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Part II: Flavor perception, from molecule to receptor and brain integration

7. Olfactory integration and odour perception

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Abstract

The olfactory system has to process the limitless chemical world of odours. Everything begins in the nose in which, the volatile odorant molecules enter in rhythm with our breathing. On the forefront are the olfactory sensory neurons (OSNs) which process sensory information by integrating simultaneously, as soon as the first sniff, quantitative, qualitative and temporal features of stimuli and, send to the next level, the olfactory bulb (OB) a well-defined description of stimulus attributes. At the OB level, the incoming peripheral message is sorted and in so doing designs an incident functional map. At this level, the sensory information is furthermore amplified, filtered and transformed, this probably resulting in an olfactory code based on fine temporal tuning of spike activities within mitral-tufted neuron assemblies. Such a multiplexed code based on both temporal and frequency parameters would further use gamma oscillations as a global clock and appears as especially adapted to face multidimensional stimuli which inputs are fragmented across OB. Then the processed olfactory information diverges to the piriform cortex where the olfactory percept forms. At the next stage, the olfactory information is combined together with the information from other sensory organs and compared with previous experiences to give the final odour perception. As all the other senses, olfaction can display genetic, gender and aging variations in performances. In addition, the olfactory function can be impacted by stress, circadian rhythm and in women by the reproductive neuro-endocrine status.

Key words: odour coding, quality coding, odour discrimination, olfactory receptor, olfactory sensory neuron, olfactory mucosa, olfactory bulb, olfactory cortex, olfactory plasticity.

Abbreviation list

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

cAMP: cyclic adenyl cyclase

cGMP: cyclic guanidyl cyclase

CIT: citral

EISO: ethyl isobytyrate

EM: ethyl maltol

GABA: gamma aminobutyric acid

GR: glucocorticoid receptor

IP3: inositol-1, 4, 5-trisphosphate

ISO: isoamyl acetate

LiSS: ligand-induced selective signalling

MTC: mitral-tufted cell

OB: olfactory bulb

OCT: octanal/ octanol

OM: olfactory epithelium

OR: olfactory receptor

OSN: olfactory sensory neurons

PC: piriform cortex

WL: whiskey lactone

XME: xenobiotic metabolism enzymes

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7.1. Introduction

Odours are very complex stimuli which are mainly raised by mixtures of odorant chemical compounds displaying different degree of volatility. The volatility is directly related to a substance's vapour pressure[1] at a given temperature; substances with higher vapour pressure vaporizing more readily than a substance with a lower vapour pressure. Thus, for a given combination of odorant molecules, the compounds compete with each other for constituting the gaseous phase; this competition depending on both individual volatility properties and ratios in which, the compounds are present. Altogether this will result in a unique and precise fragrance of an odour item. The quasi infinite variety of odorant compounds and their combinations, combined with the wide range of their volatility properties imply that the olfactory system must be thus highly sensitive and highly adaptable to new items.

In addition to having to face limitless and constantly moving stimuli, the peripheral olfactory system needs to regenerate. Indeed, in the nose, the sensory neurons are directly in contact with the exterior and can be damaged by thermal or chemical aggressions. Such an exposition is compensated by the fact that these neurons are continuously and cyclically renewed along the life (Graziadei, 1973). Lastly, the olfactory system must be operating very early in the organism life since it intervenes in numerous survival behaviours like predator avoidance, the bounding of the young to the mother and foraging behaviour which starts at birth by the nipple research.

The olfactory system *per se* comprises three main levels, which are the olfactory epithelium (OM, peripheral level), the olfactory bulb (OB, first central relay) and the piriform cortex (PC, primary cortical level). As a phylogenetically very ancient system, the olfactory system developed various and adaptive strategies to face the world of odours and it can analyse and encode them as, either juxtapositions of odorant elements (elemental coding) or as constructions, (olfactory gestalts = synthetic coding), or both, and this, as a function of the physiological needs or motivational events.

In this chapter, the peripheral odour processing steps will be not described according to their chronological order. Indeed, the normal time frame for the operational steps, for odorant molecules reaching the OM, is binding, signalling and coding (building of the output neural message). However, to our mind, it will be easier for the reader to understand the peripheral process in the following order: binding, coding and signalling, the latter event shedding light on the coding mechanisms.

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[1] Vapour pressure: In a closed container, molecules from a volatile liquid escape the liquid phase and become vapor. These gaseous molecules strike the wall of the container, exerting what's known as vapour pressure. Vapour pressure is directly proportional to temperature. Increasing temperature will increase the ratio of gas: liquid molecules, thereby increasing vapour pressure.

7.2. Peripheral odorant processing: everything begins in the nose

7.2.1. Odorants binding

The nasal cavities comprise several turbinates (3 in Human, 4 in rat or mouse), which are lined with the respiratory and OM. However, in humans, OM is limited to the upper end of the nasal cavity, which is just below the cribriform plate, through which the primary olfactory axons connect OB. This results in a surface of OM of about 2 cm^2 in humans against 10 cm^2 in rats, for example. However, despite such a huge anatomic restriction, the human olfactory system presents remarkable performances, which placed it far ahead of visual and auditory systems (Bushdid et al., 2014).

In terrestrial animals, the nose samples odorant molecules in the inhaled air. The crucial initial step which governs the odour perception is that of the interaction between odorant molecules with specialized receptors, expressed by the olfactory sensory neurons (OSNs) lying in the OM. Through our natural rhythm of breath, the odorant molecules are captured by the mucus covering the OM and then, reach the cilia of OSNs and bind with odour receptors (ORs). In terrestrial animals ORs are devoted to airborne odorants. Over the animal kingdom, the number of gene encoding ORs varies between species and tended to decrease with the emergence of the visual perception of colours (Rouquier and Giorgi, 2007). For examples, there are 906 genes in humans (from which only 322 would be functional (Glusman et al., 2001), 1094 in dog and 1493 in rat (Quignon et al., 2005).

It was at the beginning of the 1990s that, ORs were identified (Buck and Axel, 1991). ORs are G protein-coupled receptors (GPCRs) which have a common architecture consisting of seven trans membrane domains, connected by extracellular and intracellular loops and belong to the Rhodopsin subfamily which comprises 672 family members, including 388 ORs (in humans). Because GPCRs present the general feature to be highly "druggable", since than one third of all current therapeutics are directed at them, an emerging point of view is that among these 388 ORs, most of them could be soon identified as being not only odorant targets but also drug targets (Millar and Newton, 2010).

Soon after OR identification, a core of data provided evidences that only one OR subtype (Buck and Axel, 1991, Ngai et al., 1993, Kishimoto et al., 1994) was expressed in each mature OSN in such a way that each OSN and its OR can be considered as a single unit (Chess et al., 1994, Serizawa et al., 2000, 2003); although each OSN may transiently express multiple OR at immature stage (Tan et al., 2015). OSNs expressing the same OR gene are distributed over spatially restricted zones in the OM (Ressler, et al., 1993, Vassar, et al., 1993), however, although the exact number of zones and their physiological function remains in debate (Bashkirova, et al., 2020, Coppola, et al., 2019, Horowitz, et al., 2014, Miyamichi, et al., 2005, Zapiec and Mombaerts, 2020), it can be asserted that the “one OR-one OSN rules” would have one fundamental anatomo-functional role, that of ensuring the precise wiring between the olfactory epithelium zones and bulb glomeruli during the development and then over the OSNs’ cyclic renewing.

From a functional point of view, single OSN-OR units have been demonstrated as being mainly able to interact, with more or less affinity, with large ensemble of odorant molecules leading to build a combinatorial code for odorant perception (Duchamp-Viret et al., 1999, Malnic et al., 1999; Kepchiaet al., 2017).

Because most olfactory stimuli are blends of odorant molecules, at each breath, several molecules constituting the olfactory stimulus have the opportunity to simultaneously interact with each OSN. Thus, odorant-odorant interactions occur at ORs' level and OSN-OR units are signal integrators.

Odorant binary mixtures appear as inducing two kinds of OR binding interactions: competitive and non-competitive (Rospars et al., 2008, Pfister et al., 2020, Singh et al., 2019a). which likely account for most interactions observed between two odorants; competitive ones for most suppressions (Rospars et al., 2008) and rather allosteric ones for synergistic interactions (Munch et al., 2013, Pfister et al., 2020).

In competitive interactions, the most affine and/or concentrated molecule would bind ORs at the expense of the least one. From Singh et al 2018, a minimal biophysical model of odorant–receptor interaction incorporating just the simplest possible nonlinearity, namely competition between molecules for the binding site, can successfully predict the responses of many mammalian odour receptors to complex molecular mixtures.

In noncompetitive mechanisms linked to allosteric phenomena, one odorant could change the affinity and/or efficacy of OR for another odorant. Rospars et al. 2008 concluded that probability of allosteric changes would increase logarithmically with the number of interacting molecules in mixture and would be quite common with natural complex odours.

7.2.2. Odorant coding

Odour coding at the periphery is central to solve the olfactory perception secret. Combinatorial coding and receptor modulation mechanisms reveal that odorant-binding at the periphery is not a passive interface that translates chemical data into electrical signals. Given that OSNs can function as signal integrators, thus actively structure the chemical data that reaches the brain, it is imperative to understand and to model odour coding principles based on the OSN/OR's activity (Ache, 2020, Kurian et al., 2020).

From the perceptual point of view in humans, the mixtures of volatile odorant molecules found in the environment are perceived in a non-linear way. Indeed, synergy, overshadowing, masking, synthetic (Livermore and Laing, 1998, Kay et al., 2003)) and elemental (or analytic) processing appear as being involved (Berglund and Engen, 1993). These processes are simultaneously and complementary exerted. Like other things, they allow the olfactory system, to recognize a complex fragrance made of different odorants as an homogeneous (Berglund et al., 1976) or a synthetic object (the rose) and they allow to distinguish two close fragrances (Damask or Bourbon rose) by detecting some molecule(s), sometimes present at only minute concentration(s).

The observed perceptual olfactory rules led us to think that suppressive and synergistic interactions among odorant could have a peripheral origin. The demonstration needed to identify peripheral "mixture interactions" by comparing the magnitude of the observed OSNs' responses when odorants are presented in mixture compared to when they are presented individually. In mammals, the first study giving a connection between the perceptive interactions of compounds in mixtures and individual neuronal responses was an *in vivo* electrophysiological approach (Duchamp-Viret et al., 2003). By analysing single OSNs' responses to binary mixtures, we observed several types of odorant-odorant interactions which we defined according the terminology used in psychophysics when the perceived intensities of single odours and mixtures were compared (Laing et al., 1984, 1989, Laska and Hudson, 1993, Cometto-Muniz et al., 1999). To do so, the perceived intensity was replaced by the discharge spike frequency of single OSN responses.

According to this correspondence, the OSN responses to mixture could reflect 'hypoaddition' mechanisms, i.e. the neuronal response frequency to the mixture was equivalent to the response frequency induced by the most effective component at the same concentration, the least effective compound in no way affecting its action. The OSN responses reflected also what was termed "suppression" (in psychophysics) in which, the mixture response frequency was lower than the frequency induced by the most effective component at the same concentration, or less than the response to either component, as initially defined by (Cain and Drexler, 1974; Bell et al., 1987).

By contrast to suppression, the response frequency to the binary mixture could be higher than the one induced by the most effective component at the same concentration. Such odorant-odorant interaction was termed "synergy" (comprising partial and complete additivity mechanisms termed by Cometto-Muniz et al., 1999). Synergy implies, at least, that the two odour molecules do not counteract each other in binding processes and, at best, that they act in positive cooperation. Synergy is illustrated in Fig.1. As exemplified, synergy mainly occurs on the lowest concentration range of odorants thus boosting the detection power of single OSNs, for either the mixture regarding the single compounds, or one of compounds, depending if the coding mode is elemental or synthetic for the mixture in question.

Throughout these electrophysiological *in vivo* experiments, the OSN responses have been analysed for several couples of odorants (table 1). In doing so, our major and common and unexpected outcome was that the type of odorant-odorant interaction, and the ratio in which they are expressed, relied more on the odorant identities than on the OSN/OR types (see the "odour signalling" paragraph). In our pioneer study (Duchamp-Viret et al., 2003), we designed experimental binary mixtures by associating one low volatile compound (low SVP compounds which concentration is comprised between 10^{-10} and $<10^{-6}$ mol/l: see odorant at left in table1) with one high volatile one (high SVP compound which concentration is $> 10^{-6}$ mol/l: CAM, EVAN, LIL, LYR). The major outcome of this first study was that the low SVP molecules mainly exert suppressive action on high SVP activating molecules.

Then we focused on the couple isoamyl acetate (ISO) and whiskey lactone (WL), known as bearing the fruity and woody notes of Burgundy red wine (Chaput et al., 2012). This couple is described by human subjects as evolving towards the dominance of one

compound or another, according the ratio and concentration of each of the compounds. From OSN responses, WL appeared as mainly reducing the ISO induced activation while, to a lesser extent, being able to synergize them. In suppressive interactions, fruity note responses are reduced in dose-dependent manner by low concentrations of woody odorants. The recent studies of De March et al. (2020), fully confirmed our observations with the same odorant couple ISO/WL. Such influence of the woody compound on the fruity one on OSN responses supports the observed perceptual interactions between the fruity and woody notes in wines (Atanasova et al., 2005) and could match the subtle aromatic balance between these two notes observed for red wines (Thomas-Danguin et al., 2009).

Next, we studied the couple octanal-citral (OCT-CIT, Duchamp-Viret, 2016), described as acting as agonist and antagonist for common ORs (Ukhanov et al., 2010). Interestingly, their major odorant-odorant interaction was suppression which can be explained by the signalling pathways they elicited (Ukhanov et al., 2010; Ukhanov et al., 2011; see next section).

More recently Duchamp-Viret et al. (2021) studied the couple, ethyl isobutyrate (EISO) and ethyl maltol (EM) deemed to constitute an aromatic accord (pineapple accord) at a certain ratio, or elemental mixture at another ratio (in animal: Coureaud et al., 2011, and human: Thomas-Danguin et al., 2014). The remarkable result was that the electrophysiological responses to the binary EISO/EM mixture at the elemental ratio mainly reflected suppressive interactions between the two compounds whereas at the aromatic tuning ratio they rather reflected hypoaddition, indicating that the synthetic and elemental coding was partially and initially based on the OSNs' responses.

From the whole of our electrophysiological studies, suppressive interactions appeared to be the most common form of interaction between odorants at OSNs/ORs level. Consistently, Zak and colleagues (2020) found widespread antagonistic interactions in binary odour mixtures by imaging OSN axon terminals in olfactory bulb glomeruli as well as OSN bodies within the olfactory epithelium in freely breathing mice. They further noticed that, in complex mixtures of up to 12 odorants, antagonistic interactions are stronger and more prevalent with increasing mixture complexity. In parallel, a recent and converging set of data (De March, et al., 2020, Inagaki, et al., 2020, Kurian et al., 2020, McClintock, et al., 2020, Pfister, et al., 2020, Xu, et al., 2020, Zak, et al., 2020) described how the building of the peripheral OSN combinatorial code was complexified by odorant-odorant interactions leading to widespread inhibitions. Specifically, the results show that peripheral odour coding involves odorants acting on ORs as agonists, antagonists, inverse agonists, partial agonists, and even have a synergistic effect. As an example, a two-photon imaging of OSN in vivo, reports that inhibitory responses already exist at the level of OSN somata and are widespread phenomena in the mammalian OSNs (Inagaki et al., 2020). Contemporarily, the extensive study of Xu et al 2020 confirms the quantitative importance of inhibitory mechanisms at OSN level. Altogether, antagonism leading to inhibitory mechanisms being a common feature of odour mixture encoding in OSNs, it would expand the spectrum of odour coding -allowing the combinatorial codes of mixtures to differ from the simple summation of the OR response patterns of the component odorants- (De March et al, 2020) and help in normalizing activity to reduce saturation and increase information transfer (Zak et al., 2020).

The analysis of OSN responses led us to conclude that, at the OM stage, odorant mixtures would be processed by large ensembles of OSNs/ORs throughout odorant-odorant interaction widespread mechanisms, the latter mainly depending on the compound identity and, to a lesser extent, on the OSN/OR entity. The extensive inhibition, antagonism, and synergy at the peripheral level contributes to the robust odour coding in the mammalian olfactory system.

7.2.3. Odorant signalling

As extensively described in the synthesis of Ronnett and Moon (2002), the binding between one odorant and compatible ORs initiates intracellular signal transduction mechanisms, which results in converting olfactory stimuli into electrical signals. This binding induced ORs' conformational changes which led to the olfactory-specific G-protein (Golf) activation, this resulting in stimulating adenyl cyclase (cAMP). Then, the cAMP concentration increases, causing the opening of a cyclic nucleotide-gated channel, and the entrance of Na^{++} and calcium ions (see Boccaccio et al., 2021 for a review)Nakamura and Gold, 1987, Firestein and Werblin, 1989.

Beside the major cAMP signalling, odorant binding can also increase phosphoinositide hydrolysis and the production of inositol-1, 4, 5-trisphosphate (IP3) (Ronnett et al., 1993; Breer and Boekhoff, 1991; Miyamoto et al., 1992; Schandar et al., 1998) as well as cyclic guanyl cyclase (GMP) production. The cAMP pathway has been demonstrated to be the indispensable requirement for the olfactory response genesis (Wong et al., 2000), while the IP3 one merely appears as secondary, which would mainly intervene in complement to the first one. Lastly, the GMP pathway would not be involved in the early phase of the olfactory peripheral responses, but would rather intervene in modulation or desensitization of OSN's response (Zufall and Leinders-Zufall, 2000).

How do the intracellular signalling pathways connect the odorant coding observations? Ukhanov et al. (2010; 2011) deciphered some of the intracellular signalling mechanisms, underlying odorant-odorant interactions by recordings single OSN calcium responses *in vitro*. Indeed, they demonstrated that, in a simple binary mixture, the two components could alone and simultaneously engage two distinct signalling pathways, namely cAMP and IP3 ones, acting in opposite directions on CNGC channels, thus on the OSN polarization. Finally, in agreement with previous work and hypotheses (Spehr et al., 2002; Zhainazarov et al., 2004; Brady et al., 2006; Ukhanov et al., 2011) showed that the IP3 pathway solicitation exerts an inhibitory influence and can be proposed as the intracellular signalling supporting odorant-odorant suppressive interactions. This suppressive mechanism would be a widespread property of odorants regardless the OR type (Ukhanov et al., 2011; Ukhanov et al., 2013). This observation is in agreement with our *in vivo* observations (Duchamp-Viret et al., 2003; Chaput et al., 2012 and personal unpublished data). Having more than one mechanism underlying peripheral inhibition likely reflects the importance of this functionality to olfactory integration.

However, one true question which remains is: how does the selection of PI3K (over cAMP) pathway occur regardless of the OR type? ORs could be therefore viewed as a signalling pathway gate (Ukhanov et al., 2011) wherein cAMP, the prominent signalling pathway may be engaged or disengaged in favour of PI3K pathway, according to "the nature of the ligand and the dynamically changing intracellular environment". The two pathways, IP3 and cAMP, are thus differentially triggered according to the ligand-induced selective signalling (LiSS, (Millar and Newton, 2010). The concept of LiSS was demonstrated for many G-protein-coupled receptors (GPCRs) to which ORs belong and states that the nature of the ligand and the dynamically changing intracellular environment can alter the manner of signalling for many different GPCRs (Rosenbaum et al., 2009, Millar and Newton, 2010). This implies that the receptor would be not simply activated or inactivated but would adopt many conformations; each of them leading to a highly specific ligand-receptor interaction and each conformation acting in turn with a specific intracellular signalling complex. Millar and Newton (2010) wrote: "*The LiSS concept is creating a new level of sophistication, which challenges the dogma that ligand engagement of a GPCR consistently elicits a specific intracellular signal"*. However, the preponderance of a signalling pathway in an OSN may stabilize one conformation among others, leading the OR to increase its specificity for certain ligands.

Noteworthy is that odorant binding and signalling mechanisms, linked to the GPCR functioning comprising the LiSS concept, enlighten extremely promising explanations for supporting the odorant processing sophistication observed at OSN-OR level. Indeed, depending on the OR, each putative ligand could be the weakest or the strongest one(s). Thus, from these complex and multiplexed interactions either dominating or interacting odorants will arise. For interacting odorants, molecular interactions at binding/transduction levels could be mutually suppressive or synergistic. Suppressive and synergic interactions between components directly affect the perception of odour mixtures and could make surge synthetic information about olfactory objects since the peripheral stage.

7.2.4. Perireceptor events

The term "perireceptor events" gathers all events, which could facilitate, limit, delay or block, odour signalling *i.e* interactions between chemical molecules and ORs. The nasal mucus, which is secreted by Bowman glands, protects the OM and ensures ionic environment favourable to the transport of odorant molecules and to electrogenesis in the OSN's cilia. The mucus contains some of the main elements involved in peri-receptor events: the olfactory binding proteins and xenobiotic metabolism enzymes (XME; (Heydel et al., 2013; 2019)). The lipophilic characteristic of odorant molecules involves the existence of transport mechanisms to facilitate their access to ORs; this role is filled by OBPs, secreted by nasal gland, which interact with odorant molecules (Nagnan-Le Meillour, 2018). XMEs are degradation enzymes and catalyze numerous biotransformations of the exogenous compounds which will make them excretable via biologic fluids; especially throughout the large blood vascularisation of OM. XME are very largely present in the organism, especially in the liver for example, and comprise several enzyme families which are classified according to their 3 phase-action; functionalization, conjugation and excretion. In OM, several types of toxic agents can be

present and XMEs are expressed very early in the organism life; some of them appearing as directly regulated as a function of the olfactory system development. Because OSNs, and more largely the OM, can offer a privileged gateway to the brain (Minn et al., 2002), it is especially crucial for the peripheral system to set up a line of defence via XMEs, and maybe also via OBPs (Pernollet and Briand, 2004). In addition to XMEs and OBPs, small protecting proteins (heat shock proteins) could also intervene when OM is exposed to some chemicals, odorant or non-odorant molecules (Carr et al., 2001). Lastly, antioxydative enzymes are also highly expressed in OM (Reed et al., 2003).

Because they are highly expressed in OM, XMEs could also ensure the biotransformation of odorant molecules, thereby preventing OSNs' saturation and (or) eventual toxic effects at high concentrations. The results that, in rats, OM global responses to quinoline, coumarine or isoamyl acetate (electro-olfactograms) were shown to be increased by blocking XMEs highly support such a role (Thiebaud et al., 2013). XMEs could thus both change odorant stimulating properties and (or) favour the clearance of odorant molecules (Asakawa, et al., 2017; Hanser, et al., 2017; Ijichi, et al., 2019; Robert-Hazotte, et al., 2019). Moreover, because XMEs are expressed very early in the OM, they could also be involved in perceptive modulation of some specific odour signal as for example this of mammary pheromone by the newborn rabbits (Legendre et al., 2014; Hanser et al., 2017)). As a temporary conclusion, it can be proposed that, in addition to their role of toxicological barrier, XMEs would play a role in the odour peripheral processing, which is, at the moment, undoubtedly under evaluated (Heydel, et al., 2019, Neiers et al., 2021,) and would widen the olfactory perception mechanisms; for example the expression of one XME has been shown to increase in fasting rats (Longo et al., 2000). This part is more detailed in Chapter 6.

7.2.5. Conclusion

Odour processing at the periphery is central to unravel the secret of odour final perception. Along the binding, signalling and coding events, the interactions of odorants with OR-OSN entities include several successive steps which the complexity originates first, in the ability of OR-OSN to interact with large sets of molecules, second, in duality of binding interaction modes, third in the plurality of intracellular signalling and fourth, in the LiSS concept. These successive peripheral steps probably interrelate, involving not only the various odorant qualities but their concentrations and ratios; such interdependence increasing and becoming more complex so do the odorant mixtures. The result is that the mixture components can simultaneously act as agonist, antagonist or inverse agonist and so build the unique and precise OSNs' combination which will define simple as well as highly complex mixtures. Such combined possibilities should almost infinitely widen the peripheral coding possibilities, which appears as being in perfect agreement with the quasi infinite number of stimuli.

7.3. OB odorant processing

7.3.1. Peripheral signal amplification: convergence

Once primarily integrated by OSNs, the olfactory signal is relayed in the OB, as the first central relay. Overall, electrophysiological data indicate that the OB filters and transforms the incoming peripheral message, so that, for example, signal-to-noise enhancement, normalization (Zak et al., 2020), and contrast enhancement operations (Haney et al., 2018; Adams et al., 2019) occur before the processed olfactory information diverges to the olfactory cortices (Persaud, 2013).

In OB, OSN axons make synapse at level of discrete dense sub-spherical neuropil structures, called glomeruli (Fig 2). The "one OR-one OSN rule" designs the projection map; OSNs expressing a given OR converge on the same glomeruli and each glomerulus receiving only one type of OR projection (Treloar et al., 2002; Vassar et al., 1994). Accordingly, volume of each glomerulus linearly correlates with the number of connected OSNs, making glomerulus's size a highly reliable indicator of OSN number in the OM (Bressel et al., 2016). This immutable rule allows the olfactory system to be operating very early in the organism's life and then, throughout life, a stable re-wiring for the new OSNs originating from the cyclic and constant neurogenesis (Cheung et al., 2013).

The OSN-axons convergence ratio depends on the ratio between the total number of expressed OR genes and glomeruli (Maresh et al., 2008, Zapiec and Mombaerts, 2015). For example, in mice, each OSN express only 1 of possible 1100 ORs, thus the 3600 glomeruli yield a convergence ratio that approximates 1 OR for 3 glomeruli. In humans, only 350 intact genes are expressed, thus the 5500 glomeruli yield a convergence ratio of 1 OR for 16 glomeruli. The glomerular structuring is intrinsically induced by OSNs' endings (Takeuchi and Sakano, 2014) and so robust that, if OB is experimentally removed, they form ectopic glomeruli on the first brain targets they encounter (Nakatani et al., 2003; Graziadei et al., 1978; Graziadei and Samanen, 1980).

Whatever the species, one glomerulus and the main output neurons, namely mitral-tufted cells (MTCs), connected to it, receive the peripheral information from thousands of OSNs expressing the same OR (Hellman and Chess, 2002). This quantitative convergence results in amplification of weak signals (van Drongelen et al., 1978). In computational terms, this averages out uncorrelated noise and leads to an increase in the signal-to-noise ratio (Persaud, 2013). Consequently, MTCs can statistically detect odorants at lower concentrations than individual OSNs can do (Duchamp-Viret et al., 1989).

In the OB, not only MTCs receive the OSN input but also periglomerular interneurons (PG), mainly GABAergic, which form simple inhibitory and reciprocal synapses with MTCs. We have demonstrated that GABAergic PG cells exerted a gain control mechanism: they maintain MTCs under a tonic inhibition in order to limit the effect of quantitative convergent inputs; such control results in widening the MTC coding concentration range over several log units of concentration (Duchamp-Viret et al., 1993b). Indeed, if the PG inhibitory network is pharmacologically blocked, MTCs shift their response threshold towards lower concentrations and the slope of their concentration/firing frequency response-curve became steeper. In addition, PG tonic inhibition was also shown as modulating MCT spontaneous activity and thus the signal to noise ratio. The second main inhibitory control of MTC excitability is exerted by GABAergic neurons located deeper in OB; granular interneurons which also influence MTC spontaneous and evoked

activity, and finalize the output rhythm of the OB information (Duchamp-Viret and Duchamp, 1993a), thus contributing to the synchronization of coactive MTC columns (Egger and Kuner, 2021). However, some basal forebrain GABAergic neurons target OB granular interneurons leading to a functional disinhibition of MCs (Duchamp-Viret et al., 1993b); this central modulation of intrabulbar GABAergic circuit likely reduces spike precision of MCs cells and lowers the intensity of oscillatory activity in the OB, thus influencing the MCs' temporal and spatial dynamics (Villar et al., 2021).

7.3.2. Peripheral input mapping: sorting

As seen above, the sorting out and convergence of OSNs' axons, is strictly built from the genetically pre-established "one OR-one OSN rule". As such, the stereotyped projection on OB creates a spatial map of activated glomeruli targeted by OSN responses. The pervasiveness of the glomerular map explains why many studies attempted to establish the extent to which it relates a chemotopic stimulus representation on which, quality coding and discrimination would be based (Tabor et al., 2004; Lin Da et al., 2006; Carlsson et al., 2007; Johnson and Leon, 2007; Silbering and Galizia, 2007; Grossman et al., 2008; Krofczik et al., 2008; Frederick et al., 2009; Johnson et al., 2010; Kuebler et al., 2011; Meyer and Galizia, 2012; Schubert et al., 2014). More especially, by analysing glomerular patterns for odour mixtures, the question was to know if OB processing rather prioritizes the elemental odorant components or engenders a global code, or the reverse, or ensures both. The preservation of elemental component information implies a linear summation of single compound patterns, although giving birth to a completely novel quality from mixture, would imply nonlinear summation of single compound patterns (Fig 3). The issue being raised, the analysis of the bibliography led us to report that, regardless the animal model, from insect to the mammal, data and conclusions failed to reach consensus. Indeed, according to the author, the comparison of the glomerular patterning, induced by single components or their mixtures, reflects either a linear summation or a nonlinear combination of single compound patterns. However, from recent works, the linear summation hypothesis seems more and more implausible and really too much simplistic. Indeed, Economo and co-workers (2020) report that as well as OSNs, glomerular responses quantitatively amplify and integrate the activity of OSNs endowed with a same OR and mainly show suppressive interactions between odorants. Thus, inhibitory OB circuits nonlinearly transform odour representations and support a model of selective and non-random inhibition among glomerular ensembles (Economo et al., 2016, Zavitz et al., 2020). It remains that, as shown by Bhattacharjee and colleagues, the similarity of two glomerular patterns and their activation strength can carry a part of the resemblance between two stimuli (Bhattacharjee et al., 2019); the time needed by mice to discriminate these stimuli being inversely correlated.

The apparent topographical shape of the OB information may be the tree that hides the forest since, in any case, neuronal information is not fixed in a given time and therefore in a fixed spatial configuration. Indeed, the spatial dimension must not make us forget the fine temporal dimension of the OB network activation, the electrical events which are playing at the millisecond scale, the scale of MTCs' spiking activities. Meaningful information from the OB is indeed provided by the temporal and dynamic activities of the

MTC elicited by sensory inputs; the activation time of the glomeruli itself can be exploited to extract odour-related information (Perl et al., 2020). Throughout their firing response patterns, single MTC responses could encode both elementary information about mixtures' chemical composition, or synthetic olfactory objects. Indeed, some MCT responses to mixtures were very similar to responses to one of the component and appeared as mainly devoted to the elemental mixture coding (Giraudet et al., 2002; Wilson and Stevenson, 2003; Tabor et al., 2004). By contrast, in other MTCs, temporal response patterns to mixtures were clearly distinct from those to single components. Such emergence of a specific response temporal patterns for mixture, would rather favour synthetic mixture coding (Wilson and Stevenson, 2003), the latter remaining also based, at less partly, on spatial pattern of activated glomeruli (Chong et al., 2020)

Initially, Wehr and Laurent (1996) proposed that the MTC odour code would be based on fine temporal tuning of spiking activity within cell assemblies (Fig. 4). The authors presented such a coding mode in OB as an alternative to the spatial one, the two codes can of course coexist and complement each other (Economo et al, 2016). These synchronized assemblies would transfer sensory information throughout burst sequences using the gamma oscillation as a clock (Cenier et al., 2009, David et al., 2009, Gschwend et al., 2012). Thus, the brain would assign "meaning″ to the temporal pattern in which MTC assemblies would succeed.

The perceptual responses not only depended on which groups of MTCs were activated, but also on their activation latencies, i.e., "temporal sequences akin to timed notes in a melody" (as writen by Chong et al., 2020). The latter authors using single-spot optogenetic stimulation of the OB, mimicking synthetic odours showed that temporal perturbations (<10 ms) in the sequence of activation of OB spots led to graded changes in perception in mice. They proposed that the most perceptually relevant activation latencies were defined relative to other cells; earlier-activated cells in the sequence had a larger effect on behavioural responses. In mice also, using a 2P photostimulation of individual neurons, Gill and co-workers (2020) described how inhalation of different odours leads to changes in the set of neurons activated, as well as when neurons are activated relative to each other (synchrony) and the onset of inhalation (latency). The authors underlined that stimulus detection depends strongly on the synchrony of activation across neurons; mice being able to detect single action potentials evoked synchronously across less than 20 MTCs.

OB coding has been shown as being largely impacted and morphed by wakefulness, experience and memory and further, by stimulus physiological relevance (Bhalla and Bower, 1997; Linster and Hasselmo, 1997; Buonviso et al., 1998; Carey et al., 2009; Buonviso and Chaput, 2000; Gschwend et al., 2012; Kato et al., 2012; Patterson et al., 2013); (non-exhaustive citations). Amongst others, because mammals dynamically sample odorants and can discriminate them in one breath, OB mixture coding is *de facto* impacted by breathing rhythm and wakefulness. Indeed, the OB circuit is characterized by beta and gamma oscillations nested in a slower theta carrier wave ascribed to respiration (Buonviso et al., 2003; Rojas-Lıbano et al., 2014).

In awake rodents, MTC responses constitute more discriminative odour representations than in anaesthetized animals, throughout a diversification of their

temporal dynamics (Kato et al., 2012). As a matter of fact, in addition to the basic respiratory rhythm (2-4 Hz), the arrival of volatile stimuli in the nose triggers active sampling behaviour (sniffing-rhythm) which ranges can vary from 2-12 Hz. Furthermore, even in the absence of odour the rhythmic movement of air is thought to cause activity locked to this rhythm in OSNs (Rospars et al., 2008; Iwata et al., 2017) and MTCs (Bathellier et al., 2008; Moran et al., 2021; Ackels et al., 2020), forming the fundamental rhythm that shapes much activity within the early olfactory stages.

MTC temporal synchronization (evaluated through local field potential recordings) have been shown modulated by the animal experience (Martin et al., 2004; Martin et al., 2006; Courtiol et al., 2011; Vinograd et al., 2017; Ramirez-Gordillo et al., 2018; Liu et al., 2020; Kudryavitskaya et al., 2021 etc.). Additionally, changes in the balance between sensory and corticofugal inputs to OB interneurons can alter timing of beta and gamma oscillatory states, suggesting that information transfer from the OB is influenced by top-down signalling (David et al., 2015). Very recently, Losacco and co-workers (2020) asked whether the high gamma and beta oscillations carry different information when they are observed within particular phase windows of the theta carrier wave during associative learning. The authors concluded that the encoding of stimulus identity from high gamma oscillation changed.

Indeed, by coupling experience and precise sub-millisecond synchrony, MTCs' assemblies can convey both odour identity and its reward meaning. Such a synchrony relates a small fraction of spikes in MTC pairs and was observed between MTCs which may be at any distance apart in OB. Doucette et al. (2011) proposed that the precise OB synchrony would be mainly established and reinforced by coincident excitatory centrifugal inputs (Restrepo et al., 2009; Matsutani, 2010).

Thus, by operating concurrently and simultaneously, synchrony, rate- and sniff-locked coding would specify various stimulus features giving birth to a multiplexed code (Gire et al., 2013). Such a multiplexed code at different timescales appears all the more relevant in the olfactory system since the latter has to face multidimensional stimuli which inputs can be fragmented across OB (Cleland and Sethupathy, 2006) and to link to them associational significance to arbitrary combinations of these inputs; sniff-phase MTC discharges may constitute dense identity coding and, sparse synchrony may convey behavioural relevant information.

What about discrimination for binary mixtures? MTC response temporal patterns to a binary mixture have been shown as smoothly morphing from the first component pattern to the second component one, reflecting more or less their respective concentration ratio (Shen et al., 2013). Moreover during odour morphing, some MTC responses to mixtures temporally shifted regarding the respiratory phase; such phase-position should provide supplemental neuron-level parameter for synthetic odour mixtures (Khan et al., 2012). By observing both simple additivity and novel time-locked representations of odour mixture, the latter authors concluded that MTC temporal responses to mixtures could morph from elemental to synthetic representations. To our point of view, given odorant-odorant interactions occurring at OSNs' level, the notion of "simple additivity" would not stand up facing a mixture more complex than a binary one. Indeed, Barnes et al. (2008) by using

ten component mixtures reported that MTC responses were not simply predictable from the change in stimulus (one component being removed or exchanged).

Mixture sensory coding implies both discrimination and stable representation of stimuli. Indeed, the olfactory system needs to discriminate but also to recognize, even some information missing, and to categorize stimuli according to experience or familiarity; the latter process being an appropriate "generalization'. What about the olfactory perceptual stability throughout the MTC response morphing? From Shen et al. (2013), OB temporal response patterns reflect some completion or generalization mechanisms; this of course, to a much lesser degree than piriform cortex cells (PC) do.

As a conclusion, it should be retained that MTC fine temporal activities result in morphing assemblies which activities are thus shaped by the OB intrinsic network, synchronized on respiratory, gamma or beta oscillations' rhythm and highly under centrifugal control. Throughout their activation patterns, MTC responses could encode both elementary information about mixtures' chemical composition or synthetic olfactory objects. However, a multiplexed code based simultaneously on MTC time-locked firing and synchrony appears capable to ensure simultaneously the odour quality coding and behavioural relevance. Lastly, if MTCs in responses to odour mixture appear as being especially gifted to perform discrimination among close stimulus (Khan et al., 2012; Shen et al., 2013), they are also able to make some completion or generalization, as PCs are (Shen et al., 2013).

7.4. The piriform cortex: birth of the odorant percept

7.4.1. Spatial disorganization and odour identity coding through neuron ensembles: elemental or synthetic coding mode?

The OB directly and mainly projects on the piriform cortex (PC), the largest sub-region of the olfactory cortex, which is probably the locus for the formation of the odour percept. This projection does not follow any apparent topographic rule (Ghosh et al., 2011; Miyamichi et al., 2011; Sosulski et al., 2011), in such a manner that single odours activate a distributed subpopulation of neurons across the cortex without spatial preference (Rennaker et al., 2007; Poo and Isaacson, 2009; Stettler and Axel, 2009; Zhan and Luo, 2010). The projection mode of MTCs on PC neurons is both spatially divergent (Ojima et al., 1984) and quantitatively convergent (Franks and Isaacson, 2006). Such a loss of the spatiality between OB and PC (Sosulski et al., 2011), means that, in the two structures, the coding mechanisms should be based on different odour representations (Carey and Wachowiak, 2011; Shusterman et al., 2011; Miura et al., 2012). Stettler and Axel (2009) literally wrote: "PC discards OB spatial segregation as well as chemotopy and returns to a highly dispersed organization in which different odorants activate unique ensembles of cortical neurons"(Stettler and Axel, 2009).

Indeed, in PC, two different odorant molecules elicit two distinct, sparse, and not cluster in space, and partially overlapping activity patterns of PC neurons (Roland et al., 2017). PC neurons are impinged from multiple MTCs and are activated only if these MTCs are synchronously stimulated. This mechanism increases the discrimination of odorants that are structurally similar. In fact, although two similar odorants generate very close spatial patterns in OB glomeruli, they will activate different and multiplexed PC neurons, generating two clear-cut ensembles in PC without topographic organization. The earliest co-active cells in OB have an outsized role in shaping odour representations in PC (Wilson et al., 2017; Stern et al., 2018). Blazing and Franks (2020) has just revealed that simply knowing which PC neurons fired action potentials within the first 100 msec. after inhalation is sufficient to accurately classify odours. In addition, electrophysiological recordings from large populations of PC neurons revealed that odour identity can be decoded using simple binary response vectors of activated PC neurons, while odour intensity is best decoded using the spike timing of the population. These results suggest that PC may use a multiplexed, ensemble-membership identity code and an ensemble synchrony code for odour intensity (Bolding and Franks, 2017; 2018).

Regarding odorant mixtures, the questions are: How are mixtures represented in the piriform cortex? Can the identity of components be read out from mixture representations in the piriform cortex? These two questions are tackled by Penker and co-workers (2020). In PC, interactions between components illustrates the same type of interactions previously reported from OSN and MTC responses; PC neurons thus integrate non- linear representations from OB and OM responses. They showed mainly hypoaddition and suppression, according data reported in OSNs, and rarely synergy; however, "mixture-specific" PC neurons' described by Settler and Axel (2009) likely involved synergy.

From the start, Wilson and collaborators replaced the cortical mixture coding issue in the context of experience, memory and learning (Wilson, 2003; Wilson et al., 2006). From the author, 10 or 50 seconds of odorant stimulation seem to be enough to establish a synthetic representation of mixture in PC neurons, and to discriminate it from individual components. For the authors, PC appears as characterized by a rapid neural plasticity, experienced PC neurons gaining in competence. Such, implicit memory and learning would highly contribute to PC processing in a way that odours are analyzed regarding where, when and in what context their perception occurred. Wilson and Stevenson (2003), propose that this functioning rather promotes a synthetic than an analytic coding, and that analytical feature discrimination is only an initial step. As a matter of fact, most common tasks that mammals should achieve are mixture identifications and involve a synthetic treatment of olfactory information (gestalt recognition) rather than an elementary analysis of distinct odorants.

However, such a most common functioning does not alter the fact that mixture elemental information is kept in PC. Indeed, by comparing electrophysiological PC neuron responses to a configural mixture to those evoked by an elemental mixture. Wilson and co-workers (2020) reported that the elemental mixture was coded as similar to the components while the configural mixture was coded as distinct from its components. Moreover,

mixture components can be identified from PC activity by pooling responses of a small population of neurons (Penker et al, 2020).

Altogether, elemental and synthetic olfactory coding modes appear as being simultaneously performed all along the olfactory pathways. Thanks to the olfactory system performances, we are not obliged to choose between one or the other since the two information types are available, even being more or less easily accessible. Intuitively, the synthetic mode should mainly depend on learning and memory and would likely occur at both OB and PC levels. However, at OSNs' level, some synthetic attributes of odorants early emerge from mixture interactions (Duchamp-Viret et al., 2021).

7.4.2. Discrimination against generalization: pattern separation or pattern completion?

The important features of PC neurons should be linked to experience, learning and memory thanks to which PC neuron ensembles appear as capable to ensure the perception stability throughout "completion" processing, while it remains acute for discriminating the perception variability throughout "separation".

The olfactory system discrimination abilities are high and could be exerted on very similar stimuli and PC representations are well suited to perform signal to background discrimination without the need for learning (Penker et al. 2020). Recent models even propose that target single odorant can be detected against background mixture thanks to some single PC neurons (Mathis et al., 2016; Singh et al., 2019b). However, if some tasks or behaviours require discriminating between very close odours, others require assimilating these similar odours as being the same general percept. The olfactory system abilities should thus balance the two main perceptual necessities, which are stability (for recognition despite missing element) and discrimination (for relevant choice). Barnes et al. (2008) reported that, despite the fact that some single PCs respond differentially to close, overlapping mixtures, the cortical ensemble could disregard some missing and consistently functions with pattern completion. Such a completion allows minor variation in the stimulus to be disregarded, a function that is critical for stability of olfactory percept of complex stimuli (Wilson, 2009).

Interestingly, changes in PC neuronal responses are more important when one constituent was substituted in the mixture than when one was simply removed (Barnes et al., 2008). Thus these authors showed that PC neuron ensemble responses progressively de-correlated when the initial mixture was progressively depleted in components. However, some individual PC neurons easily "refilled" one missing element, by processing some "pattern completion". By contrast, if one mixture element is replaced by a new one, the PC perceptual balance became clearly in favour of discrimination; PC neurons clearly detected the novel element by processing some "pattern separation" (Barnes et al., 2008). Thus this suggests that one compound replacement in an odour mixture should be easily detected. Some available data on behavioural discrimination abilities in rats (Barnes et al., 2008; Lovitz et al., 2012) and humans (Ferreira et al., 2002) confirm this suggestion.

In addition to operant learning, recent evidence suggests that PC can also support unsupervised learning, in which repeated presentation of an odour selectively strengthens synapses between co-active neurons to form odour neuron assemblies that can then help stabilize odour-evoked cortical activity patterns, and therefore presumably odour percept (Bolding et al., 2020; Pashkovski et al. 2020)

7.4.3. Piriform cortex: a pure associative cortex?

PC neuronal circuits transform OB input to implement different computations that support features of odour perception such as concentration invariance and odour learning. Thus PC is not a static sensory feature detector, but is instead a dynamic circuit that continuously shapes odour representations to extract statistical regularities in the odour environment to facilitate adaptable, odour-driven behaviours (Endo et al., 2020).

PC appears as an archeo-cortex which the pure associative processing (Wilson and Rennaker, 2010) may be based on random both convergent and divergent excitatory inputs from MTCs (Stettler and Axel, 2009; Blazing and Franks, 2020). The associative processing rather promotes synthetic than analytical coding modes (Wilson and Rennaker, 2010; East and Wilson, 2020). The processing of complex stimulus patterns defining objects by associative circuits, both allows the robust stimulus recognition despite missing inputs and discrimination of overlapping patterns .

Because the odorant world contains a limitless number of items, OSNs are not selective in order to face this reality, and both OB and PC structures may match a pure associative processing. Let us admit for a while that the olfactory function would be based on absolutely not pre-formatted neuron networks (on a functional point of view) and let us follow the related line of reasoning. Since the organism birth, the olfactory hard-wiring, managed by OR-dependent immutable rules, ensures the anatomical stability of OB inputs. On this basis, the representation of the stimulus at the OB level would mainly depend on, and evolve with, the animal experience. In naïve animals, the hard-wiring would ensure an olfactory perception since the first odorant molecule docks OSNs. No recognition, no discrimination, only perception. Then, molecule by molecule, scent by scent, the olfactory experience would enrich by matching sensory information with encountered olfactory items and segregating odorous signals; relevant from irrelevant, nociceptive from innocuous, palatable from non-palatable etc. Here qualitative and quantitative parameters of the olfactory signals are connected with the story of individuals, throughout individual and collective memory and learning. Progressively the olfactory software will develop, establishing in the OB and cortex, highly adapted and adaptable working networks, which would process the information according to the organism holistic point of view. Of course, such a hypothesis although proposing OB and PC processes entirely based on experience networks does not exclude some invariants which are imposed by wiring rules; reproducible glomerular maps can be observed in several animals. Altogether the ancient sense of olfaction is robust, suitably efficient, and especially highly adaptable to the changing extrinsic or intrinsic environment of living organisms.

7.5. Plasticity mechanisms at the peripheral and ob levels

Throughout the phylogenetic evolution, given the crucial involvement of olfaction in vital behaviours, the olfactory system has given priority to the functioning sustainability and robustness. In addition, given the limitless and constantly changing number of potential stimuli, the olfactory system also gave priority to plasticity. Such priorities may account for some of the exceptional features which are expressed all along the olfactory pathways, from the periphery to cortices.

7.5.1. Peripheral olfactory experienced induction or imprinting

In olfaction, a major process that implements and modulates perception and contributes to the immediate and long-term adaptation of organisms to their environment is plasticity, which occurs from the peripheral captors. Olfactory perceptual changes (plasticity) induced by sensory experiences have been originally described in humans by Wysocki et al. (1989); these changes have been termed “experienced incidental induction” or imprinting (Nevitt et al., 1994). The mechanisms underlying such plasticity have been then mostly studied in animals, insects and rodents. Here we will focus on findings regarding plasticity of olfactory perception and on the recent reports, linking this plasticity to molecular, cellular and functional changes, in the first two stages of the olfactory system.

OSNs are continuously renewed along the lifetimes of individuals (Graziadei, 1973) (turnover: every 6-8 weeks) and the renewal can be paired with OR expression plasticity. During their maturation, neo-OSNs would be “educated” by the surrounding adult OSNs. Indeed, odour induced activities of the latter might direct their OR expression choice (Mombaerts, 2004; Yu et al., 2004), an established mechanisms which would ensure both continuation and plasticity. However, OR expression could also be modulated independently from the OSN cyclic renewal, by the olfactory environment, experience and internal parameters.

Is perceptual plasticity a general phenomenon? Since the eighties, Wysocki et al. (1989) reported that the ability to perceive an olfactory stimulus could be acquired by anosmic people. Indeed, several weeks of discrete exposures to androstenone increased the subject sensitivity to this molecule. More recently, olfactory training (Pekala et al. 2016; Hummel et al. 2018; Jiang et al. 2019) and aversive learning in humans (Cavazzana et al. 2018) have been shown to increase OSNs’ responses and olfactory performances for the conditioned stimulus (CS), in normosmic, hyposmic or anosmic subjects. In animals odorant exposition or learning have been shown to increase the electrophysiological responses of OSNs (Wang et al., 1993, Nevitt et al., 1994; Youngentob and Kent, 1995). The latter result fits with our recent study in rabbit neonates (Duchamp-Viret et al., 2021).

We showed that a single and brief MP-induced odour learning episode was sufficient to alter OSNs' responses to CS and mixtures including it. Moreover, using behavioural tests, we evidenced that CS detection threshold was shifted towards lower concentrations, supporting that MP-induced odour learning relies on induction phenomenon.

Other experiments did not experimentally manipulate the olfactory environment of animals but only reported observations made at different seasons, feeding states or in coincidence with breeding. European starlings show seasonal differences in their ability to respond to odour cue (De Groof et al., 2010). In Drosophila, the expression of chemoreceptor genes such as OBPs proteins was shown to change with age, reproductive state and social interaction (Zhou et al., 2009). In the mosquito, blood meals were shown to induce a general reduction in antennal transcript levels of chemosensory genes, although a subset of ORs was modestly enhanced after feeding (Rinker et al., 2013). In honeybees, some results suggested that scent environment may regulate floral scent perception (Reinhard et al., 2010). Although no study investigated odour learning and olfactory receptor expression per se, it suggests that experience-induced olfactory receptor plasticity may be a phenomenon occurring in all animals that have to manage changing odour environments.

Is plasticity in OR expression a general phenomenon? Recent experiments done in invertebrates and vertebrates established a clear relationship between changes in perception and OR expression. In insects submitted to an olfactory learning paradigm consisting in pairing the queen pheromone with glucose reward, the expression of the specific OR was down-regulated while the peripheral OSN global electrophysiological response was reduced (Claudianos et al., 2014).. Although down-regulation of some ORs following odour chronicle passive exposition intuitively makes sense, it may seem counter-intuitive during memory formation resulting from an olfactory learning. However, a reduced number of ORs can be sufficient for the detection of familiar odorant. Correspondingly, it would be advantageous to have other ORs comparatively up-regulated; for example, to ensure that new floral scents are detected, allowing honeybees to adapt to their ever-changing scent environment (Menzel and Muller, 1996; Eisenhardt, 2014).

In mice, effects of odorant exposure on some OR quantitative expression and sensitivity are contradictory depending on the context (either passive or active, via a positive or negative associative learning, through a continuous or discontinuous exposure). Passive odorant exposure has contrasted effects (Barbour et al., 2011 ; Cadiou et al., 2014). By contrast, aversive or fear learning using odorant as CS induces huge changes in early sensory processing at OM and OB levels. This increases CS-dedicated OR number and transmitter release probability from activated OSNs, enlarges glomerular size, reduces OB presynaptic inhibition mediated by $GABA_b$ receptors (Jones et al., 2008; Bhattarai et al., 2020) and the incidence of lateral inhibition in OB interneurons. This latter effect can even lead to a lesser discrimination resulting in a generalisation of the fear reaction to several nearby stimuli (Kass and McGann, 2017). Such Effects can persist over time and can even be transmitted to the next generation through still unknown mechanisms (Dias and Ressler, 2014). When performed in the perinatal period, which could be assumed to a positive associative learning due to motherly presence, odour exposure also influences glomerular

refinement and functioning with contrasted effects on OSNs/ORs (Kerr and Belluscio, 2006; Todrank et al., 2011; Valle-Leija et al., 2012; Geramita and Urban, 2016; Monjaraz-Fuentes, 2017, Dewaele et al., 2018).

Two recent reports reconcile most of the studies by showing that changes in OSN repertoire abundance (Ibarra-Soria et al., 2017) as well as birth rates of neurons expressing given ORs, would be highly dependent on the environment, therefore on olfactory stimulation (Van der Linden et al., 2020). Along this line, in rabbit neonates, conditioned using mammary pheromone odorant (Duchamp-Viret et al., 2021), the increase of OSNs' response to CS supports an increase of either the density of ORs dedicated to CS processing or of the number of OSNs expressing such ORs. This suggests the existence of activity-dependent regulation of OR expression, in adult or newly mature ORNs, or both.

Thus, the analysis of the literature currently leads to consider induction as a generic phenomenon, with a "positive side" (enhancement of olfactory abilities) that would mainly occur after discontinuous exposure and/or conditioning, whereas passive and continuous exposure to odour cues would rather reveal a "negative side" (loss in olfactory reactivity or habituation). It can be proposed that such plasticity while, rather leading to a stronger processing of experienced reinforced stimuli, would drive the expression of the most adapted peripheral captors (Kass et al., 2016); this selection could potentially lead to quantitatively reduce their number. In conjunction, the system would favour the detection of new odours (new experiences) at captor level. Such a hypothesis would be perfectly adapted to the olfactory system, a sensory system approached by a quasi-infinite number of stimuli. Moreover, olfactory training appears as a potent tool to increase as well as to restore specific olfactory abilities since the periphery (Kim et al., 2019).

7.5.2. Plasticity in OB: tight interdependency between neurogenesis and centrifugal neuromodulator systems

OB integrated the primary sensory information throughout a complex neural network, which is largely under centrifugal controls. Indeed, several neuromodulator systems massively project to OB and are known as crucially involved in plasticity and learning (Matsutani and Yamamoto, 2008) as in food-intake control (Schneider et al., 2020). The main modulator systems are the cholinergic, which centrifugal fibres pass throughout the horizontal part of the Broca band, the serotoninergic, originating of raphe nucleus (McLean and Shipley, 1987) and the noradrenergic systems, originating of Locus Coeruleus (Shipley et al., 1985). These modulator systems mainly target the OB periglomerular and granular interneurons, with an emphasis on the latter.

Yet, OB benefits lifelong from the arrival of precursor GABA-ergic interneurons: up to one thousand daily, migrating from the rostral flow from the sub-ventricular zone (Imayoshi et al., 2008). The integration and survival of these newborn interneurons have been shown as depending on sensory inputs, perceptive or operating learning experiences (Li et al., 2018; Livneh et al., 2009) and centrifugal inputs (Moreno et al., 2012; Hanson et al., 2017; 2020). Indeed, sensory deprivation has been shown as decreasing survival of newborn neurons (Livneh et al., 2009).

From a global point of view, in OB, perceptive plasticity, learning mechanisms, neurogenesis and centrifugal neuromodulation are strongly interconnected and highly interdependent. Indeed, for example, a blocking of the neurogenesis in the rostral sub-ventricular flow, as well as a manipulation of noradrenergic transmission by OB centrifugal inputs, prevent improvement in odorant discrimination which is normally induced by perceptual learning (Moreno et al., 2009) or by operant learning (Lepousez et al., 2013). In addition, the OB newborn interneurons display a higher level of survival and integration into active OB network, i.e. in animals submitted to odorant exposures (Rochefort and Lledo, 2005) or operant learning (Mandairon et al., 2011). For the latter, neurogenesis seems essential whereas it does not for some simple discrimination tasks (Imayoshi et al., 2008; Sakamoto et al., 2011). Similarly, a recent study demonstrated the necessity of OB newborn interneurons in complex perceptual learning (Forest et al., 2020) and thus their essential role for olfactory adaptation.

The continuously renewed interneurons are GABAergic, mainly exerting inhibition on MTCs and the centrifugal modulator system highly targets these interneurons. On the whole, these interneurons would especially come to reinforce the OB function of pattern separator (Shani-Narkiss et al., 2020) linked to discriminatory processes. By the way, improvement in discrimination performance is widely observed after training or conditioning. As for example after fear learning, which has been shown to enhance perceptual discrimination abilities of very close odour cues (Li et al., 2008) and alter odorant-evoked neural activity in the piriform cortex and olfactory bulb (Li et al., 2008; Fletcher and Bendahmane, 2014). In agreement, in mice, Kass et al. (2013) showed that the pairing of a neutral olfactory stimulus with a shock enhances the OSN responses to this neutral stimulus, and thus their input to OB glomeruli. In addition, such pairing also increased the numbers of OSNs expressing M71 (paired odour specific ORs) and increases the size of target glomeruli in OB (Jones et al., 2008). However, the emotional salience strength of fear learning would be not only especially potent to induce plasticity in conditioned mice, which effects could be evidenced throughout all the olfactory pathways, but could influence olfactory behaviour and OR expression in subsequent generations (Dias and Ressler, 2014). The prospects opened by the latter results are that experienced induction of genotypic alterations could be transgenerationally inherited.

Altogether, in rodents, the olfactory system appears as especially tuned towards plasticity since within it, the local intrinsic neurogenesis of OSNs and induction mechanisms of ORs are coupled with OB interneuron continuous replacement by newborn neurons coming from the brain subventricular zone. Shani-Narkiss et al. (2020) propose a theoretical model explaining how a small proportion of young and excitable neurons contribute to efficient coding in the OB mature circuit and hypothesize that such a model would hold in the hippocampus. Moreover, in both the OB and hippocampus, continuous adult neurogenesis has recently been proposed to be involved in the constitution of the neural trace of social memory (Lunardi et al., 2021). However, as expressed by Brennan and Keverne (2015), this raises the question as to how the system balances the necessity of keeping some “old” memories and faces, or prioritizes new information. Of course, the olfactory system could quickly adapt to new environment chemical cues, however even in humans, it appears also trustable to make surge very ancient remembrances and place the brain under emotional influences. Brennan and Keverne (2015) write that the olfactory system adaptability is extravagantly supported by the vast deployment of ORs’ gene and

neurogenesis phenomena, and would be especially adapted to the lifestyle of small brain mammals. Indeed, in primates, the gene pool and OB neurogenesis would tend to decrease. Nevertheless, even if, with phylogenetic evolution, neocortex, auditory and visual information had apparently taken the place of the primary sensory systems for decision, the human olfactory function displays remarkable performances which placed it far ahead of visual and auditory systems (Bushdid et al., 2014).

7.6. Genetic, gender and ageing variations in the olfactory system performances

7.6.1. Genetic variations

In humans, the olfactory sensory perception varies, not only between populations, but also between individuals within a population. Genetic factors largely contribute to these inter-individual differences. Indeed, if the genes encoding olfactory signal transduction cascade are roughly conserved between humans, OR gene loci are one of the most genetically diverse regions in their genome, not only in the coding regions, but also in promoters (Ignatieva et al., 2014). Thus, variations in human smelling abilities could partly result from different functional OR repertoires, variable expressional levels and polymorphisms in the copy number or sequences of the OR genes (Gilad and Lancet, 2003; Hasin et al., 2008; Trimmer et al 2019). As a consequence, each individual has a unique set of OR gene repertoire. Such uniqueness should contribute to the diversity of odorant-specific sensitivity phenotypes and appears as supporting a variety in changes in olfactory perception, from subtle odorant-specific to general anosmia (Hasin-Brumshtein et al., 2009, Karstensen and Tommerup, 2012).

Anosmia for specific odorants has been described for dozens of odorant molecules. For the specific anosmia to androstenone described by Wysocki and Beauchamp (1984), the link between an olfactory sensitivity genetic polymorphism originated from gene single mutation of a narrow-tuned receptor, the *OR7D4*, and the specific and complete anosmia has been recently demonstrated (Keller et al., 2007). Elevated detection threshold for the sweaty odorant isovaleric acid, methanethiol, cis-3-hexen-1-ol, or β-ionone were also described for allelic variants of *OR11H7P*, OR2M7, *OR2J3* or *OR5A1*, respectively (Menashe et al., 2007; Eriksson et al., 2010; McRae et al., 2012; Jaeger et al., 2013). At the OB level, a single-nucleotide polymorphism in the voltage-gated potassium Kv1.3 channel was associated with a decreased performance in healthy humans tested with odorant sticks (Guthoff et al., 2009).

In addition to odorant-specific anosmia, more complex disorders, such as general anosmia or severe hyposmia are described in human populations. Congenital general anosmia, an inherited loss of smell, associated or not with other anomalies, is described in a few familial cases. Despite evidence for a strong degree of heritability, no causative mutation has been yet found in the olfactory signalling pathways of these cases

(Feldmesser et al., 2007), except a stop mutation in the cyclic nucleotide gated gene CNGA2 recently identified in two brothers (Karstensen et al., 2015). Anosmia is also part of the clinical picture in various syndromic diseases, for which molecules expressed in the olfactory mucosa are mutated (Karstensen and Tommerup, 2012): in ciliopathies and congenital insensitivity to pain, anosmia results from loss of function mutations in intraciliary transport proteins or in the voltage-gated sodium channel SCN9A which affects OSN functioning (Kulaga et al., 2004; McEwen et al., 2007; Weiss et al., 2011). In the Kallmann syndrome, a heterogeneous genetic disorder characterised by gonadotrophic deficiency and anosmia, the neuronal migration process during embryogenesis is impaired. Mutations in the KAL1 locus in the X-linked recessive form and other genes in the autosomal dominant form, such as fibroblast growth factor receptor 1 (FGFR1/KAL2), fibroblast growth factor 8 (FGF8/KAL6), PROKR2 and PROK2 are observed (Falardeau et al., 2008; Kim et al., 2008; Dode and Hardelin, 2009; Sarfati et al., 2013). Loss of function of these genes disrupts embryonic migration of the gonadotropin-releasing hormone (GnRH)-synthesizing neurons from the OM to the hypothalamic region of the brain results in OB structural abnormalities that prevent its functioning from the birth. Even if they are rare, these genetic diseases usually result in serious problems in the everyday life of impacted people. Together with problems in the detection of noxious environments, the enjoyment of fragrances and food are diminished, resulting in nutritional imbalances.

Considering the high number of genes involved in the regulation of odorant sensitivity (and among them, the olfactory receptors family), these data reveal a relative low occurrence of dramatic phenotypic effect associated to polymorphism. However, it remains difficult to correlate odour perception and genotype at the peripheral level; genetic OR allele polymorphisms only partly explain the observed variations in perceived intensity or valence (Mainland et al., 2014). In addition, the combinatorial receptor coding rules as well as the peripheral plasticity and induction mechanisms which impact the olfactory system sensitivity spreads confusion and reduces our chances to identify genetic variations in odorant perception (Wysocki et al., 1989; Wang et al., 2004). However, the exploration of the genetic diversity using high-throughput based tools such as GWAS (genome wide association studies) or next-generation transcriptome sequencing will probably illuminate hundreds of new candidate auxiliary olfactory genes putatively impacting the perception (Keydar et al., 2013). Their identification will be the first step to the development of gene-based therapy.

7.6.2. Gender variations

In chemosensory perception in humans, gender differences are known since the nineteenth century in terms of detection, discrimination and identification of odorous substances, particularly regarding the physiological and psychological effects of odorous sex-specific steroids. Women typically outperform men, whatever their age, mostly thanks to sex-specific hormonal, neural and cognitive advantages. This is particularly true when considering the olfactory sensitization, which is observed in women upon repetitive exposure to previously unscented odours (Dalton et al., 2002; Diamond et al., 2005). Most

studies describe a higher sensitivity in women, while some of them fail to show any discernible sexual dimorphism in normal (reviewed in (Brand and Millot, 2001; Doty and Cameron, 2009)) or symptomatic situations (Malaspina et al., 2012). A gender effect was observed on the ability to detect food odours, women displaying better perception than men (Michon et al., 2009). A recent meta-analysis confirms a weak superiority of female in terms of threshold, discrimination and identification (Sorowkowski et al., 2019). However, none of these studies gives any convincing proof of the functional difference at the OM or OB level.

Up to now, there are very few insights into gender differences at the cellular and molecular levels that support published sensibility differences. At the perireception level, sparse data suggest that mucus composition differs between male and female. The alpha-glutathione S transferase, a biotransformation enzyme putatively involved in the termination of odorant signals, and two cyclic nucleotides cAMP and cGMP, are expressed in higher levels in female mucus as compared to male (Krishna et al., 1995; Henkin and Velicu, 2008). Regarding OSNs, no morphologic difference in the number or density of neurons in the mucosa was found between male and female, whatever the age of subjects (Jafari et al., 2008). There is no major sex-related difference in olfactory gene receptor expression too (Verbeurgt et al., 2014). In the human OB, the data related to gender indicate an overall smaller volume of the OB, a larger number of neurons and glial cells, but a lower number of tyrosine hydroxylase- and aromatic l-amino acid decarboxylase-positive dopaminergic neurons in women in various regions of the bulb (Buschüter et al., 2008; Oliveira-Pinto et al., 2014; Alizadeh et al., 2015). The results suggest that the olfactory information might be differentially integrated in women and men OB. On the contrary, other authors noticed there is no gender-related difference in MTCs number and size, which rather supports that the olfactory information processing is similar in men and women (Sama-ul-Haq et al., 2008). Therefore, although minor sexual dimorphisms in the chemosensory performances are evidenced in humans, peripheral olfactory system structural differences should be further documented to support these observations.

In animal models, despite numerous works dealing with this issue, the question is not fully resolved. Most of the reports claiming that the olfactory system of adult rodents is sexually dimorphic have been done in the accessory olfactory system, which responds to sex-differentiated pheromones. This was particularly investigated in flies, where sexually dimorphic neural circuits are described. In rodents, the analysis of the transcriptome of the main and accessory olfactory tissues in mice reveals that some olfactory receptors and OBPs are up- and down-regulated in males as compared to females, these variations being minor (Shiao et al., 2012). In contrast, no difference in the total number of OSN after stereological analyses (Kawagishi et al., 2015) or in the catalogue of expressed genes after deep sequencing were found between males and females OM (Kanageswaran et al., 2015). This observation should be weighted according to recent data showing that at least a small population of OSN, devoted to sex-specific semiochemicals and generated by individual experience through a mechanism involving the pro-apoptotic gene Bax, is differentially represented between the sexes (Vihani et al., 2020). At OB level, biochemical analyses revealed minor sex differences: a higher concentration of dopamine and its metabolites, a less restricted clustering of the cell adhesion protocadherin-20 labelling in adults, and a

higher number of neurocalcin-immunoreactive interneurons were observed in male (Gomez et al., 2007, Lee et al., 2008). A more conclusive study using *in vivo* optical neurophysiology has shown that various odorants elicit a more rapid odour-induced signaling response and the activation of more glomeruli in females than in males (Kass et al., 2017). Therefore, sex differences in olfactory abilities likely originate in the variability and functioning of primary sensory neurons and associated glomeruli, but do not exclude other molecular changes supporting the behavioural differences at higher levels as recently shown for the treatment of sexual odours in the amygdala (Kikusui et al., 2018).

7.6.3. Ageing variations

Age-related physiological decline in olfactory function has been largely documented in a rich and detailed literature in psychophysiology in humans (Pinto et al., 2015; Godoy et al., 2015). Indeed, such a decline reaches around 2% of the population at 65 years of age, and then rises till 80 years; over 80 years, olfactory deficits being described in 75% of elderly (Doty, 2009). With aging, all the authors conclude to a decreased detection threshold as well as impaired odour identification and detection, due to cognitive processing deficits as well as peripheral changes in the olfactory system (Rawson, 2012; Mobley et al., 2014; Attems et al., 2015; Kondo et al., 2020) and references herein. Although age-related general olfactory loss (presbyosmia) is a prevalent impairment, ageing can differentially affect the olfactory performances. The phenomenon is gradual and multifactorial, since associations with neurodegenerative diseases are found in aged populations. The decline in odour identification performance and cognitive measures with age seems to be sex-dependent, making gender a good predictor of episodic memory (Wehling et al., 2016b; Wehling et al., 2016a). Some old subjects seem to display subtle differences in odour sensitivity depending on odorant type; they would become less sensitive to heavy molecules and thus would differentially impair their detection and identification (Sinding et al., 2014).

At the peripheral level, anatomical modifications of the olfactory network due to ageing occurs quite early and are visible since 65 years; it consists in a disparate decrease of the OSNs' population and a patchy replacement of the olfactory epithelium by the respiratory one (Paik et al., 1992). These structural modifications may be attributed to a local diminution in nutritive supply to OSN turnover, a diminution in local immunologic or enzymatic defence mechanisms (critical for maintaining the integrity of the epithelium) as well as to possible defaults in the metabolites' clearance attributable to a decrease of adrenergic innervation of OM blood vessels (Chen et al., 1993; Krishna et al., 1995; Getchell et al., 1995). This could result in changes in mucus composition and *de facto* affect proteins involved in inflammation, metabolism and detection of odorants. The abundance of some of these proteins being correlated to age-dependent sensory impairments (Yoshikawa et al., 2018), they could provide early markers of neurodegenerative conditions, such as for schizophrenia, Alzheimer disease, multiple sclerosis, and Parkinson disease (Escada et al., 2009; Kondo et al., 2020). In Alzheimer disease, the olfactory problems would precede classical symptoms, making the latter a crucial indicator for an early detection of this disease (Doty, 2009).

When *in vitro* OSN calcium responses were compared between young and aged human donors, the unexpected results was that OSNs are more responsive in older than in younger subjects (Rawson et al., 2012). The authors interpreted such result as an age-dependent modification in OSN selectivity; the latter, decreased in aged subjects and may be responsible, at least partly, for their difficulties in odorant detection and recognition. Changes in OSN response rate and selectivity could affect glomerular structure and OB processing, even if contradictory data are reported. Indeed, in some cohorts, OB and olfactory tract volumes, number of glomeruli as well as number of MTCs decline after 50 years of age (Bhatnagar et al., 1987; Yousem et al., 1998; Meisami et al., 1998). Other studies found an unaffected number of glomeruli, but a higher incidence of atypical glomerular patterning (Maresh et al., 2008).

In rodents, age-related changes in the olfactory system appear similar to those in human while deeper investigations can be done, especially thanks to the use of transgenic mice. Most studies, usually conducted in animals older than 2 years, described a decline in OSN density (Hinds and McNelly, 1981; Lee et al., 2009), paired with a reduction in OSN proliferation associated to a decrease in growth factors signalling (e.g. EGF and IGF-1), and an increase in inflammatory cytokines (Ohta and Ichimura, 2000; Ueha et al., 2018). Surprisingly, despite such age-dependent structural and molecular changes, OR gene expression is relatively stable (Khan et al., 2012) and the overall sensitivity for a variety of odorants is roughly preserved (Loo et al., 1996; Schoenbaum et al., 2002; Lee et al., 2009). However, the detection threshold for simple odorants such as ethyl acetate is better for young rodents than for old ones (Patel and Larson, 2009; Kraemer and Apfelbach, 2004) for which moreover, the fine discrimination of binary odorant mixtures is impaired (Enwere et al., 2004). Consistent with the decreased in OSN densities and impairment in glomerular patterning observed in humans, glomerular axon targeting is increasingly diffuse with age: glomeruli being only partially innervating by OSNs' axons in elderly mice (Costanzo and Kobayashi, 2010). In OB Alterations inneuronal long-term survival and differentiation, as well as a diminution in neurons responsiveness to environmental enrichment would also participate to the impairment in elderly (Rey et al., 2012; Moreno et al., 2014). Yet, *in vivo* optical neurophysiology observations in old mice recently showed that normal aging does not alter OSN response dynamics at OM level, or neurotransmission release and intensity of glomeruli responses, at OB level (Kass et al., 2018). This suggests that a local circuitry plasticity could preserve odour sensitivity in aging nose, and that changes in higher-order neural circuits that mediate olfactory-driven behaviours may counteract this adaptation.

Thus, in animals and humans, as for other sensory functions, olfaction declines with aging, maybe rather early, while some anatomical and physiological indices are found, since the peripheral stages, and may support such a decline. However, when "olfactory professional brains" are imaged, the story is obviously reversed. Indeed in "old" experienced perfumers, the olfactory expertise does not only counteract this decline but, on the contrary, induces a higher anatomic development of olfactory brain area, as compared with young beginners (Royet et al., 2013).

7.7. Olfactory function, under neurohormonal controls (other than these involved in metabolic status)

7.7.1. Stress

Anxiety- and stress-inducing stimuli largely affect the brain structures by activating the hypothalamic-pituitary-adrenal (HPA) axis. If such environmental adversity may temporarily rewire neural circuitry to modulate the cortical processing of odours, data obtained in animals support the idea that HPA activity can impact the peripheral olfactory system level. First, in rodents, the presence of functional glucocorticoids receptors (GR) in the olfactory epithelium strongly suggests that the OM, and especially the OSNs, are sensitive to natural or induced variations of the HPA axis functioning: GR are expressed in the OM apical region, including the sustentacular cells' cytoplasm and dendrites of OSN, but also within the *lamina propria*, in Bowman glands and in olfactory nerve bundles (Robinson et al., 1998; Nishimura et al., 2002; Vaz et al., 2018). Second, acute *in vitro* or *in vivo* chronic treatment with the synthetic glucocorticoid, dexamethasone, alters the OSNs' responses to odorants (Kamakazu et al., 2003; Wei et al., 2009; Meunier et al., 2020), induces changes in OM gene expression (Nishimura et al., 2002,;Tian et al., 2015), and could inhibit the OM cell proliferation (Ohta et al., 2002) but not its neurogenesis (Siopi et al., 2016). Lastly, a chronic variable stress exposure in rodents induces a reduction in electrophysiological responses to odorants and increases the OM apoptosis level, suggesting that stress events encountered could result in structural and functional long-lasting effects (Raynaud et al., 2015; Vaz et al., 2018).

In addition, GR are also expressed in the OB, since the embryonic stages in rodents (Kitraki et al., 1996), being localised in OB granular interneurons and MTCs, in adults (Sousa et al., 1989). However, the consequences of stress events on the OB plasticity are not yet clear, probably due to species and susceptibility's window differences. Whereas a stressful event rapidly induces granule cell death in adults (Komano-Inoue et al., 2015), a prenatal stress has no impact on adult bulbar neurogenesis and plasticity in mice (Belnoue et al., 2013).

In human, the deleterious consequences of major chronic stressing conditions encountered during early life, such as childhood maltreatment, have been reported as being both anatomical and functional: both the OB volume and olfactory sensitivity for various odorants are decreased in women (Croy et al., 2013). Among possible mechanisms, these authors proposed that the stress would mainly impact the OB neurogenesis, thus impairing olfactory plasticity and learning mechanisms as confirmed by Siopi et al. (2016) who showed that Corticosterone treatment induces a pronounced deficit in olfactory acuity, i.e. fine discrimination of odorants, and olfactory memory associated to a 2-fold decrease in the number of new interneurons in all OB layers. Conversely, some recent studies have shown that a short acute stress increases the detection threshold for a malodour, thus over-raising the sensory vigilance (Pacharra et al., 2015) and, furthermore that increased cortisol levels are associated with a higher odour identification performance and intensity ratings (Hoenen et al., 2017) .

Therefore, if stress obviously impacts olfactory sensitivity in various situations, the direction of modulations might depend on differences in protocols (window of exposure, type of stressing agent, odorant nature) and models. Among others, confounding effects could be involved. For example, long-term effects of dexamethasone treatment on OM could be indirectly attributed to its anti-inflammatory properties rather than its effect on HPA axis (Crisafulli et al., 2018).

7.7.2. Circadian rhythms

In addition to the master clock located in the hypothalamic suprachiasmatic nucleus, an increasing number of brain areas are revealed as functioning according to endogenous regulators responsible of circadian rhythms, and among them, the OB (Granados-Fuentes et al., 2004; Guilding and Piggins, 2007). OB can oscillate independently and does not require signals from the SNC for sustained rhythmicity, thus olfactory sensitivity fluctuations over during the 24h have long been described in humans (Lotsch et al., 1997; Nordin et al., 2003, Herz et al., 2017). Accordingly, levels of olfactory sensitivity in rodents are also far higher during the early nightime than the daytime (Granados-Fuentes et al., 2006; Granados-Fuentes et al., 2011).

A subset of genes of the core molecular 'clock' are expressed in the OB, such as Per or Cry family genes, and exhibit a circadian rhythm *in vivo*, the latter one being under the control of vasoactive intestinal peptide in interneurons of the external plexiform and periglomerular layers of the OB (Miller et al., 2014). Melatonin receptor mRNAs are also functional and fluctuate over 24h in the OB (Corthell et al., 2014). The final enzyme in melatonin biosynthesis is locally present, also suggesting a possible paracrine effect. Connexins, AMPA receptors, and monoamines also display diurnal variations (Corthell et al., 2012; Corthell et al., 2013). Thus, rhythmic fluctuation of these molecules and neurotransmitters could influence OB dynamic responses to odorants at various levels. For example, fluctuations of core clock genes and of Bmal1 are observed upon scheduled feeding and could participate to food anticipatory rhythms in the OB (Natsubori et al., 2013; Patton et al., 2014). Very recently, an autonomous circadian rhythm of these genes was also demonstrated in the OM, suggesting that these genes also could promote circadian function of OSNs, by controlling the expression of several OSN-specific genes involved in odour processing (Saleh et al., 2015). Accordingly, OM sensitivity varies during the day in part due to modulation of the very first step of odorant detection (François et al., 2017).

7.7.3. Reproductive neuroendocrine status

Influence of menstrual phase cycle

The relationship between olfactory sensitivity and menstrual ovarian cycle-related changes has been largely investigated by several groups who have published various, and

contradictory conclusions, making complex the relationship between reproductive hormones and olfaction (Doty and Cameron, 2009). Indeed, if cyclic alterations in the olfactory sensitivity are doubtless in humans for a number of odorants, none of the studies performed provided firm evidence of a systematic and large shift, probably due to differences in frequency of sample collection, method of categorization of the cycle phases, cohort sizes and tested odorants. The olfactory sensitivity has usually been determined by calculating the threshold for various odorants, such as for the pheromone candidate, the synthetic musk-like odorant, exaltolide, while others have used more general odorants with no obvious biological relevance. Increased sensitivity has been reported for some substances a few days before mid-cycle or at ovulation (Le Magnen, 1952; Doty et al., 1981; Mair et al., 1978), whereas other authors have reported an increase of sensitivity during the follicular phase or menstruation (Henkin, 1974; Vierling and Rock, 1967). One study has reported a decrease of sensitivity at menstruation (Schneider and Wolf, 1955), some results suggesting that the modulation may depend on odorant volatility (Mair et al., 1978). Other claimed that olfactory sensitivity was not significantly influenced by the menstrual cycle in humans whatever the odorant challenged (Herberhold et al., 1982; Amoore, 1982; Hummel et al., 1991; Pause et al., 1996; McNeil et al., 2013). Finally, by scoring the olfactory contrast that measures the ability to recognize a change in the odorant intensity, a better olfactory performance at menstruation has been confirmed (Watanabe et al., 2002), as for the ovulation phase (Navarrete-Palacios et al., 2003b). Thus, despite conflicting results, it could be concluded from human studies that olfactory sensitivity varies moderately across the menstrual cycle and is partly linked to the gonadal hormonal changes occurring across cycle, since ovariectomy (Pietras and Moulton, 1974), but not oral contraceptive use (Doty, 1986), eliminates the cyclicity. However, the use of contraceptives lowers the perception of social chemiosignals (Renfro and Hoffman, 2013; Endevelt-Shapira et al., 2020). Although naturally ovulating females display a decline in body odour discrimination when entering the luteal phase, women under oral contraceptives display such decline later, at the pre-menstruation time, during the withdrawal period of oral contraception (Endevelt-Shapira et al., 2020). Such ovarian cyclical changes in odour detection have also been published in female rodents, which show a peak in detection ability during either oestrus or proestrus, in the same period as for humans (Schmidt et al., 1982; Kumar and Archunan, 1999).

Concerning male, no alteration in detection threshold for relevant odours, such as female urine, or for ethyl acetate was observed upon castration (Carr et al., 1962, Doty, 1986).

If the molecular bases for such modulations reported in chemosensory function during menstrual cycle are poorly understood, and very few mechanisms have been yet investigated, some data indicate that ovarian hormones obviously act on olfactory structure and function at both short- and long-term. Evidence of steroids receptors expression in the nasal epithelium and OB (Leimola-Virtanen et al., 2000; Mitra et al., 2003) together with cytological modifications of the mucosa along the ovarian cycle (Navarrete-Palacios et al., 2003a) are in favour of a direct role for ovarian hormones, even if the attempt to find receptors for female sex hormones in the nasal epithelium of cycling women failed (Paulsson et al., 1997).

Once again, animal models helped to increase our knowledge of the mechanisms throughout which female sex steroids modulate olfactory signalling. Data support both genomic and non-genomic actions. Indeed, long-term estradiol treatment increases basal cell proliferation in the OM, that could potentially lead to an increase in tissue thickness, preserves the OB by increasing synaptogenesis following ovariectomy (Nathan et al., 2012) and influences adult neurogenesis (Veyrac and Bakker, 2011). Moreover, estradiol has acute effects by decreasing odour-induced responses in the mice vomeronasal organ (Cherian et al., 2014). Recently, using electrophysiological approaches such as EOG and whole cell patch-clamp recordings in mice, Kanageswaran et al. (2016) showed that a direct application of progesterone or estradiol rapidly decreases odorant-evoked signals in OSNs. As for metabolic hormones (see chapter 15), a local synthesis of sex steroids-metabolizing enzymes in rat OM questions the physiological relevance of a pathway for sex steroids genesis in this tissue (Horie et al., 2017).

The biological significance of the olfactory cyclicity remains to be determined, but it could participate in mate finding or choice, since the larger variations were observed with musk-like odours (Mair et al., 1978; Vierling and Rock, 1967). Some data suggest that it might help to food selection upon physiological needs (McNeil et al., 2013) or to orientate food preferences (Bignetti et al., 2009).

Influence of pregnancy

Even if pregnancy hyperosmia is a commonplace observation due to abundant anecdotal experience (Gilbert and Wysocki, 1991), the direction and timing of changes are less clear in the literature given the variety in experimental designs and cohorts, questionnaire formulation and type of olfactory measurements. However, it can be ad minima reported that the gonadal hormones but also, some placental ones (steroids, gonadotrophins, metabolic hormones) dramatically fluctuate during this period and thus, inescapably impact the olfactory perception.

The first full longitudinal study that tested olfactory sensitivity towards twelve odorants of pregnant and age-matched controls has revealed a significant higher detection threshold in the last trimester (Cameron, 2007), a critical period where olfactory alteration was confirmed using TDI scores (Ochsenbein-Kölble et al., 2007), or threshold tests, but not for all odorants (Laska et al., 1996). Accordingly, absence of changes in olfactory threshold or odour discrimination between pregnant and non-pregnant height and weight-matched women has been registered when taking into account the first trimester (Kölble et al., 2001). Only two studies noticed an increase in olfactory sensitivity in this period, after a self-rating study (Cameron, 2007) or when considering specific odours (Nordin et al., 2005), in a way that might participate to odour intolerance development. However, no correlation between olfactory sensitivity at early pregnancy and scores to a nausea tests was found (Hummel et al., 2002), nor evidence of an adaptive mechanism (Swallow et al., 2005). Finally, olfactory sensitivity was not significantly different between nulliparae and women who had given birth to at least one child, indicating that the number of pregnancies has no effect (Wohlgemuth et al., 2008).

Altogether, these data consistently indicate that fluctuations in olfactory sensitivity during pregnancy are not large enough to be significant using validated methods for measuring thresholds, and support that anecdotic hyperosmia comes primarily from changes in the valence of odours, thus heightening the attention to odours, as shown by Cameron (Cameron, 2014). Therefore, few efforts have been done to identify physiological bases for such changes at the olfactory bulb and mucosa levels. Some works mention that hormonal changes linked to pregnancy affect nasal airflow (Demir et al., 2015), olfactory structure and vascularisation (Guven and Ortug, 2006), that estrogen could mediate enhanced proliferation of neurons as shown in vomeronasal organ (Oboti et al., 2015) but that progesterone reduces sensitivity to odorants in the OM (Kanageswaran et al., 2016).

In rodents, prolactin, whose concentration is high during the first half of pregnancy and decreases until term, can increase the number of interneurons in the OB, whereas such an effect is not observed with estradiol or progesterone (Shingo et al., 2003). Such a neurogenic activity in the OB, as well as in the other regions of the brain, participates to the expression of maternal behaviours in several species (Larsen and Grattan, 2010; Levy et al., 2011). Pregnancy-derived hormones could support neural bases for a differential stimulus discrimination as shown for the activation of early genes in sensory processing: late-pregnant female display a reduced neural activity as compared to virgin ones for socially neutral stimuli, but display an increase of early genes for pup's odours (Navarro-Moreno et al., 2020).

Besides, in women, cognitive higher level of integration involving attentional mechanisms has been also recently reviewed to explain changes in olfactory perception during pregnancy (Cameron, 2014). Such plasticity, that increases awareness of potentially harmful chemicals, odorous and toxic environments to extend maternal protection, probably originates from central cognitive processes.

7.8. Conclusion

In order to encode olfactory stimuli and give the most relevant representation of the environment, the olfactory system needs to process the olfactory cues per se, but also to evaluate them, according to individual's history and physiological current status. Thus, any changes in the internal physiological reproductive, emotional, circadian status will result in chemical signal releases which directly or indirectly will dynamically impact the olfactory processing at several levels: all regulations being intended to facilitate the individual's adaptive behaviours. However, on the current state of knowledge, the mechanisms, by which these multiple internal cues are orchestrated and prioritised, regarding the nature and valence of the external stimuli, still need to be deciphered.

Figure caption

Figure 1: Unitary electrophysiological responses of one OSN, recorded *in vivo* in rat, illustrating the synergic action of CITral and OCTanal (raw spike recordings). On the left, are shown the 5 stimulation sequences recorded in response to OCT or CIT at increasing concentration from top to bottom. OCT induced excitatory responses which spike frequency increased with concentrations. CIT did not induce any response. Top right: OCT+CIT mixture induced, as OCT alone, excitatory response which spike frequency increased with concentrations. However, even by eye it can be seen that the 3 lowest concentrations (stars) of mixtures elicited higher frequency firing bursts than OCT alone. This increased efficiency is ascribed to the presence of OCT, which acts in synergy with OCT although, it was not stimulating alone. The response-curve graph plots OSN response frequencies against the total concentration for CIT, OCT and mixture. The curves evidenced that CIT and OCT act in synergy for the 3 lowest mixture concentrations (stars) but at higher ones, the compounds rather act according hypoaddition mechanisms: the presence of CIT did not alter the concentration/response curve, which perfectly overlapped the curve obtained with OCT alone. Thus, because CIT alone did not induce activation, in perceptual terms, we propose that OCT may be the dominating compound for which the perceptive intensity is increased by the presence of CIT, in the lower range of concentrations. The black horizontal bars under the single recordings indicate the 2-second stimulation delivery.

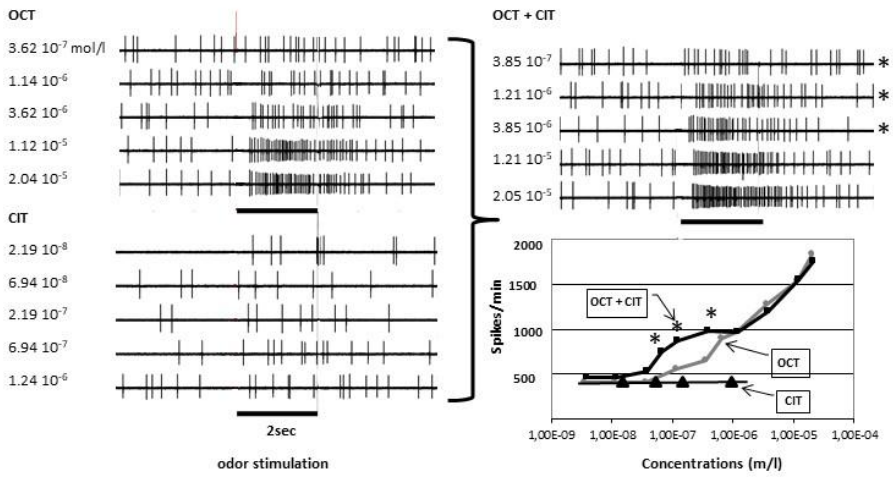

Figure 1

Table 1: Synthesis of the odorant-odorant interactions observed throughout single OSN recorded *in vivo* in rats. Odorant molecules: camphor (CAM), cineole (CIN), citralva (CITV) menthone (MENT), isoamyl acetate (ISO), anisole (ANI), acetophenone (ACE), *l*- and *d*-carvone (*l, d*-CAR); Methyl-amyl-ketone (MAK); LIM), ethylvanillin (EVAN), lilial (LIL), Lyral (LYR), whiskey lactone (WL), citral (CIT), octanal (OCT), ethyl isobutyrate (EISO), ethyl maltol (EM). See the extended description in the text.

	Odorant molecules (by couple)			SUPPRESSION	SYNERGY	HYPO-ADDITION
Duchamp-Viret et al., 2003	**Low SVP odorants** CIN, CITV, MENT, ISO, ANI, ACE, CAR, MAK, LIM.	**High SVP odorants** CAM, LIL, LYR EVAN	***Experimental High SVP + low SVP***	21%	20%	59%
Chaput et al., 2012	ISO	WL	***Real wine aroma***	45%	25%	30%
Duchamp-Viret, 2015	CIT	OCT	***Agonist/antagonist***	62%	25%	13%
Petryzyn, Ferry, Duchamp-Viret, *(Unpublished data)*	EISO	EM	***Aromatic accord***	28%	43%	28%

Figure 2: Anatomical scheme of first two stages of the olfactory system detailing the projection of OSNs' axons on OB: OSNs expressing the same OR type (light grey, dark grey or black), converge to the same glomerulus. This stereotyped projection originates a spatial map in glomeruli.

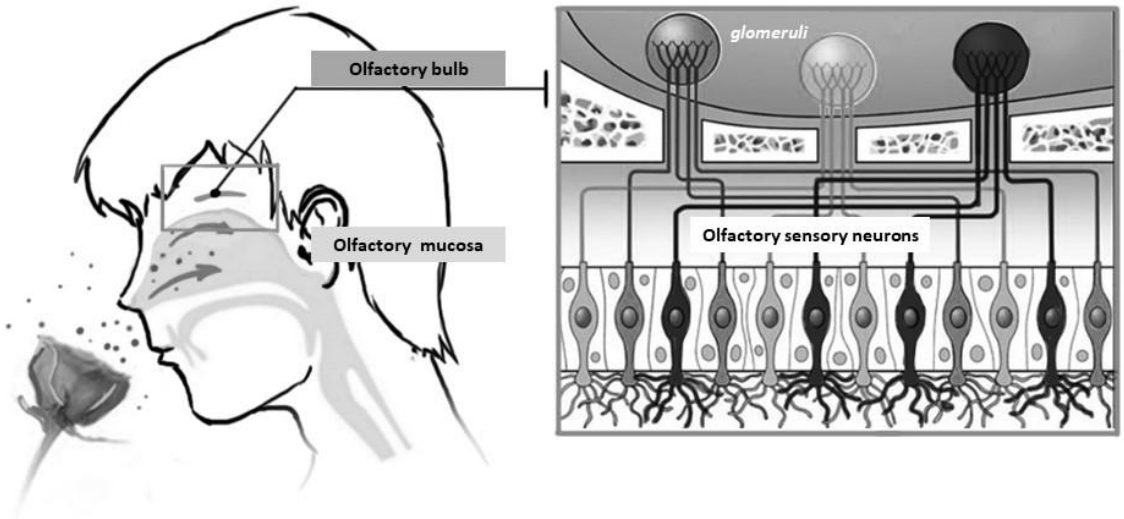

Figure 2

Figure 3: Schematic and theoretical representation of an odour-induced glomerular map (view of OB dorsal part). Glomeruli are represented by dots. No activated glomeruli remain in light grey, activated glomeruli are the black countered dots or stars; darker the dot/stars, more activated the glomerulus. By activating glomeruli, the odorant A gives birth to the left map and B, to right one. The binary mixture A+B gives birth to a glomerular map which is, either the linear addition of A and B maps (top right corner) or a recombination (lower right corner). The proposed recombination includes inhibited glomeruli (white-filled black-countered dots) as recently described by Zavitz et al., 2020 but is totally hypothetic and various other types may have been imagined.

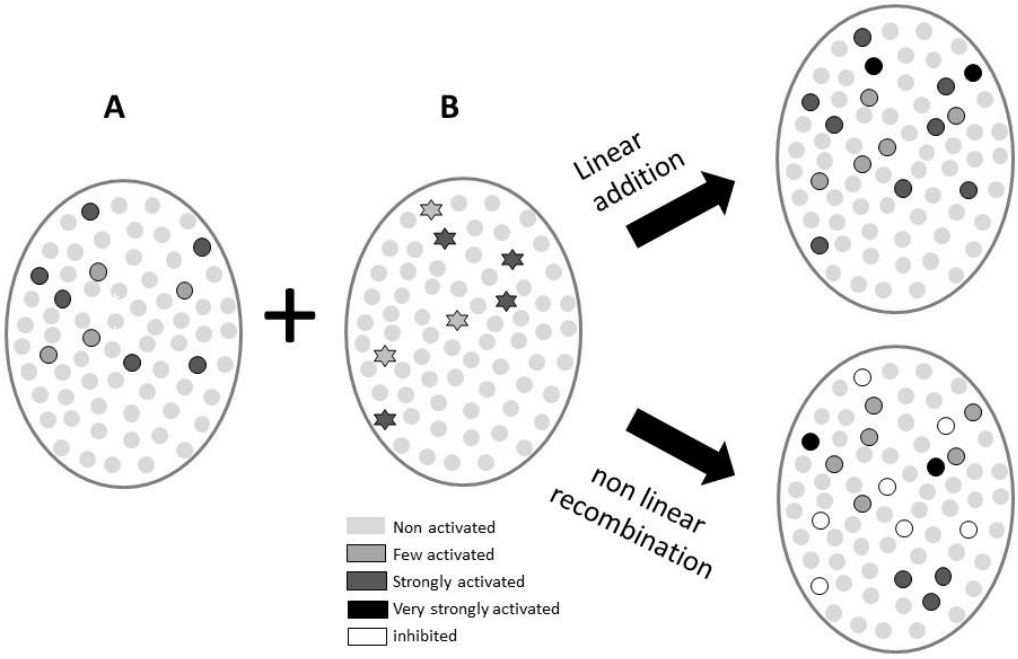

Figure 4: Illustration of the coding theory based on synchronized neural assemblies. In response to olfactory stimulus, some MTC are activated and some synchrony occurs in small fractions of spikes (black surrounded rectangle) thus defining 3 neural assemblies. Here, the code is not only defined by the activated MTCs, but also by the precise temporal sequence (black, light gray, dark grey and light gray again) in which the three assemblies intervene. The MTC synchronization is furthermore clocked on gamma OB oscillations. Such a code offers a reliable, robust, very precise and flexible code and supports the complex mixture combinatorial codes.

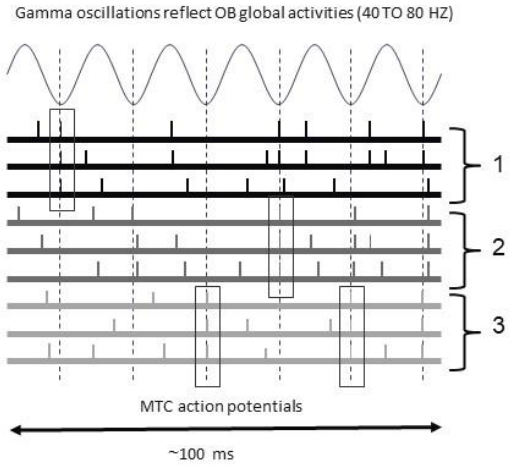
Gamma oscillations reflect OB global activities (40 TO 80 HZ)
1
2
3
MTC action potentials
~100 ms

Figure 4

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