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COMMENTARY

Biological constraints on configural odour mixture perception

G rard Coureaud^{1,*}, Thierry Thomas-Danguin², Jean-Christophe Sandoz³ and Donald A. Wilson⁴

ABSTRACT

Animals, including humans, detect odours and use this information to behave efficiently in the environment. Frequently, odours consist of complex mixtures of odorants rather than single odorants, and mixtures are often perceived as configural wholes, i.e. as odour objects (e.g. food, partners). The biological rules governing this ‘configural perception’ (as opposed to the elemental perception of mixtures through their components) remain weakly understood. Here, we first review examples of configural mixture processing in diverse species involving species-specific biological signals. Then, we present the original hypothesis that at least certain mixtures can be processed configurally across species. Indeed, experiments conducted in human adults, newborn rabbits and, more recently, in rodents and honeybees show that these species process some mixtures in a remarkably similar fashion. Strikingly, a mixture AB (A, ethyl isobutyrate; B, ethyl maltol) induces configural processing in humans, who perceive a mixture odour quality (pineapple) distinct from the component qualities (A, strawberry; B, caramel). The same mixture is weakly configurally processed in rabbit neonates, which perceive a particular odour for the mixture in addition to the component odours. Mice and honeybees also perceive the AB mixture configurally, as they respond differently to the mixture compared with its components. Based on these results and others, including neurophysiological approaches, we propose that certain mixtures are convergently perceived across various species of vertebrates/invertebrates, possibly as a result of a similar anatomical organization of their olfactory systems and the common necessity to simplify the environment’s chemical complexity in order to display adaptive behaviours.

KEY WORDS: Odour-guided behaviour, Odour object, Elemental perception, Comparative olfaction, Vertebrates, Invertebrates

Introduction

In complex sensory environments, the extraction of information is a prerequisite to survival. For adult animals, odours (see Glossary) are critically involved in behaviour but are rarely experienced as single odorants (see Glossary). Animals must rapidly extract pertinent information from the mass of environmental molecules and assign meaning to certain mixtures before responding. To cope with this complexity, the olfactory system either breaks down a complex stimulus into its elements – elemental odour perception (see

Glossary) – or combines the elements into new, synthetic information – configural odour perception (see Glossary). The elemental strategy involves responding to certain (or all of) the odorants within a mixture, i.e. to key odorants (e.g. Laloi et al., 2000; Reinhard et al., 2010) or certain pheromones (e.g. Renou et al., 2015; Wyatt, 2015). By contrast, the configural strategy results in the attribution of additional or unique information (weak or robust configural odour perception, respectively; see Glossary) to a whole mixture, which carries a value distinct from that of its component values (Kay et al., 2005; Lei and Vickers, 2008). This contributes to the elaboration of stable, background-detached representations of complex signals as meaningful objects (Stevenson and Wilson, 2007). Configural processing in olfaction may thus allow complex patterns of stimuli to be grouped into perceptual units and facilitates the representation of complex sensory ‘objects’ (e.g. partners, prey). These processes are probably vital for organisms to maintain constant perception of certain information despite changes over time (e.g. circadian, seasonal changes) and to allow individuals to focus on the most salient stimuli. These considerations about the adaptive advantages of each perception mode are largely theoretical, and key questions remain unanswered about the biological mechanisms that support elemental/configural perception, e.g. under what circumstances and through which mechanisms do complex odour stimuli constitute for the receiver a sum of elements or blend into a unique percept, and for what benefit?

Here, we begin by discussing configural processing of odour mixtures that seem to be species specific and then consider non-species-specific configural processing. Further, we present some models of configural odour perception and possible neural mechanisms underlying this perception. We conclude with perspectives on the convergent configural perception of odour mixtures between species, and future prospects for the field.

Configural odour perception in the animal kingdom

Many species of invertebrates and vertebrates show evidence of configural perception (see Table 1 for some examples). Configural processing allows behavioural responses to specific stimuli in a species-specific manner, i.e. an organism from a given species can be ‘tuned’ to respond (e.g. lay eggs, mate, feed) to a specific combination of molecules presented in a specific ratio. Thus, a mixture processed configurally by one species to evoke a particular behaviour may be processed elementally by other species and trigger no or a different behaviour.

Several factors may alter the perception of odour mixtures, although their respective roles remain to be clearly established. First, the chemical nature of the mixed odorants plays a role: with the same number of components, some mixtures are perceived configurally and others elementally, sometimes as a result of particular odorants being more salient than others (e.g. Thomas-Danguin et al., 2014). This is the case for some food aromas (Laska and Hudson, 1993). A similar effect has been found in rats, where removing an individual odorant can affect the odour quality of the whole mixture (Chapuis and Wilson, 2011). Second, the ratio of

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Glossary**Configural odour perception**

Perception of an odour mixture wherein the mixture evokes a specific odour, distinct from the odours of its individual components.

Electro-olfactograms

Negative electrical potential recorded at the surface of the olfactory epithelium. It represents primarily/exclusively the summated generator potential in the olfactory receptor neurons.

Elemental odour perception

Perception of an odour mixture wherein the perceptual quality of the mixture matches one or the other of the components, and/or allows identification of the components.

Hyper-addition

A case of odour mixture interaction observed when the magnitude of the response (sensory or electrophysiological) for a mixture is higher than the sum of responses to its components.

Hypo-addition

A case of odour mixture interaction observed when the magnitude of the response (sensory or electrophysiological) for a mixture is lower than the sum of responses to its components.

Odorant

A volatile chemical compound or mixture of chemical compounds that induces an olfactory percept.

Odour

The perceptual quality emergent from odorants. Most natural odours are composed of multiple different chemical compounds, many or all of which may have unique perceptual qualities if experienced alone.

Partial addition

A case of odour mixture interaction observed when the magnitude of the response (sensory or electrophysiological) for a mixture is higher than the response to the stronger component, but lower than the sum of responses to the components.

Robust configural odour perception

Perception of a mixture through the unique quality of the mixture itself, to the detriment of the qualities of the mixture components.

Weak configural odour perception

Perception of a mixture through the quality of the mixture itself in addition to the qualities of one or several of the mixture components.

components can affect mixture perception. For example, rats discriminate binary mixtures according to the molar ratios of their components (Kay et al., 2003), which ensures mixture recognition at higher/lower concentrations (Uchida and Mainen, 2008). The ratio of odorants in binary mixtures is also the driving factor for configural perception in insects (Clifford and Riffell, 2013), catfish (Valenticic et al., 2000) and humans (Olsson, 1998). Third, the perception of odour mixtures is affected by the number of components: humans rarely identify more than 4 odorants in a mixture (e.g. Livermore and Laing, 1998) and are thought to perceive an ‘olfactory white’ in artificial 30-component mixtures that span the physicochemical odorant space (Weiss et al., 2012). Adult rats show difficulties identifying components within mixtures including more than 3–4 components, whereas adult honeybees and newborn rabbits display higher elemental abilities (e.g. Laloi et al., 2000; Sinding et al., 2013).

The mechanisms underlying the neural processing of elemental versus configural perception remain to be clarified. Neuroanatomical similarities that exist between the olfactory systems of vertebrates and invertebrates (Hildebrand and Shepherd, 1997; Eisthen, 2002) suggest, however, that commonalities in the processing of odour mixtures may exist (Box 1).

In summary, specific mixtures are perceived as the sum of odour elements, whereas others are perceived as configural odour objects in terrestrial/aquatic vertebrates and invertebrates, which present remarkable similarities in their olfactory architecture. Could there be

common rules for complex odour processing across animals? Below, we consider work that has recently addressed this question by studying configural perception of the same mixtures in five different species.

Non-species-specific configural processing

Cross-species analyses of defined perceptual functions can provide unique insights to the basic processes underlying critical behaviours (Jourjine and Hoekstra, 2021). We have used behavioural assays that differ between species in order to test the robustness of the suspected inter-species conservation of configural perception. Here, we summarize the main findings obtained so far and their generalization.

A model binary mixture, the AB mixture

We explored configural processing primarily using the binary AB odour mixture, which has been designed to evoke configural perception in human adults, i.e. the perception of a pineapple odour completely different from the odours of the components A (ethyl isobutyrate, strawberry odour) and B (ethyl maltol, caramel odour). The perception of AB was compared between humans, rabbits, rodents and bees, despite the lack of known biological significance in the non-human species. The goal was to evaluate whether AB could, by its physicochemical properties, generate configural perception not only in humans but also in the other species.

Experiments in humans

As in every species, humans are exposed to odour cues that support the categorization of objects and detection of noxious sources or environments, and contribute to driving behaviours such as food choices (Prescott, 2015) and inter-personal communication (de Groot et al., 2017). Because most of these odours rely on the perception of complex mixtures of odorants, we have been developing a series of experiments to gain insight into the processing of odour mixtures.

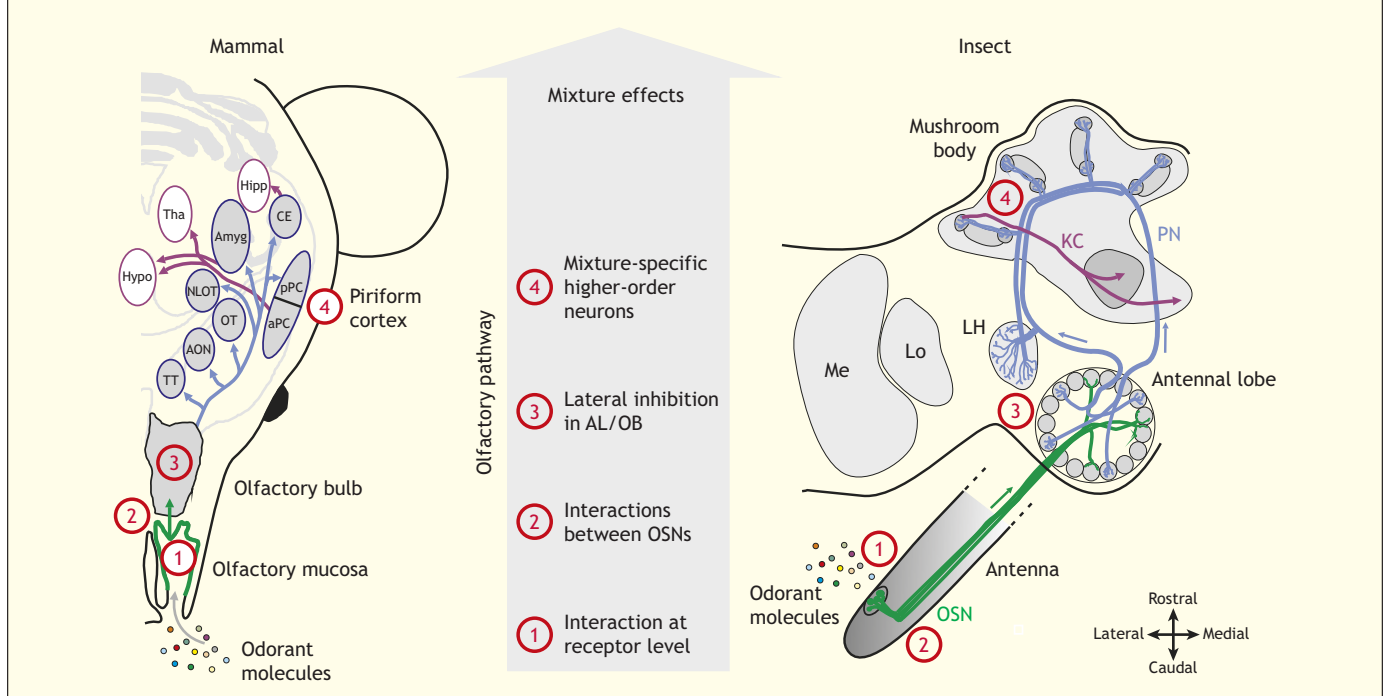
As configural processing should confer on a mixture an odour quality that is not (or is less) present in the components, the sensory paradigm used was based on a typicality rating task with the pineapple odour as the target for the AB mixture (Le Berre et al., 2008a, 2010; Barkat et al., 2012). Participants had to rate typicality of distinct stimuli, delivered by a static olfactometric method, according to the following question: ‘is this odour a good or a poor example of the odour of pineapple?’.

The AB mixture, at the specific 30/70 ratio of A/B, evoked an odour quality more typical of pineapple than of its components (Fig. 1A) (Le Berre et al., 2008a). Not all mixtures of fruity and caramel odours produced the configural perception of pineapple. Indeed, in a binary mixture of ethyl caproate (fruity green-banana odour) and furaneol (caramel odour), the pineapple odour typicality of ethyl caproate itself was actually the highest (Fig. 1B) (Barkat et al., 2012). Moreover, a very small variation of component proportions impaired the mixture configuration and induced a decrease in pineapple typicality (Le Berre et al., 2008a).

These results underline the specificity of configural odour processing as a function of the stimulus chemical features. Humans’ perceptual experience/expertise and attentional processes can also modulate configural processing (Le Berre et al., 2008b; Barkat et al., 2012; Sinding et al., 2015). For instance, pre-exposure to the single components A and B further altered configural processing of the AB mixture, a result not found after pre-exposure to control components or mixtures (Fig. 1C) (Sinding et al., 2015).

Box 1. Organisation of the olfactory system in vertebrates and in invertebrates and possible neural structures involved in configural processing

In the figure, numbers indicate structures/neurons where mixture-specific properties can emerge (see 'Potential neural mechanisms underlying configural processing' for details). During olfaction, odorants are sampled by olfactory receptors (ORs) located in the cilia of olfactory sensory neurons (OSNs) in the olfactory epithelium of vertebrates or cuticular sensilla of insects (ORs from mammals and insects belong to different receptor families). In the brain, OSNs enter the olfactory bulb (OB; in mammals) or antennal lobe (AL; in insects) and connect with second-order neurons [the mitral cells (mammals) or projection neurons (insects)] (Buonviso and Chaput, 1990; Vosshall et al., 2000). OSNs expressing the same OR converge onto the same glomerulus, giving rise to odorant-specific maps in the OB/AL (Joerges et al., 1997; Johnson and Leon, 2007; see also Friedrich and Korsching, 1997, for results in fishes). Regarding superior brain areas, mammalian mitral cells project mainly to the anterior olfactory nucleus, anterior and posterior piriform cortex (aPC, pPC), lateral entorhinal cortex and amygdala (Mori and Sakano, 2011). In insects, higher-order centres comprise the mushroom bodies (MBs) and the lateral horn (Mobbs, 1982; Jefferis et al., 2007). The MBs are composed of numerous intrinsic neurons, the Kenyon cells, which are each highly selective to the activation of a different combination of projection neurons (Perez-Orive et al., 2002). Thus, the architecture of the olfactory system presents similarities in vertebrates and invertebrates from the periphery to higher-order levels. Hipp, hippocampus; Tha, thalamus; Amyg, amygdala; Hypo, hypothalamus; NLOT, nucleus of the lateral olfactory tract; OT, olfactory tubercle; AON, anterior olfactory nucleus; TT, taenia tecta; KC, Kenyon cells; PN, projection neuron; LH, lateral horn; Lo, lobula; Me, medulla.



Experiments in rabbits

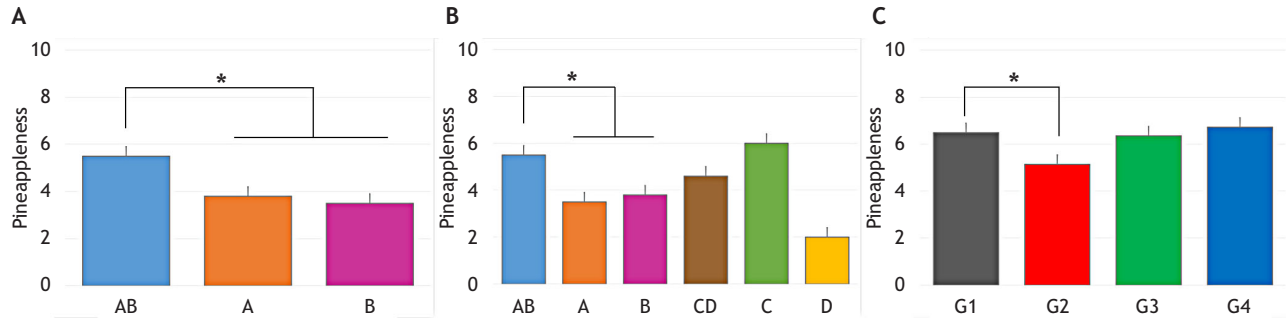
Olfaction allows rabbit neonates to suck during the once per day nursing (Zarrow et al., 1965; Hudson and Distel, 1982). The mammary pheromone (MP; 2-methylbut-2-enal) emitted by adult females triggers neonatal orocephalic movements used for nipple location/seizing (e.g. Coureaud, 2001; Coureaud et al., 2010; Schaal et al., 2003). The MP is perceived among

150 volatiles that compose the rabbit milk, which highlights the ability of pups to perceive at least some mixtures elementally. Moreover, as the MP promotes the learning of new odours through single-trial associative conditioning (Coureaud et al., 2006), we used it to induce learning by the pups of odorants A and B, and of mixtures of A/B, before later testing their orocephalic responsiveness.

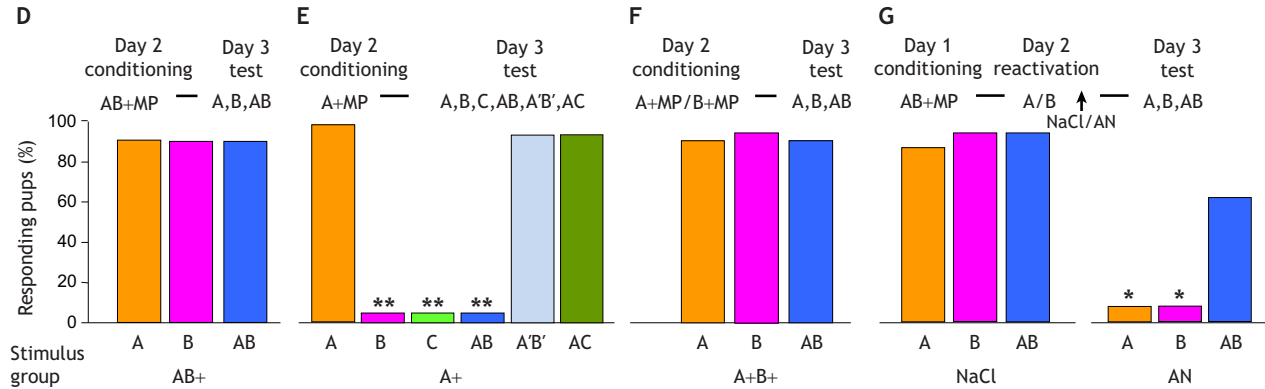
Table 1. Examples of configural odour processing in invertebrates and vertebrates

	Species	Behavioural context	Reference
Invertebrates	Bumblebees	Attraction to plants	Byers et al., 2014
	Braconid wasp	Host location/parasitism	Morawo and Fadamiro, 2016
	Fruit fly	In-flight orientation	Kundu et al., 2016
	Honeybee	Flower discrimination	Wright et al., 2002
	Moth	Pollination	Riffell et al., 2009
	Spiny lobster	Feeding	Fine-Levy et al., 1989
Vertebrates	Terrestrial slug	Aversive guidance	Hopfield and Gelperin, 1989
	Catfish	Food searching	Valentincic et al., 2000
	Humans	Coffee flavour detection	Czerny et al., 1999
	Humans	Food categorization	Gottfried, 2009
	Military dogs	Explosive detection	Lazarowski and Dorman, 2013
	Rat	Foraging	Linster and Smith, 1999

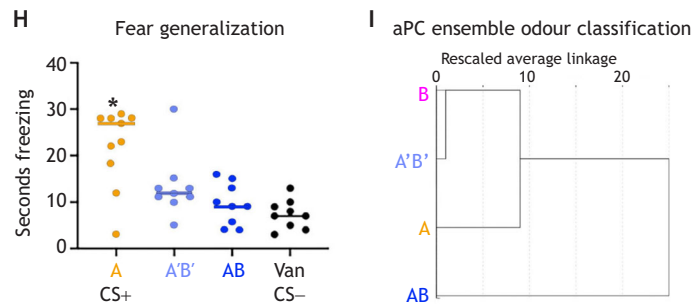
Humans



Rabbits



Mice



Honeybees

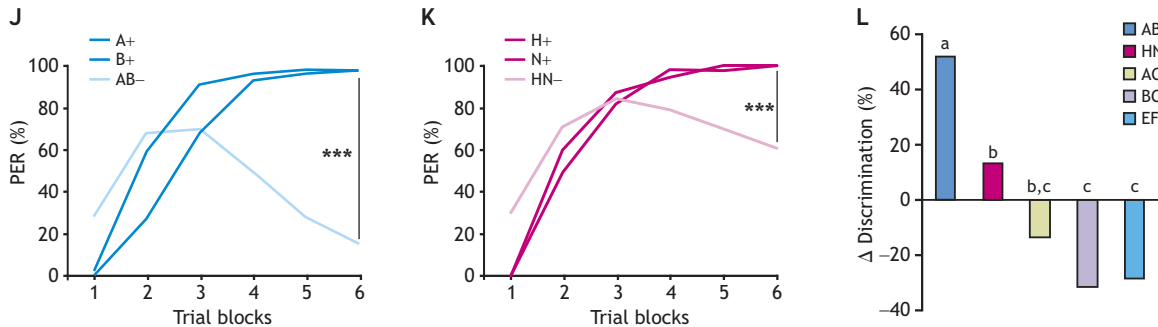


Fig. 1. Demonstration of configural perception of the AB mixture in four different species. In humans: (A) mean pineappleness of the AB mixture compared with its components; (B) replication including the CD mixture (ethyl caproate+furaneol); (C) mean pineappleness of AB in participants pre-exposed to AB (group G1), A and B separately (G2), a control mixture (G3), or the components of the control mixture (G4). In rabbits: (D,E,F) proportions of rabbit pups responding orally to odorants A, B or C and to the AB, A'B' or AC mixtures 24 h after the learning of AB (D), A (E) or A then B (F); (G) responses 48 h after the learning of AB then re-exposure to A and B followed by NaCl or anisomycin (AN) injection. MP, mammary pheromone. In mice: (H) freezing of mice exposed to the conditioned stimulus (CS)+ odorant A, the elemental mixture A'B', the configural mixture AB, and the CS- odorant vanillin (Van); (I) hierarchical cluster analysis of mouse single-unit ensembles recorded in the anterior piriform cortex (aPC) after exposure to A, B, the AB mixture or the A'B' mixture (similar results were observed in rats, not shown). In honeybees: (J,K) proboscis extension responses (PER) in a protocol in which bees received rewarded presentations of mixture components (A/B, or hexanol/nonanol H/N) but non-rewarded presentations of the mixture (AB or HN); (L) comparison of differentiation scores (sum of responses to the rewarded elements minus those to the mixture over the whole procedure) for the AB and HN mixtures, and the control AC, BC and EF mixtures. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

The AB mixture appeared to be perceived configurally in pups at the same 30/70 ratio as in humans: after conditioning to AB, the pups responded to both AB and its components (Fig. 1D), whereas after conditioning to A they responded to A (not to B or C; where C is guaiacol), A'B' (68/32 A/B ratio) and AC, but not to AB (Fig. 1E) (Coureaud et al., 2008, 2009, 2011; Sinding et al., 2011). The pups therefore perceive AB in the weak configural way (perception of 3 cues: the AB odour in addition to the A and B odours) and A'B' and AC in the elemental way (perception of 2 cues only: the element odours). After conditioning to A, the pups did not respond to AB because it included 2 unfamiliar cues (out of 3) compared with A'B' and AC (1 out of 2); conversely, when conditioned to AB, the pups learned the 3 cues and could later respond to the mixture and its elements. After learning of A then B, the pups responded to AB (Fig. 1F) because they knew 2 of the 3 mixture cues (Coureaud et al., 2008).

The weak configural perception of AB has been confirmed (1) behaviourally: after conditioning to AB, pups displayed a longer memory of A and B compared with the AB configuration (Coureaud et al., 2014b); (2) pharmacologically: after conditioning to AB, reactivation of the memory of A and B, then injection of anisomycin (a blocker of reconsolidation), pups became amnesic for A and B but still responded to AB (Fig. 1G); with A'B', the same experiment ended with no response to A, B or A'B'. This demonstrated the independent perception and memory of the AB configuration compared with the A/B components, although A'B' was perceived and retained as its components (Coureaud et al., 2014a).

Recent results highlight that the perception of AB changes from weak to robust configural between postnatal days 2 and 9, whereas that of A'B' becomes weak configural at postnatal day 24, i.e. close to weaning (Coureaud et al., 2020).

Experiments in mice and rats

Rodents have been used extensively for understanding odour perception and memory. They have excellent odour discrimination ability (Laska and Shepherd, 2007), though rodent odour discrimination is shaped by both past experience (Chapuis and Wilson, 2011; Chen et al., 2015; Rabin, 1988) and the nature of the odour discrimination assay (Cleland et al., 2002). Discrimination of odour mixtures from each other and from their components by rodents is influenced by the identity and relative proportions of the molecules involved in the mixture (Kay et al., 2003).

Evidence for configural processing of the AB mixture (30/70 A/B ratio) has been found in mice using a standard odour-specific fear conditioning task with odour A as the CS+ (i.e. predicts shock). Animals froze significantly more in response to A than to the configural odour AB, with some generalization to the elemental odour mixture A'B' (68/32 A/B ratio) (Wilson et al., 2020) (Fig. 1H). Similarly, single-unit neural ensembles in the anterior piriform cortex (aPC) – a region critically involved in odour perception and configural processing (Gottfried, 2010; Wilson and Sullivan, 2011) – processed AB as distinct from both A'B' and the components A and B as assessed with hierarchical cluster analysis in both rats and mice (Wilson et al., 2020) (Fig. 1I). Interestingly, this pattern was not observed in posterior piriform cortical ensembles, consistent with the known distinct roles of the anterior and posterior piriform in odour processing (Kadohisa and Wilson, 2006; Howard et al., 2009).

Similar results were found with odour habituation/cross-habituation assays (Coureaud and Wilson, 2019), a procedure widely used as a metric of odour discrimination (e.g. in humans: Rabin, 1988; Goyert et al., 2007; in rodents: Fletcher and

Wilson, 2001; Cleland et al., 2002). The rate of habituation can also be used to extract information about the stimulus. For example, in both humans (Caron and Caron, 1968, 1969; Cohen et al., 1975; Hunter et al., 1982) and animal models (Brennan et al., 1984), the rate of habituation is shaped by stimulus complexity: perceptually more complex stimuli induce slower habituation. We hypothesize that an odour perceived configurally should induce more rapid habituation than an odour perceived elementally. In fact, in mice, the rate of habituation to the elemental A'B' mixture was significantly slower compared with that to the configural AB mixture (Coureaud and Wilson, 2019). Thus, the more rapid habituation to AB is consistent with the hypothesis of a configural perception of AB (i.e. simple stimulus) and elemental perception of A'B' (i.e. complex stimulus). These results also suggest that associative training or familiarity are not required for the expression of this perceptual discrimination between these two mixtures.

Experiments in honeybees

Configural processing of olfactory mixtures in honeybees has been demonstrated using Pavlovian conditioning of the proboscis extension response (Bitterman et al., 1983; Menzel, 1999; Giurfa and Sandoz, 2012), in which bees learn to associate odours (conditioned stimulus, CS) with a sucrose reward (unconditioned stimulus, US). Negative patterning, a special type of differential conditioning task, involves discriminating between a binary mixture and each of its components. In this procedure, two odorants are rewarded when presented alone (X+, Y+) but not when presented in a mixture (XY–; Deisig et al., 2001). Negative patterning is a difficult task for bees and only a small proportion manage to differentiate the stimuli at the end of training (Deisig et al., 2001, 2002, 2003; Komischke et al., 2005; Devaud et al., 2015). Indeed, each element (X or Y) is presented as often with the sucrose reward as without, so configural processing of the mixture is necessary to solve this task (Deisig et al., 2001; Devaud et al., 2015). Recently, bees' negative patterning performances were compared between AB (91/9 – the ratio was adapted so that bees detected the two components equally well) and a list of control mixtures (Wycke et al., 2020).

The control mixtures included two mixtures known to be elementally perceived in newborn rabbits: AC (67/33 ethyl isobutyrate and guaiacol) and BC (17/83 ethyl maltol and guaiacol) (Coureaud et al., 2009); and two mixtures often used in bees (Guerrieri et al., 2005; Schubert et al., 2015): HN (50/50 1-hexanol and 1-nonanol) and EF (50/50 2-octanone and octanal). The conditioning procedure included 6 blocks of 4 trials. In each block, bees received a presentation of each single odorant alone with a reward and two unrewarded presentations of the mixture (1A+, 1B+, 2AB–). In the case of the AB mixture (Fig. 1J), bees quickly differentiated between the components and the mixture. At the end of training, responses to AB were much lower than responses to A and B. These performances were compared with those obtained with the four other mixtures. The second-best performances were observed with the HN mixture (Fig. 1K). At the end of training, the bees responded more to the elements than to the mixture, but differentiation was less marked than for the AB mixture. Likewise, for the 3 other mixtures, differentiation at the end of training was generally low or non-existent. The amount of differentiation observed between the elements and the mixture throughout the training [responses to the components (CS+) minus responses to the mixture (CS–)], was higher for AB than for all other tested mixtures (Fig. 1L). The same was observed when comparing differentiation at the end of training. Thus, in honeybees

too, the mixture of A and B has remarkable qualities which suggest configural processing of this mixture.

Generalization of the results

In humans and rabbits, results very similar to those observed with the AB mixture have been obtained with a senary mixture. This mixture, robust-configurally perceived in humans (called RC because it smells like red cordial) is perceived in the weak configural mode in rabbit pups at the same ratio of odorants as in humans (Sinding et al., 2013; Romagny et al., 2014, 2018; Coureaud et al., 2020). Whereas the 6 odorants appear to contribute equivalently to the configural perception of RC in rabbits (Romagny et al., 2014), in humans, 2 odorants mainly contribute to it (Romagny et al., 2018). The fact that a limited number of key odorants may promote configural perception has also been shown in psychophysical human food studies (e.g. Rochelle et al., 2018).

Theoretical models of configural odour processing

Two main models have been proposed to explain configural odour perception (Harris, 2006). The unique-cue theory proposes that an XY mixture activates the representations of the X and Y elements but also of a 'U' (unique cue) percept, specific to the mixture (Rescorla et al., 1985). During learning, X, Y and U separately receive associative strength, allowing the animal to differentiate between mixtures and elements. Another theory (Pearce, 1994) states that the mixture gives rise to a single configural unit 'XY', and does not evoke elemental units. During learning, animals may respond to the X/Y elements through a generalization rule.

Our experiments generally support the unique-cue theory, which predicts that during conditioning to the AB mixture, three main units A, B and U are engaged. In rabbits, after conditioning to AB, pups distinctively retain AB compared with A and B, and A and B can be forgotten but not AB (Coureaud et al., 2014a,b). In humans, the configural perception of AB is lower after learning of its odorants, suggesting that the subjects' attention is then mainly focused on the elements' odours (Le Berre et al., 2008b). Behavioural work in honeybees also supports the unique-cue account (Deisig et al., 2003; Lachnit et al., 2004) and imaging experiments show that before any training, the neural representation of a mixture XY is not the pure sum of the representations of X and Y (Deisig et al., 2006; Chen et al., 2015). This difference may be used by the brain as a unique cue. As associative learning modifies odorant representations in the bee brain (Faber et al., 1999; Sandoz et al., 2003; Fernandez et al., 2009; Chen et al., 2015; Locatelli et al., 2016), the particular treatment of AB observed in our negative patterning experiment may result from learning-induced plasticity. A similar explanation could support the mouse fear conditioning results and piriform mixture coding.

According to Pearce's theory, mixtures are represented as single configural units, which can support rapid acquisition of mixture-specific behaviours (Pearce, 1994). Some of our results fit into this framework. Thus, humans spontaneously perceive a pineapple odour in the AB mixture, distinct from the strawberry/caramel odours of A/B (such distinction does not appear with other binary mixtures, or senary mixtures in Sinding et al., 2013). In rabbits, after single conditioning to A, pups do not respond to AB, suggesting spontaneous perception in the mixture of a cue different from the sum of its elements. Similarly, the habituation rate shows different processing of the AB and A'B' mixtures in mice, with the simpler configural mixture inducing more rapid habituation than the elemental one.

Actually, we propose that odour mixture processing could lie in between the two theoretical frameworks. Thus, because of the stimulus properties (e.g. structural features of odorants targeting specific olfactory receptors, concentration of odorants shaping receptor response) and/or coding processes, some mixtures would be perceived elementally and others configurally. Then, under the effect of experience and odour learning/attentional processes, the initial perception may be tuned to either the elements or the configuration. In this respect, it has been shown in rats with mixtures other than AB/A'B' that elemental perception can be conditioned such that sniffing can modulate which odours in a mixture are perceived, i.e. that the physical properties of both the odorants and the mucosa contribute to the ease with which odorants can be detected in a mixture (Rojas-Libano and Kay, 2012). Ultimately, odour mixture processing may allow organisms to decrease environmental complexity by building experience-dependent perceptual associations (e.g. Wilson and Stevenson, 2003; Deisig et al., 2003; Gerber et al., 2011; Coureaud et al., 2014a).

Potential neural mechanisms underlying configural processing

The neural substrates underlying configural perception remain to be clearly determined, though some clues exist at different levels within the olfactory system.

At the periphery, each olfactory receptor (OR) and olfactory sensory neuron (OSN) responds to a variety of odorants so that molecular identity is encoded by the combination of activated ORs/OSNs (e.g. Malnic et al., 1999; Duchamp-Viret et al., 2000). The overlapping responses and proximity of OSNs favour interactions during mixture processing. Electrophysiological comparisons between OSN responses to mixtures versus their components have revealed diverse interactions, such as hypo-addition, partial addition, hyper-addition (see Glossary), inducing inhibition or enhancement effects reconcilable with perception in a variety of species (e.g. Ache et al., 1988; Chaput et al., 2012; El Mountassir et al., 2016), including insects (e.g. Akers and Getz, 1993; Ochieng et al., 2002; Su et al., 2011; Deisig et al., 2012). Single sensory cell responses (Xu et al., 2020; Pfister et al., 2020; Rospars et al., 2008; Singh et al., 2019) highlight that interactions occurring at the OR level (Box 1, interaction 1) can account for interactions at the OSN level, and contribute to receptor-mediated computation of mixture information in the olfactory epithelium prior to transmission to the olfactory bulb. This would enhance the capacity of the olfactory system to discriminate between some mixtures and their components (Kurian et al., 2021).

In newborn rabbits, recent recordings of electro-olfactograms (EOG; see Glossary) in olfactory turbinates suggest that the configural AB mixture is differently processed by ORs compared with the elemental A'B' and AC mixtures (Duchamp-Viret et al., 2021). Direct mixture-related interactions at the OR are presumably related to the physicochemical features of the odorants (Sanz et al., 2008); therefore, diverse species sharing homologous ORs or presenting similar response spectra may show similar mixture interaction patterns at the olfactory periphery and thus similar constraints on mixture perception. Although this explanation could theoretically apply for insects, insect ORs belong to a completely different receptor family (Benton, 2006). Therefore, if this hypothesis holds for both mammals and insects, evolutionary convergence in the response ranges of their ORs responding to the AB mixture should be invoked.

In addition, interactions between peripheral neurons, in particular OSNs housed within the same sensillum, exist in insects (Box 1,

interaction 2). For instance, inhibition between adjacent OSNs, without the use of chemical synapses, has been observed in *Drosophila* (Su et al., 2012). Thus, unique encoding of mixtures similar to the ligand–ligand interactions evoked above may take place within an insect sensillum. Interactions between mammalian OSNs can also occur through ephaptic interactions between axons as they pass to the olfactory bulb (Blinder et al., 2003), which could serve a similar function.

More centrally, input from different ORs converges, directly or indirectly, which may be critical for odour mixture processing (Wilson and Sullivan, 2011). Within the olfactory bulb (OB)/antennal lobe (AL) of mammals/insects (Box 1, interaction 3), lateral inhibition modifies the information projected to higher-order areas and therefore contributes to mixture representation (Dulac, 2006; Deisig et al., 2010; Szyszka and Stierle, 2014). The ratio of configural mixtures is also coded in the AL in some insects (Lei et al., 2013). In mammals, mitral/tufted OB cells respond to odorants alone or in mixtures, but the firing rates evoked by mixtures (compared with elements) are partially suppressed (Kadohisa and Wilson, 2006; Davison and Katz, 2007). Inhibition may result from overlapping activation patterns favoured by the physicochemical similarity between mixed odorants (Grossman et al., 2008). Moreover, perceptual responses rely not only on which specific ensemble of cells is activated but also on the relative temporal sequence of cell activation (Chong et al., 2020). In line with configural processing, computational modelling suggests that mixing odorants with similar glomerular patterns results in lateral inhibition, leading to information loss about the odorants which could favour specific bulbar activation and coding for the mixture by itself (Linster and Cleland, 2004). Such phenomena may explain why, in pseudo-conditioned rabbit pups, the AB and A'B' mixtures induce similar activation in the OB glomerular layer, although AB induces higher activation than A'B' in the granular layer (Schneider et al., 2016). Moreover, in pups conditioned to B, AB induces higher activation than A'B' at the glomerular level, and the opposite at the granular level (Schneider et al., 2016). In the AL of honeybees and fruit flies, processing by local neurons changes mixture glomerular activity maps so that they are more different from those of the components at its output (projection neurons) than at its input (Deisig et al., 2006, 2010; Silbering and Galizia, 2007).

Mixture-specific representations can be found in higher-order centres (Box 1, interaction 4); for instance, in the olfactory cortex (e.g. Litaudon et al., 1997; Wilson, 2003; Barnes et al., 2008; Bekkers and Suzuki, 2013). Piriform cortical neurons can discriminate a mixture from its components in adult mammals, while the OB still computes the mixture as the sum of odorants (rats: Wilson, 1998, 2000). More precisely, the aPC and posterior piriform cortex (pPC) can respectively encode odorant identity and similarity/quality (rats: Kadohisa and Wilson, 2006; humans: Gottfried, 2009, 2010; Howard et al., 2009). The ensemble single-unit data from rodents suggest that the unique quality of the configural mixture is differentially encoded in the aPC. Similarly, in newborn rabbits, the piriform cortex is distinctively activated by the configural/elemental AB/A'B' mixtures, although the configural/elemental distinction occurs in both aPC and pPC (Schneider et al., 2016). In humans, recent functional magnetic resonance imaging data obtained using the configural AB mixture suggest the specific involvement of the left orbital part of the inferior frontal gyrus in configural processes (Sinding et al., 2021). In insects, the mushroom bodies, which house neurons (Kenyon cells) that are only activated by concomitant patterns of second-order neurons from the AL, may present configural units activated

only by a mixture and not by its components (Sandoz, 2011), supporting successful performance in configural learning tasks (see also Devaud et al., 2015). Such units could be especially numerous in the case of the AB mixture, allowing high discrimination performance.

Conclusions

How odour mixtures are perceived, and whether there are general rules across species regarding elemental and configural mixture processing, is poorly understood despite the biological relevance of these questions. The comparative approach reviewed here has identified that the same AB mixture triggers the perception of a particular odour quality different from the qualities of its elements in various phyla: lagomorphs, rodents, primates and insects. The results are expressed regardless of the behavioural assay. Moreover, the AB mixture does not have any known intrinsic biological value, except in humans, where it was designed to generate the perception of pineapple. These findings support convergence in configural perception in both vertebrates and invertebrates, at least in the species described here, and lead us to hypothesize that physicochemical properties of some odorants (e.g. chemical family, concentration, volatility) and component ratios promote configural processing at the receptor and/or central circuit level, whereas other odorants do not.

More generally, we propose that organisms from different phyla, exposed to similar constraints during development at the individual level, and during evolution at the species level, may have conserved important neurophysiological mechanisms to efficiently process odour mixtures. Such mechanisms would support the decrease of perceptual complexity of the chemosensory environment and enhance the ability of organisms to behave selectively toward social and non-social odours contributing critically to their adaptation. This may explain why different species present converging traits in the way they perceive the same mixtures of odorants. Further experiments are required to precisely understand this processing of odour mixtures in the animal kingdom, and the diverse fascinating ways species, including humans, represent by smell the world in which they are living.

Competing interests

The authors declare no competing or financial interests.

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