Elemental and configural processing of odour mixtures in the newborn rabbit

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SUMMARY

The processing of odour mixtures by young organisms is poorly understood. Recently, the perception of an AB mixture, known to engage configural perception in adult humans, was suggested also to be partially configural in newborn rabbits. In particular, pups did not respond to AB after they had learned A or B. However, two alternative hypotheses might be suggested to explain this result: the presence in the mixture of a novel odorant that inhibits the response to the learned stimulus, and the unevenness of the sensory and cognitive processes engaged during the conditioning and the behavioural testing. We conducted four experiments to explore these alternative hypotheses. In experiment 1, the learning of A or B ended in responses to mixtures including a novel odorant (AC or BC). Experiment 2 pointed to the absence of overshadowing. Therefore, a novelty effect cannot explain the non-response to AB after the learning of A or B. In experiment 3, pups having learned A or B in AC or BC did not respond to AB. However, they generalized odour information acquired in AB to AC or BC in experiment 4. Thus, the balancing of the perceptual tasks between the conditioning and retention test does not enhance the response to the AB mixture. To sum up, the present experiments give concrete support to the partially configural perception of specific odour mixtures by newborn rabbits.

Key words: neonatal behaviour, appetitive learning, configural perception, olfaction, blending mixture, mammary pheromone, rabbit.

INTRODUCTION

The olfactory system can solve complex computational problems in which complex chemosensory signals are transformed into information used to guide actions. Beyond olfactory discrimination, concentration-invariant recognition and mixture segmentation are examples of such computations. However, these computations remain poorly characterized at the behavioural level, and weakly investigated both in terms of development and at the neural level (Mainen, 2006).

Complex stimulus representations have been described in several modalities and different theoretical proposals have been put forward to describe the underlying mechanisms (for a review, see Harris, 2006). According to elemental theories (e.g. stimulus sampling theory, Rescorla-Wagner model) stimulus patterns are composed of elemental units, each of them entering potentially into an associative structure during associative learning. Alternative configural theories (e.g. replaced elements theory, Pearce's configural model) treat stimulus patterns as distinct configurations, so that when an association occurs it operates on the configuration as a whole (and not on its components). An intermediate approach combines aspects of both theories and adopts an elemental framework to explain the interaction between stimulus representations and associations, but incorporates the notion that mixtures of two or more stimuli are represented by a configural element unique to the mixture in addition to the individual elements that constitute the stimuli.

Within the olfactory modality, the perception of odours as individual odorants or mixtures appears partially modified by the life-history of the organism, by its experience (e.g. pre-exposure, classical conditioning). In that point of view, several phenomena have been described as influencing olfactory perception, e.g. blocking effect, feature-positive design or external inhibition (Pearce, 1987). Apart from these phenomena linked to experience,

the processing of odorants in mixtures may also result from perceptual interactions that probably occur during olfactory information processing. Thus, overshadowing or odour blending have been suggested to happen both in animals and humans (Laing and Jinks, 2001; Dreumont-Boudreau et al., 2006).

Some researches have focused on the behavioural consequences of these perceptual interactions of odours, with the aim of improving the understanding of odour-guided behaviour in the natural environment (Derby et al., 1996; Valentincic et al., 2000; Wiltrout et al., 2003; Kay et al., 2005; Deisig et al., 2006). Indeed, chemosensory signals are often present in nature as, or in, complex mixtures. In the ecological context, it has been suggested that the perception of odour mixtures is elemental (analytical) or configural (configurational, synthetical) (Kay et al., 2005; Harris, 2006; McNamara et al., 2007). Elemental processing refers to the in-mixture perception of the specific odour of each constituent (Laing et al., 1989; Laska and Hudson., 1993; Wiltrout et al., 2003; Linster and Cleland, 2004). Conversely, configural processing occurs when the mixture's odour differs from those of the single odorants (Kay et al., 2005; Derby et al., 1996; Smith, 1996; Jinks and Laing, 1999; Valentincic et al., 2000). In this latter case, it has even been proposed that the mixture may give rise to a novel perceptual odour quality (Jinks and Laing, 2001; Thomas-Danguin et al., 2007). Indeed, for certain mixtures of two or three odorants, very precise ratios of the components release an odour blending process in humans, i.e. a process leading to the perception of the mixture's odour as more typical of a target odour as compared to the odour of each constituent (Le Berre et al., 2008a; Le Berre et al., 2008b). Linster and Smith (Linster and Smith, 1999) performed a series of experiments in adult rats which aimed to examine the assumption that binary odour mixtures are perceived as novel qualities that are totally independent of their components. The results indicate that some mixtures retain

adults as a result of odour-blending (Thomas-Danguin et al., 2007; Le Berre et al., 2008a). Mixtures AC and BC included 0.5×10^{-5} g ml^{-1} of odorant A or B, and 0.5×10^{-5} g ml^{-1} of odorant C, respectively. This 50:50 v/v ratio was chosen since it does not generate any blending phenomenon in humans (Atanasova et al., 2005) (unpublished preliminary data confirmed the heterogeneous perception of this mixture, i.e. the perception of both components at this ratio). Behavioural assays were run with the same solutions as those prepared for the conditioning.

Odour conditioning and behavioural assay

The conditioning sessions and behavioural (retention) assays were run in a room isolated from the breeding room. The pups from a same litter were transferred into a box lined with nest materials and maintained at room temperature for the duration of the conditioning or the assay (10 min maximum).

The MP-induced conditioning was carried out on 2-day-old pups, following a procedure previously described (Coureaud et al., 2008). Two millilitres of the MP-single odorant or MP-binary mixture blends were pipetted on a pad (19 cm $\times$ 14 cm, 100% cotton), then held 2 cm above the litter for 5 min. Five minutes after the end of the conditioning, the pups were individually marked (with scentless ink) and returned to their nest for 24 h. The box containing the litter was rinsed with alcohol and distilled water after each conditioning.

The behavioural assay consisted in an oral activation test (Schaal et al., 2003; Coureaud et al., 2006; Coureaud et al., 2008) during which the pup was immobilized in one hand of the experimenter, its head being left free. The test odour was presented for 10 s with a glass rod 0.5 cm in front of the nares. A test was considered positive when the stimulus elicited head searching movements (vigorous, low amplitude horizontal and vertical scanning movements of the head, displayed after stretching of the neck toward the rod) eventually followed by oral grasping movements (labial seizing of the rod extremity). Non-responding pups displayed no response other than sniffing the stimulus. Each pup participated in only one experiment, but was successively tested for its responses to three or four stimuli. The successive testing involved the presentation of a first stimulus to all the pups from a same litter, then a second stimulus and so on, with an inter-trial interval of 120 s. If a pup responded to a stimulus, its nose was softly dried with absorbing paper before the next stimulation. The order of stimuli presentation was adjusted so that the MP was always applied last, as a control. As the level of response to the MP was always high in these present experiments (range: 92.3–100%), the pups were considered awake and at the similar state of general responsiveness during the testing of our different groups.

To minimize litter effects, each experimental group was drawn from four to six litters, with a maximum of five pups conditioned and/or tested per litter. No litter effect appeared in each group exposed to the different stimuli [$\chi^2 \leq 4.53$, d.f.=4, $P \geq 0.34$ in all comparisons by generalized estimating equations (GEE) modelling of binomial data (SAS v. 9, SAS Institute INC., Cary, NC, USA)]. The conditioning and testing was always run in the morning, 1–2 h before the daily nursing, to equalize the pups' motivational state and limit the impact of satiation on the response (Montigny et al., 2006).

Statistics

As the comparisons concerned dependent variables, i.e. rates of responses of pups from the same group tested with several stimuli, the frequencies of responding newborns were compared using the Cochran's Q test (multiple comparisons) or χ^2 test of McNemar

(2×2 comparisons). Degrees of freedom were indicated when more than one. Data were regarded as significant when the two-tailed tests ended with $P < 0.05$.

RESULTS
Experiment 1: evaluation of the novelty effect

To investigate whether the presence of a novel odorant in a binary mixture restrains the response to the mixture despite the presence of another odorant previously learned, 26 and 25 pups (from six and five litters), respectively, were exposed to MP-A (group 1) and MP-B (group 2) and tested the day after for their response to A+ (the conditioned stimulus), C and AC (group 1) or B+, C and BC (group 2). This experiment should also permit to evaluate the non-blending properties of AC and BC for rabbit pups.

Pups from the group 1 responded differently to the three stimuli (Q=29.8, d.d.l.=2, $P < 0.001$), displaying a high responsiveness to A+ (69.2%), no response to C, and an equivalent responsiveness to AC (73.1%) as to A+ (comparisons A+ and AC vs C: $\chi^2 > 16.05$, $P < 0.001$; A vs AC: $\chi^2 < 0.5$, $P > 0.05$; Fig. 1A). The pattern was nearly the same in group 2, with distinct responses of pups to the three stimuli (Q=31.7, d.d.l.=2, $P < 0.001$), a high and equivalent responsiveness to B+ and BC (84 and 72%, respectively; χ^2=0.57, $P > 0.05$) and a low responsiveness to C (4%; comparisons B+ and BC vs C: $\chi^2 > 15.05$, $P < 0.001$; Fig. 1B).

Thus, the pups detected and responded to the odorant in AC and BC that they have learned during the conditioning. Therefore, these mixtures did not blend, and the presence of C did not seem to disturb the perception of, and response to, the learned component.

Experiment 2: control for overshadowing

Since pups responded to heterogeneous mixtures (AC, BC) after the learning of one of their components (Exp. 1), one might consider discarding the novelty effect as an explanation of the non-response of newborn rabbits [noted by Coureaud et al. (Coureaud et al., 2008)] to the AB mixture after the learning of odorants A or B. However, overshadowing (Cain and Drexler, 1974; Livermore and Laing, 1998; Sokolic et al., 2007) may constitute an alternative explanation of the results obtained in experiment 1: after learning of A or B, pups could respectively respond to AC or BC since A and B predominate and mask the perception of the novel odorant C in these mixtures. To investigate this, two other groups of 23 and 25 pups
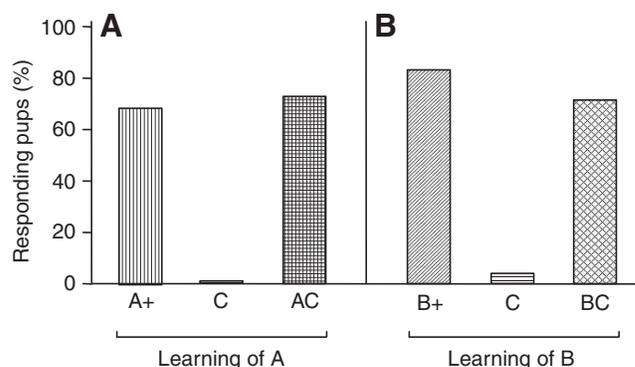

Fig. 1. Percentage of 3-day-old newborn rabbits responding in an oral activation test to a single odorant that they had learned (A+ or B+), a novel odorant distinct in quality (C), and mixtures of the two (AC or BC), 24 h after their mammary pheromone-induced conditioning to (A) the odorant A (N=26 pups, from six litters) or (B) the odorant B (N=25 pups, from five litters).

(each from five litters) were conditioned either to AC (group 1) or BC (group 2) and tested the day after for their response to AC+, A and C (group 1) or BC+, B and C (group 2).

As a result, 65.2% of the pups from group 1 responded to AC+, a rate of response similar to that for A (82.6%) and C (56.5%; comparison AC+ vs A vs C: Q=3.92, d.d.l.=2, P>0.05; Fig. 2A). The responsiveness of pups from group 2 was also equivalent between the three stimuli (Q=0.66, d.d.l.=2, P>0.05): 88, 92 and 96% of them responded to BC+, B and C, respectively (Fig. 2B).

Thus, rabbit pups conditioned to AC or BC appeared able to detect and learned both components of the mixture, since they later showed a similar rate of response to the constituents (A and C, or B and C) presented separately.

Experiment 3: impact of the sensory processes engaged in the conditioning and the behavioural test

In this second block of experiments, we aimed to assess the putative impact of the unevenness that may exist between the processing of a single odorant (in addition to the MP) during the conditioning session but of a binary mixture during the retention test. Trained to learn a single odorant, rabbit pups may later respond only to single odorants, a fact that could explain why they do not respond to AB after they have learned A or B (Coureaud et al., 2008). Here, we therefore evaluated whether pups conditioned to A in the AC odour mixture or B in the BC mixture (group 1 and group 2, respectively; N=20 pups from four litters/group) responded later to AC+ or BC+ but also to AB.

The pups conditioned to AC highly responded to AC+ (65%) but did not respond to AB (5% only; χ^2=10.1, P<0.01; Fig. 3A). Similarly, 70% of the pups conditioned to BC responded to BC+, but not one responded to AB (χ^2=12.1, P<0.001; Fig. 3B).

Thus, as occurred when the odorants A or B were learned outside the context of a binary mixture, the learning of A or B in a mixture did not induce the later response to AB.

Experiment 4: control for an ability to generalize from one to another odour mixture

The results of experiment 3 suggested a specific processing of the AB odour mixture by the newborn rabbit, since no response to AB followed the learning of one of its constituents in another (heterogeneous) mixture. However, one may also suggest that rabbit newborns do not have the capacity to generalize the odour information learned in one mixture to another mixture. To date, this ability had never been evaluated. Here, we therefore conditioned pups to the AB mixture (N=17, from four litters) and tested their response the day after to AB+, AC and BC. Previous results showed that the learning of AB was followed by a response to A or B (Coureaud et al., 2008), and we therefore hypothesized that pups would have the ability to detect and respond to these odorants even if they are included in another (non-blending) mixture.

As expected, pups conditioned to AB later responded to AB+ (76.4%). But they also responded to AC and BC at levels of response that did not differ (82.3 and 88.2%, respectively) from that to AB+ (Q=1.2, d.d.l.=2, P>0.05; Fig. 3C).

Thus, having learned the AB mixture, the pups responded to both AC and BC, a result that confirmed their learning of A and B as separate odorants during the conditioning (Coureaud et al., 2008). These results also highlighted their ability to respond to one of the single odorants that they have learned, when they encountered it later in the AC or BC mixtures. Thus, rabbit pups appeared able to detect in a novel mixture, part of the information that they have previously learned in another mixture.

DISCUSSION

The main objective of the present study was to evaluate the possibility that certain odour mixtures elicit configural perception whatever the species and the development state. We have previously shown that a mixture of ethyl isobutyrate and ethyl maltol (AB), blending in human adults, could be processed both elementally and configurally by newborn rabbits, thus suggesting that the same mixture also gives rise to an odour blending phenomenon in neonates from this latter species (Coureaud et al., 2008). Here, we tested alternative hypotheses to this conclusion, knowing that experimental paradigms such as blocking, feature positive design or external inhibition (Harris, 2006) cannot account for our previous results. However, we examined whether overshadowing (Kay et al., 2005), odour novelty effect (i.e. the inhibitory perception of a non-familiar odour in a mixture containing a conditioned one) or task unevenness (the exposure to one odorant versus an odour mixture in conditioning and retention test, respectively) may contribute to our initial observations.
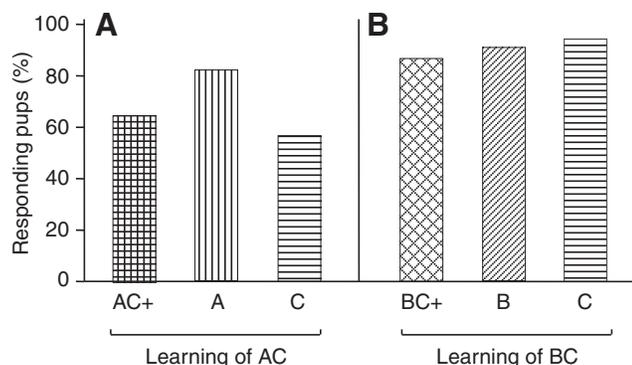
Fig. 2. Percentage of 3-day-old newborn rabbits responding in an oral activation test to a binary mixture that they had learned (AC+ or BC+), and the constituents of the mixture (A and C or B and C), 24 h after their mammary pheromone-induced conditioning to (A) the AC odour mixture (N=23 pups, from five litters); and (B) the BC odour mixture (N=25 pups, from five litters).
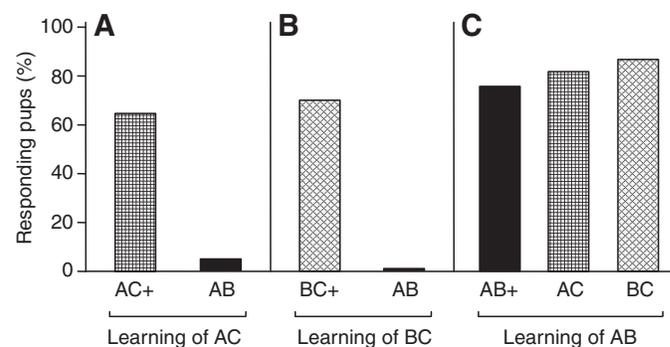
Fig. 3. Percentage of 3-day-old newborn rabbits responding in an oral activation test to the odour mixture that they had learned (AC+ or BC+) and the AB mixture (suspected to blend), 24 h after their mammary pheromone-induced conditioning to (A) the AC mixture (N=20 pups, from four litters), (B) the BC mixture (N=20 pups, from four litters). (C) Percentage of pups responding to the mixture that they have learned (AB+) as compared with the AC and BC mixtures, 24 h after their MP-induced conditioning to AB (N=17 pups, from four litters).

Overshadowing has been defined as the decrease in representation of one binary mixture's component by an increase in concentration of the other, such that at some concentration ratio after conditioning to the mixture, one component and the trained mixture are recognized, while the other component is ignored (Kay et al., 2005; Linster and Smith, 1997; Smith, 1996). In some cases, the recognition of only one component in a binary mixture may occur (complete overshadowing), therefore improving the risk of classifying such mixture as a configural mixture (Wiltrout et al., 2003). It has been proposed that overshadowing results from masking during learning, which might be due to intensity differences or interactions at the receptor or glomerular level (Kay et al., 2005). However, from our observations (experiment 2), overshadowing cannot be a possible explanation for the absence of recognition of the mixture after conditioning to one element. Indeed, the pups always displayed a very positive response to the distinct components of a mixture (AB, AC or BC) after learning that mixture.

Overshadowing has also been sometimes defined as only partial (Kay et al., 2005). In that case, a significant difference is observed between the perception of the trained mixture and the strongest element, after learning the mixture; this difference is probably due to the weakest component. Partial overshadowing may also work when the intensity of a conditioned odour is lowered in a tested mixture (incomplete masking) because of the perception at test of an unfamiliar odour (adulterant) in the mixture (Linster and Smith, 1999). In that case, the novel odour quality (adulterant) perceived in the mixture suppresses the behavioural response to the mixture even if the conditioned odour is still perceived in the mixture. This latter case is what we call here the novelty effect hypothesis. According to this hypothesis, our AB mixture might be miscategorized as configural. However, this alternative can be discarded because of the results of experiments 1 and 2. Indeed, when pups were tested with a mixture of ethyl isobutyrate and guaïacol (AC) or a mixture of ethyl maltol and guaïacol (BC) after they have been conditioned to a single component (A or B, respectively), they did respond to the mixture (experiment 1). Moreover, AC and BC appeared to trigger elemental, but no configural perception (experiment 2). Taken together, these results show that both components of the AC and BC mixtures were perceived in these mixtures and that the presence in the mixture of the novel odour, carried by the unfamiliar component (C), did not prevent the behavioural response during the test. Thus, newborn rabbits can generalize from a component to a non-blending mixture including a novel (unfamiliar) odorant in addition to the learned component. Moreover, the present results offer additional elements giving credit to the specificity of perception of the AB mixture, in rejecting the novelty effect as a possible reason for the non-response of pups to AB after the learning of one constituent. This strengthens the hypothesis of a configural perception of the AB mixture.

In our previous experimental conditions (Coureaud et al., 2008), it was possible that the unevenness between the conditioning and retention tasks induces a difference in the pups' responses towards odours perceived in one or the other tasks. Indeed, the training to one odorant at conditioning but the enforced exposure to a binary mixture at test may create a perceptive and/or cognitive difficulty for the pups to generalize to the mixture the odour information initially learned out of the mixture. This could lead to non-response to AB after conditioning to A or B. To circumvent this potential problem here, some pups were conditioned to A or B in mixtures (AC or BC) before to be tested for their response to AB. Clearly, odorants A and B were perceived and learned in respective heterogeneous mixtures with odorant C. Moreover, those pups did

not respond to AB, i.e. they exhibited the same pattern of non-response as when they were conditioned to A or B alone (Coureaud et al., 2008). Thus, when conditioned to A or B either as pure components or in a non-blending mixture, pups did not generalize to the AB mixture. Again, this reinforces the idea of a perceptual specificity of the AB mixture. Importantly, this absence of response to AB even after learning A or B in another mixture did not result from a general incapacity of pups to generalize from one mixture to another. Indeed, results of Exp. 4 showed that when conditioned to AB, pups responded later to AC and BC, and responded to these latter mixtures as well as to A or B alone (Coureaud et al., 2008).

Taken together, the present results confirm the specificity of the perception of the ethyl isobutyrate–ethyl maltol mixture (AB) as previously suggested in newborn rabbits (Coureaud et al., 2008). The absence of response to AB after learning one of its constituents implies that this binary mixture is more than, in perceptual terms, the sum of its two distinct components. It is therefore probably that the AB mixture, in 30/70 (v/v) proportion, gives rise to an odour blending phenomenon for rabbit pups, as has been suspected for this and for other mixtures in adult humans (Le Berre et al., 2008a; Le Berre et al., 2008b) and rodents (Kay et al., 2003). For instance, Linster and Smith (Linster and Smith, 1999) reported that, for some mixtures, rats perceived novel qualities that are only partially similar to the quality of the components. The symmetry of their results after both component and mixture trainings accounted for changes in perceived quality independently or in addition to possible changes in perceived intensity.

Owing to its blending properties, the AB mixture seems therefore to engage a configural processing in newborn rabbits. The notion of configural perception, discussed in the sensory field [e.g. in audition (Purwins et al., 2008); vision (Noudoost et al., 2005); audition and vision (Kubovy and Van Valkenburg, 2001); gustation and olfaction (Batson et al., 2008)], according which stimulus compounds (mixtures) are represented by their components and an additional configural element that represents the conjunction of those stimuli, is consistent with blending process in odour mixture. The present study confirms for rabbit pups that the blending effect of the AB mixture is incomplete (Dreumont-Boudreau et al., 2006), and thus that the configural perception of AB is weak (Kay et al., 2005), as was previously hypothesized (Coureaud et al., 2008). In other words, when smelt, the AB mixture would give rise to the perception of the odour of the components as well as the additional odour of the configuration related to the mixture. It is probable that the perception of this configuration is then sufficient for the mixture to be dissimilar enough from the components to not release the orocephalic behaviour of rabbit pups after the learning of only one component. Conversely, after having learned the mixture, pups are able to respond to its components, meaning that they perceive each element of the mixture and can extract the odour of each component in the mixture.

Although the neural regions selectively involved in configural or elemental processing of odour mixtures remain debatable, both in vertebrates and invertebrates (Sicard and Holley, 1984; Lynn et al., 1994; Deisig et al., 2006), perceptual blending in olfaction finds support in neurobiological studies. A primarily configural representation of odour mixture might indeed result from molecular competition at a single olfactory receptor level where elements could act both as agonists and antagonists (Spehr et al., 2004; Sanz et al., 2008). Configural processing may also occur as soon as mixture components activate a set of significantly overlapping receptors (Jinks and Laing, 1999; Kay et al., 2003). At the glomerular level, recent results show that no specificity characterized the processing

of a binary odour mixture as compared with the processing of its constituents. Indeed, spatial pattern of activated glomeruli for binary, or more complex mixtures, are mainly the sum of the responses to individual components (Deisig et al., 2006; Lin et al., 2006; Carlsson et al., 2007). However, Linster and Cleland (Linster and Cleland, 2004) suggested that interglomerular inhibition may account for configural processing. Finally, such odour processing may also occur at the level of the piriform cortex, in particular in its anterior part [encoding odour quality (Wilson and Stevenson, 2003; Gottfried et al., 2006)], where it has been demonstrated that binary odour mixtures stimulate neurons that are not stimulated by the single components of the mixtures (Zou and Buck, 2006).

Finally, these results add new information on the capacity of rabbit pups to perceive odour mixtures both configurally and elementally, and underline more generally that both processes are functional early in life in mammals. This may certainly contribute to decision making in newborns [as it might do in adults (Grabenhorst et al., 2007)], and therefore to the rapid orientation towards odour stimuli emanating from the complex chemosensory surroundings. For altricial newborn rabbits, the ability to perceive some elements in a complex mixture is extremely adaptive. This elemental processing of odour signals may provide rapid responses to key odour cues of the individual mother [e.g. aromas related to the female's diet, prenatally learned by pups, and postnatally encountered on her abdomen and milk (Coureaud et al., 2002)] or to molecules bearing species-specific and pheromonal properties (e.g. the mammary pheromone in rabbits). In a complementary way, one may suggest that the configural perception of odour mixtures expands the panel of odour cues to which newborns can respond, in adding supplementary contrasts in their representation of the environment and in improving their discrimination of other social, feeding or general odour information (e.g. complex odours carried by the body of the mother, by all conspecifics, or emanating from the nest). Indeed, as odour signals vary in natural conditions, and may even change from one to another day (Hosler and Smith, 2000), the ability of young organisms to perceive odour mixtures both through their elements and their configuration may improve the rapidity and efficiency of their response to the environment, and therefore their adaptation.

Interestingly, our results suggest that such processes could be independent of any prior exposure. Indeed, rabbit pups showed weak configural perception of the artificial AB mixture used here, despite probably not having been exposed to this mixture and its components before the experiments (in our breeding conditions). To date, it was commonly suggested that configural processing of odour mixture greatly rely on experience and memory (e.g. Staubli et al., 1987; Cleland et al., 2009). For instance, Wilson and Stevenson (Wilson and Stevenson, 2003) proposed that prior experience with an odour could be a condition to perceive complex mixtures of odorants through a strong synthetic (configural) processing and in the meantime to display strong elemental figure-ground discrimination. The present results may therefore open the way to further investigations on the putative spontaneous configural perception of odour mixtures, which could be a combination of the mixture specificity associated with the specific architecture of the olfactory system.

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