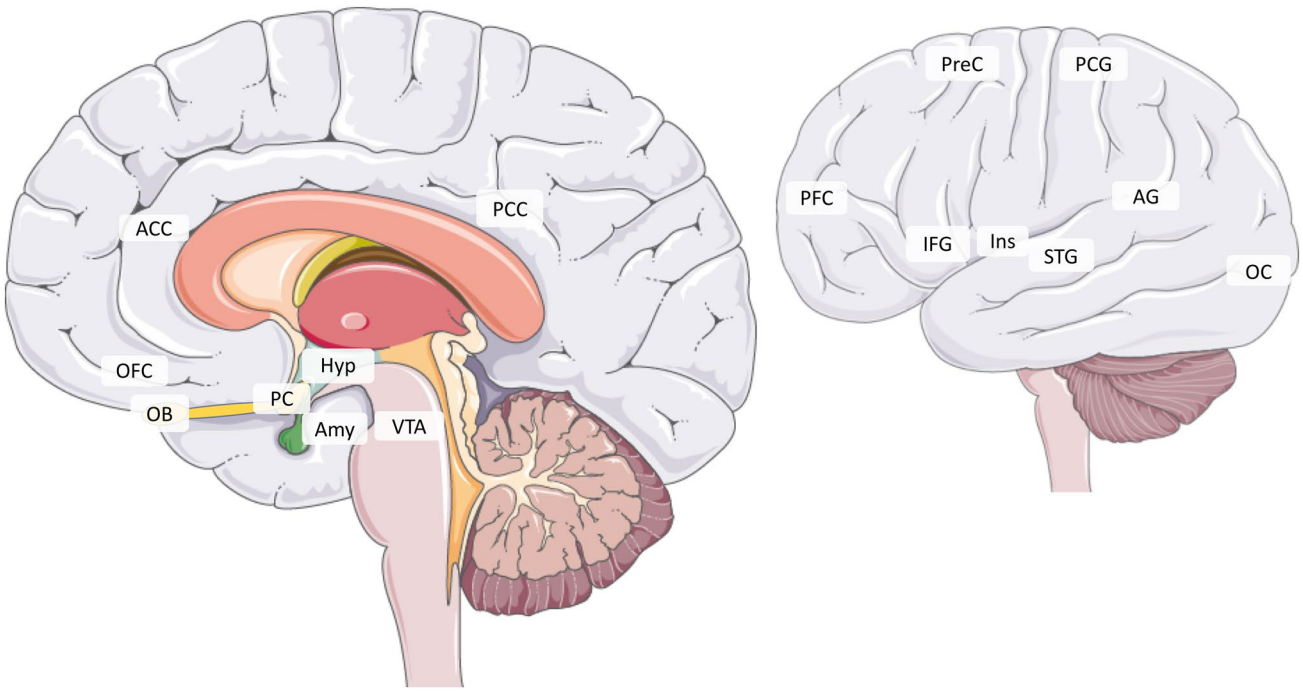

Fig. 1 Schematic localization of brain areas reportedly involved in hedonic and social processing of odors. Left panel: sagittal view of the brain; right panel: lateral view of the brain. *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex, *Ins* insula, *Hyp* hypothalamus, *OFC* orbitofrontal cortex, *OB* olfactory bulb, *PC* piriform cortex, *Amy* amygdala, *VTA* ventral tegmental area, *PFC* prefrontal cortex, *IFG* inferior frontal gyrus, *STG* superior temporal gyrus, *PreC* precuneus, *PCG* post-central gyrus, *AG* angular gyrus, *OC* occipital cortex. Adapted from Brain, Servier Medical Art (Creative Commons Attribution 3.0 Unported License)

piriform blood oxygen level dependent (BOLD) responses than pleasant odors. More specifically, this is the case in the right frontal part of this area, rather than its temporal part (Zelano et al. 2007). This result, in line with Gottfried et al. (2002a, b) and Gottfried and Dolan (2003), lends support to the view for functional heterogeneity in the piriform cortex. In another fMRI study, Bensafi et al. (2007) showed that this was true not only for actual smelling but also for imagining odors: in participants who alternated between smelling and imagining pleasant and unpleasant odors, the frontal portion of the piriform was more activated in response to an unpleasant odor for both tasks. Nevertheless, such association between activity within frontal piriform cortex and odor hedonics is more complex than thought. Indeed, as shown by Gottfried et al. (2002a, b), whereas BOLD signal in the frontal piriform cortex was strong in response to an unpleasant odor but decreased steadily over time, BOLD activity within this area was sustained in response to a pleasant odor, suggesting that odor hedonics modulates frontal piriform cortex habituation. That being said, intensity, another perceptual dimension related with pleasantness (Distel et al. 1999), is also processed in the piriform cortex. Anderson et al. (2003), by controlling the intensity of pleasant and unpleasant odors, showed that a part of the temporal piriform cortex responded mainly to odor intensity, and not to differences in odor hedonics. In another fMRI study, Rolls et al. (2003) exposed human participants to a series of pleasant and unpleasant smells and showed a positive relationship between odor intensity and BOLD activity in piriform cortex, lending support to the idea of increased activity in the temporal piriform cortex in response to increased odor intensity.

The amygdala is also known for encoding perceptual characteristics of odors. As in the piriform cortex, unpleasant odors induce greater amygdala activation than pleasant smells (Royet et al. 2003), even if amygdala activation is observed in response to both disgusting and pleasant odors (Wicker et al. 2003). In fact, it seems that the hedonic strength is the most important parameter, as in their PET study, Zald and Pardo (1997) showed that highly aversive smells induced significant rCBF increases, which was not the case for less unpleasant smells. However, the study of Anderson et al. (2003) mentioned above showed that the amygdala responded mainly to odor intensity, and not to differences in odor hedonics. Thus, the role of the amygdala in processing the affective content of smells has been the topic of a series of studies which findings are not always consensual. For instance, Winston et al. (2005) showed that BOLD activity in the amygdala is influenced neither by odor hedonics (as observed by Zald and Pardo 1997; Royet et al. 2003) nor by odor intensity (as shown by Anderson et al. 2003; Rolls et al. 2003), but by a combination of these factors in that BOLD response in this area was greater during presentation of high intensities (vs. low intensities) of both pleasant and unpleasant odors, but not neutral odors, suggesting according to the authors that the amygdala is involved in the overall emotional value of an olfactory stimulus. A few years later, an fMRI study from the same group showed that this area is a site of representation of the complete spectrum of odor hedonic valence (Jin et al. 2015). Finally, Fournel et al. (2016) showed that rather than odor hedonics per se, the human amygdala represented another affective dimension, more related to the irritating and painful aspects of odor perception.

Another prominent olfactory area is the orbitofrontal cortex. In their studies, Anderson et al. (2003) and Rolls et al. (2003) examined BOLD activity in response to both pleasant and unpleasant smells and they both observed that comparing pleasant and unpleasant stimuli revealed activations in a medial portion of the orbito-frontal gyrus. The opposite contrast (unpleasant vs. pleasant) revealed activations in a more lateral portion of the orbito-frontal gyrus. Complementary correlation analyses in both studies revealed significant relationship between subjective positive hedonic valence and medial OFC activity, and between subjective negative hedonic valence and lateral OFC. This hedonic-dependent dissociation within the OFC was replicated in a series of studies (de Araujo et al. 2005; Grabenhorst et al. 2007; Reske et al. 2010). Non-olfactory brain imaging investigation suggest that this region plays a higher-order role in the representation of hedonics, by integrating other sensory modalities (O'Doherty et al. 2000; Kringelbach 2005; Schoenbaum and Esber 2010).

Regarding the insula, Fulbright et al. (1998) observed with a fMRI study that a pleasant odor activated more the left insula than an unpleasant one. However, Royet et al. (2003) revealed that unpleasant odors induced greater ventral insula BOLD responses than pleasant odors. In another fMRI study (Wicker et al. 2003), the same group showed a dissociation within the insula, whereby disgusting odors activated its anterior part and the pleasant odors activated a more posterior portion of the insula. Finally, as for imagined odors, the left anterior and posterior insula were more activated in response to the perception of an unpleasant odor compared to a pleasant odor (Bensafi et al. 2007).

Besides these main regions, some studies showed the implication of other olfactory areas in the representation of hedonics. Indeed, Rolls et al. (2003) observed that both pleasant and unpleasant odors activated the anterior cingulate cortex, but a more anterior part of this area was correlated more with the subjective positive hedonic valence. In the same line, Bensafi et al. (2012) showed that, compared to an unpleasant chemosensory stimulus, a pleasant stimulus activated the anterior part of the cingulate gyrus and the ventral tegmental area, an area known as being part of the reward system.

Neural Underpinnings of the Olfactory Experience of Social Odors

How "social smells"—namely odors produced or conveyed by an emitter's body, perceived by a receiver and potentially containing relevant information about the emitting individual—influence brain activity has been the topic of several investigations in the last two decades (see for a review, Lundström and Olsson 2010; Pause 2012; Krajnik et al. 2014). Although some scientists have claimed the existence of "pheromones" influencing human behavior (especially the steroid molecules androstenone, androstenol, androstadienone and estratetraenol), this term is controversial, as the definition of a pheromone is debated and seems difficult to apply to complex human behaviors (Doty 2010). Moreover, compared to animal research, the way human pheromones have been investigated in humans is highly questionable and no rigorous demonstration of the existence of human pheromones has been provided to date (Wyatt 2015). Therefore, in this section we decided to use the term "putative chemo-signals" when presenting the works targeting the steroids cited above. This section summarizes current knowledge about the brain networks involved in social odor processing, by first introducing the pioneer works using mostly single isolated molecules, and by then presenting the more recent studies focusing on natural complex odor.

One of the first studies was conducted by Sobel et al. (1999) who used fMRI to localize cerebral responses to a putative chemo-signal (*oestra-1,3,5(10),16-tetraen-3yl acetate*, presented at two different concentrations but below perceptual threshold). Results showed a trend towards greater activation in the thalamus in response to the high (vs. low) concentration suggesting that undetectable putative chemo-signals can be processed by the human brain. In the same line, Jacob et al. (2001) used PET imaging in women to explore how a "male" steroidal compound (*4,16-androstadiene-3one*, or "AND", presented at a very low concentration masked in clove oil) influenced cerebral activity. A sustained presentation of AND altered brain responses (by either increasing or decreasing rCBF) in a wide network including both olfactory and non-olfactory areas, suggesting according to the authors a prominent role of this chemical compound in regulating olfactory behavior but also emotional and attentional states. Note that Gulyás et al. (2004) used PET imaging in women participants and showed that compared to common odors, AND (presented at a supra threshold concentration) activated two different networks in the pre-frontal cortex and in the superior temporal lobe suggesting, as in Jacob et al. that this putative chemo-signal is involved in other than olfactory functions, including social and attentional processing.

To explore whether sex can modulate the effect of putative chemo-signals on brain activity, Savic et al. (2001) examined whether AND on one side, and a putative "female" chemo-signal (*oestra-1,3,5(10),16-tetraen-3-ol*, "EST") on the other side, influenced differentially brain activity in men and women. They reported sex- and compound-specific brain activations in response to AND and EST: compared to smelling plain air, EST preferentially activated the hypothalamic region in men and the olfactory region in women, whereas AND activated the hypothalamic region in women and, to a lesser extent, the olfactory region in men. According to the authors, such sex-dissociated activity within the hypothalamus should be seen as the neural underpinnings of a sex-differentiated behavioral response in humans. In a second PET study, Savic et al. (2005) examined the effects of AND and EST on brain activity in homosexual men, heterosexual men, and heterosexual women. They showed that as heterosexual women (and in contrast to heterosexual men), homosexual men showed a significant activation in the hypothalamus in response to AND. Common odors induced the same pattern of activations in all three groups. Using the same design, the same group further showed that homosexual women, in contrast to heterosexual women but in accordance with heterosexual men, treated AND in olfactory areas (and not in the hypothalamus), whereas they processed EST in the hypothalamus (Berglund et al. 2006). These results suggest, according to the authors, a relationship between neurobiological responses to chemo-signals and sexual orientation rather than sex. In a fourth study (Berglund et al. 2008), they further tested the same question in non-homosexual male-to-female transgenders (MFTRs) and showed that whereas smelling EST activated an olfactory network (piriform cortex and amygdala) in MFTRs (as in heterosexual women), smelling AND activated the hypothalamus. Nevertheless, a conjunction analysis showed that MFTR shared a common cluster of activation in the hypothalamus: (i) with women in response to AND, (ii) with men in response to EST (this effect with EST was however limited).

In a fifth study, Savic et al. (2009) asked whether AND and EST are processed at the periphery by the olfactory epithelium or whether they are treated by parallel ways such as the vomeronasal pouch (VNP), a part of a structure belonging to the accessory olfactory system and involved in social communication in mammals (Døving and Trotier 1998), although its specific functionality in humans is discussed (Witt and Hummel 2006). To this end, Savic et al. set up a PET imaging protocol (similar to their previous studies) and compared brain responses to AND, EST and common odors in both a control group of heterosexual males free of olfactory deficits, and heterosexual males with chronic anosmia due to nasal polyps (which mostly hampers transduction via the olfactory mucosa but probably not—or less—via the VNO). Smelling common odors and AND

activated olfactory areas in controls but not in anosmics, whereas smelling EST activated the anterior hypothalamus in controls but not in anosmics. According to the authors, the absence of activity in the hypothalamus in response to EST in anosmics suggests that in control men, EST is processed via the olfactory system but not via other pathways such as the VNO. However, many anosmic patients with polyps have chronic rhinosinusitis, which typically affects the whole respiratory tract, and one may not discard the possibility that some anosmic patients may thus have a damaged VNP as well, thus potentially affecting the interpretation of the results. In the same vein, Frasnelli et al. (2011) explored functionality of the receptor system (putative VNP vs. olfactory epithelium) through which AND is treated. To this end, they tested women volunteers in a PET imaging study whereby a common odor and AND were presented in two conditions: VNP closed and open. Their results revealed that whereas the common odor induced activations in piriform cortex, OFC, putamen, occipital cortex, and hypothalamus, AND activated the occipital lobe and the hypothalamus. Interestingly, when AND-evoked activation was compared in the ≪ opened-VNP ≫ versus ≪ closed-VNP ≫ , no significant difference was observed, suggesting no involvement of the VNP in processing AND. This result is in line with the current main view about a non-functionality of the VNP in humans, even if it is still debated (Meredith 2001).

Finally, in a sixth study, the group of Savic and Berglund (2010) examined the effect of another putative sex-steroid "male" chemo-signal, namely *androstenol*. Using PET imaging, they showed that whereas smelling common odors activated areas involved in odor processing (piriform cortex, amygdala, insular, cingulate gyrus), androstenol activated the hypothalamus of women. These findings are similar to those observed with AND and suggest, according to the authors, a more general neurobiological pathway than just an olfactory one for this family of volatiles released by the human body.

However, the sex-specific nature of these effects were questioned by a subsequent study by Burke et al. (2012) who examined whether the sex-specific hypothalamic activation in response to AND was observed when lower concentrations of this compound were used. In their protocol, AND was presented at low, medium and high levels of concentrations to heterosexual women and men in an fMRI study. Results revealed that whereas the high concentration of AND activated more the hypothalamus of women than that of men, the medium concentration of AND activated more the hypothalamus of men than that of women. Although these results replicated previous findings that AND activate the hypothalamus, they also showed that AND impacts heterosexual individuals of both sexes. In another study, Burke et al. (2014) tested whether the sex-dependent hypothalamic activation when smelling AND was already present before puberty. To this end, they conducted an fMRI study in pre-pubertal and adolescents (including boys and girls). Their results showed greater hypothalamic activation in response to AND (at a high concentration) in pre-pubertal and adolescent girls (vs. boys), showing that sex-specific effects in hypothalamus in response to AND are established early during brain development.

In an "naturalistic" effort to consider the whole bouquet of the human body odor and not only a small fraction restricted to derived-steroidal compounds such as AND, several research groups further examined how biological body odor (used unfractionated into different components) influenced brain activity. Using PET imaging, Lundström et al. (2008) investigated in heterosexual women, how natural odors extracted from the human body are processed in olfactory and non-olfactory areas. Odors were collected on the human body of donors (underarm area; from both the women participants themselves and her long-time close friend; mean length of friendship: 60 months). From this, three conditions were tested: "Friend odor", "Stranger odor", "Self-odor". Body odor processing from all three conditions induced increased rCBF in a large network including posterior cingulate cortex, posterior occipital gyrus, dorsal postcentral gyrus, and angular gyrus. Interestingly, none of these odors activated primary olfactory areas. Rather, whereas comparing the "Stranger" condition with the "Friend" condition showed significant increase of activity in the precuneus, ventral insula, inferior frontal gyrus and the amygdala (a network known to process fearful stimuli according to the authors), the opposite contrast showed significant activation in a different network including pre/postcentral gyrus, occipital cortex, and pre-SMA (a network known to process familiar stimuli according to the authors). In a second PET study, Lundström et al. (2009) examined the neural underpinnings of human kin recognition by measuring rCBF from women smelling body odors from either their sister or their same-sex friend (collected in the underarm area). Their results suggest that in female individuals, kin recognition is sustained by a distinct network: comparing the "Sister odor" with the "Friend odor" conditions (i.e., odor-based kin recognition contrast) revealed significant increase of activity in frontal–temporal junction, insula, and interestingly in the dorsomedial prefrontal cortex, an area known to be involved in kin recognition according to Lundström et al. (2009). In a third study, using fMRI, Lundström et al. (2013) tested how neonatal body odors were processed in the brain of women. Results revealed that the body odor of 2-day-old newborn infants induced activation in the putamen, and caudate nucleus, reflecting the rewarding properties of these chemo-signals. To further ask how inter-individual factor such as social openness can modulate the effect of biological body odors on brain activity, Lübke et al. (2014) compared highly socially open women and lowly socially open women in response to body odors collected from (men and women) donors (in the axillary

area). Results revealed a greater activation in both the inferior frontal gyrus and the caudate nucleus in highly socially open women compared to lowly socially opened women. According to the authors, body odors may thus constitute a rewarding social cue in women with high social openness.

Interestingly, the underarm area was not the only body odor source investigated. Gelstein et al. (2011) asked whether human tears can contain chemo-signals that can act on behavior and brain activity. To this end, negative-emotion tears from women donors who watched sad films were collected. Psychophysical experiments confirmed that participants who sniffed these emotional tears did not report any discernable smell compared to a saline solution. An fMRI study showed that men who smelled these women's emotional tears showed a decreased activity in brain substrates of sexual arousal (e.g., hypothalamus and fusiform gyrus) suggesting a role of such chemosensory source on human communication and reproductive behavior.

In conclusion, this brief tour within the olfactory system and associated areas suggests that hedonics are represented at each step of processing from primary areas to secondary/tertiary areas and are modulated at a higher level by cognitive processing and multisensory integration (cf. Table 1). Putative chemo-signals may recruit specific social and attentional networks, that are often associated with a low or no activation of primary olfactory areas. In addition, the hypothalamus seems to have a prominent role for this type of odors, even if this finding has been challenged in terms of compound specificity (common odors also activate the hypothalamus; Frasnelli et al. 2011) and sex-specificity (at moderate level of concentrations, AND activates the hypothalamus not only in women but also in men; Burke et al. 2012).

However, these patterns of results are based on a paradigm of invariance of the neural responses, which is associated to statistical and mathematical methodologies aimed at extracting common mechanisms between individuals. This type of paradigm, leading to the idea of a common network, neglects the olfactory experience at the individual scale, which weakens the state of the art cited above. Thus, it is likely that the research on human olfaction is far less successful that we may think, as it is focused on universality more than diversity. The aim of the following section, and of this article as a whole, is to make the scientific community aware of this issue, which is not an easy one to solve.

Toward a Deeper Understanding of Hedonic and Social Processing: Individual Variability as a Key Factor

When considering this descriptive picture of the neural processing of odors, we need to consider human olfaction at the individual level. For example, when considering odor hedonics, the fMRI studies described here mainly consider pleasant versus unpleasant odors through the average pleasantness rated by a certain sample of individuals. This would perfectly acceptable if the hedonic value of an odor was something inherent to it. However, this is not always the case. Although some odors universally evoke negative feelings and rejection, like sulfur compounds, there is a large inter and intra-individual variability in how the same molecule is rated by people. Parameters such as age, sex, or cultural background matter. We can evoke the case of the durian fruit, which is consumed in South Asia, but whose smell is very unpleasant to westerners (Ferdenzi et al. 2013). Genetics are also involved: the hundreds of genes coding for olfactory receptors are actually expressed differently in the nasal mucosa among individuals (Menashe et al. 2003; Verbeurgt et al. 2014). This can lead to phenotypical hedonic variations, such as those observed with androstadienone, a compound found in human sweat (Keller et al. 2007). Even for the same person, their level of hunger (Albrecht et al. 2009) or associative learning (Barkat et al. 2008) can modulate the pleasantness of an odor.

Furthermore, if we come back to the detailed analyses performed in the fMRI studies on hedonic representation, we can see that the results can change drastically depending of the fact that individual ratings or group means are considered. For example, Zald and Pardo (1997) investigated the activation of amygdala and OFC for highly aversive odorants. By first looking at the mean activation for the unpleasant smells, they found a significant activation in OFC and both the amygdalae. However, when accounting for the correlation between individual subjective pleasantness ratings and brain activation, only the left amygdala is significantly related to hedonics. Fulbright et al. (1998) also computed the correlation of hedonic ratings with cerebral activation and found that only the left insula actually correlated with the pleasantness of the unpleasant odorant, and that for tangerine, only the left Broadmann area 49/6 did. This is different from the results obtained from the classical mean activation process. Regarding the studies on social odors, the same issue arises: depending on which inter-individual factors (such as sex, age or sexual preference) are accounted for by the researchers, diverse neural patterns of activation are reported, and studies do not integrate all these dimensions together. In summary, considering or not the specificities of the participants can lead to different scientific conclusions. We see here that without the integration of individual specificities in the analysis of the brain imaging data, one may obtain results that would then be interpreted by the researchers as reflecting common cerebral processes while not being able to explain the individual patterns.

Here, we focused on the issue of variability in olfaction, as we saw that there is great diversity in both perceptual and neural levels. However, this is not exclusive to this

area of research. Any researcher using fMRI for example is confronted to the different neural patterns evoked for specific tasks or even at resting state. Recently, Gordon et al. (2017) investigated the individual differences in the functional connectivity in a resting state. Interestingly, they showed that even after anatomical correction and reduction of noise, there were still unique individual patterns that could not be related to the group level. This means that even with current techniques designed to reduce interindividual differences, we cannot assume that brain activity is comparable among individuals. Instead of minimizing or ignoring it, we should thus find a way to account for this variability and relate it with the unique behavior and perception collected from the participants. This will allow us to better interpret neural data and how cognitive, perceptual and emotional elements are represented in the brain.

To do this, we need a reliable and accurate methodology, both at the acquisition level and for the data analysis of brain activity. As Dubois and Adolphs (2016) stated, the key aspects are the following: ensure that the individual differences in brain activity are indeed associated to differences in neural processing and not noise due to the signal acquisition, define regions of interest personalized for each individual, consider individual differences in blood physiology, model the known sources of variance. For the statistical analysis itself, some interesting techniques have been developed in the recent years, among which representational similarity analysis (Kriegeskorte et al. 2006; Kriegeskorte 2008). This enables the comparison between several spaces of representation with different types of data on the basis of the similarity between individuals. It has consequently been used in fMRI and EEG research in order to study the relationship between neural and cognitive data (e.g., Fournel et al. 2016 in olfaction; Fischer-Baum et al. 2017 in reading; Salmela et al. 2018 in attention) and better accounts for individual diversity. In the end, with the upcoming technical and analytical developments, the account of individuality in neural processes should be easier, as long as researchers recognize it is necessary to pretend to a complete understanding of the human functioning. These proposed brain imaging analyzes should be accompanied by an accurate characterization of olfactory perception at the individual level. Here, an inter-disciplinary dialogue between neuroscientists, philosophers, psychologists and/or linguists are needed to setup adapted methodologies.

In sum, accounting for individual variability is necessary for human olfaction research. It is a reachable task that necessitates to develop new techniques for the analysis of fMRI data (to better account for the individual brain imaging data) but also new protocols to collect accurate characterization of olfactory experience.

Acknowledgements This work was supported by the French-German ANR/DFG SHS FRAL program (MEROD Project, ANR-15-FRAL-0002).

Compliance with Ethical Standards

Conflict of interest The authors declare no competing interests.

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