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Configural memory of a blending aromatic mixture reflected in activation of the left orbital part of the inferior frontal gyrus

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ABSTRACT

Blending aromatic mixtures components naturally fuse to form a unique odor - a configuration- qualitatively different from each component's odor. Repeated exposure to the components either in the mixture or separately, favors respectively, configural and elemental processings. The neural bases of such processes are still unknown. We examined the brain correlates of the experienced-induced configural processing of a well-known model of binary blending odor mixture, the aromatic pineapple blending (AB, ethyl maltol + ethyl isobutyrate). Before fMRI recording, half of the participants were repeatedly exposed to the mixture (AB, group Gmix), with the other half exposed to its separate components (A and B; Gcomp). During the fMRI recording, all participants were stimulated with the mixture (AB) and the components (A and B). Finally, participants rated the number of odors perceived for each stimulus. Gmix perceived the AB mixture as less complex than did Gcomp. While Gcomp perceived the mixture as more complex than its components, Gmix did not. These results show the presence of experience-induced configural or elemental processing of the AB mixture in each group. Contrasting the brain activity of Gcomp and Gmix, when stimulated with AB, revealed higher activation in the left orbital part of the inferior frontal gyrus. This result sheds light on this area's function, commonly found activated in olfactory studies, and closely connected with the lateral orbitofrontal cortex. We discuss the role of this area as a mediator of configural percepts between temporal and orbitofrontal areas involved in configural memory processes.

Keywords: odor, olfaction, experience, learning, blending mixture, fMRI

HIGHLIGHTS

- Mere-exposure to a binary blending mixture favors configural perception
- The "learned" configuration involves the left orbital part of the inferior frontal gyrus
- The IFGorb could be a mediator of configural percepts between other brain areas

I. INTRODUCTION

Commonly encountered odors are often complex compositions of tens to hundreds of different odorants; for example, the odor of coffee contains approximately 200 different odorants [1]. The human brain and olfactory sensory neurons have developed strategies to rapidly process such complex odor mixtures as a unique odor, which may serve highly beneficial behaviors, such as selecting familiar harmless food. Configural perception synthesizes the ensemble of odors belonging to a mixture into a unique odor, which may differ significantly from the odor of each separate component. Conversely, elemental perception consists of the separate analysis of each odor belonging to the mixture [2]. These two types of olfactory processing have been studied in both animal [3–8] and human models [6,9–12]. However, configural and elemental strategies have rarely been studied simultaneously on the same mixture [8,13–17]. One way of comparing the relative effects of elemental and configural odor processing is by studying so-called blending mixtures. Blending mixtures, even those consisting of only two components, are those that are more prone to be perceived as a configuration, although the chemico-physiological causes are not known. A better comprehension of these mechanisms would help understand food's mental representation, mostly shaped by odor perception. The involvement of learning and memory in food perception is decisive in food choices. Indeed, perceptual learning increases familiarity and quick recognition of food [18,19]. Quick food recognition is facilitated by configural processing [18,19]. This process allows for a better selection of beneficial foods.

We previously showed that the perception of a binary blending AB mixture (pineapple like odor, composed of the odorant A with a strawberry-like odor; and the odorant B with a caramel-like odor) could be shifted from a configural perception to a more elemental perception when participants were previously and repeatedly exposed (mere-exposure) to the components separately [20]. In contrast, when participants were repeatedly exposed to the AB mixture, we could not measure an increase in the configural perception of AB. Nonetheless, we had strong reasons to think that the configural strategy was reinforced. In the same study, with the same mere-exposure design, when an initially non-blending mixture was tested (banana and smoky odors), components came to share qualities after being repeatedly experienced together, e.g., the smoky component subsequently smelled more banana-like. Similar effects have been shown in humans in several labs, and there is now a broad agreement as to the central role of learning in shaping odor mixture perception [7,8,15,19,21–26]. The AB pineapple mixture figures now as a relevant model of blending mixture, which was repeatedly shown in human and rabbit pups to reveal configural perception and especially configural learning mechanisms [12, 13, 15, 20, 23].

Several brain areas, which are likely involved in perceptual learning, have been highlighted in functional brain imaging studies in humans. Some attempts to find brain correlates of olfactory learning

have been performed with single odorants. Dade et al. [27] exposed participants to 12 odorants separately, and participants had to rate whether they recognized or not each odorant. Three fMRI recordings were performed: i) during the odorant first exposure and no rating was asked, but participants were passively exposed, ii) then participants were exposed again in the magnet and had to recognize the odorants and finally, iii) the last session was performed after 4 exposures to the odorants and participants had to recognize the odors again. Results showed different levels of activity in the piriform cortex (PC) depending on the degree of exposure to the odorant (odor first exposure, 1 pre-exposure, 4 pre-exposures) and on the task (passive perception, recognition task). That is, no activity was noted in the course of the first odorants' encounter during a passive perceptual task, which corresponds to the odor encoding phase, a small activity appeared in the PC during the first recognition task (after 1 pre-exposure), and higher activity was observed during the second recognition task (after 4 exposures). PC appears as a critical brain area for perceptual learning, which involvement depends on the degree of exposure to the odor. In a different study, Li et al. [28] habituated participants to an odor, and this perceptual learning allowed increased discrimination between the habituated odorant and quality-related or chemically-related odorants. This enhancement in discrimination was paralleled by a learning-induced increase of neuronal activity in PC and orbitofrontal cortices (OFC), with the magnitude of OFC activation correlated with improvement in perceptual differentiation. Thus, two main brain areas, the piriform and orbitofrontal cortices, are seemingly involved in perceptual learning following habituation [27,28]. These findings suggest that OFC and PC may have an active role in odor memory processing and not only in odor perception.

Other studies highlighted the role of experience in mixture perception and the involvement of different brain regions in configural or elemental perceptions in humans. While evidence suggests a dedicated brain network for the configural processing of odor mixtures, not all studies agree upon specific brain regions' roles. Boyle et al. [29] performed a passive perceptual task during a PET recording. They found that the anterior OFC was similarly activated in response to all binary odor mixtures and deactivated for single components, suggesting that OFC's anterior portion acts as an on-off detector of odor mixtures. Howard & Gottfried [30] investigated learned configural processing with a habituation paradigm induced by satiety to peanut butter. The authors highlighted that a configural processing of the peanut butter aroma occurred in the posterior PC, but they also showed that OFC and amygdala presented a reduced activity to the odorants separately. This result suggests that during satiation processes inducing odor habituation, some areas process the mixture configurally while, in parallel, others process the mixture elementally. These results appear contradictory to Boyle et al. [29]; however, the methods were different.

Contrary to Boyle et al., Howard and Gotfried [30] used indirect measures of the configural/elemental brain processings. Boyle et al. used a passive perceptual task, and Howard &

Gottfried used an original habituation procedure, the sensory-specific satiety. Howard & Gottfried build their conclusions upon the generalization of the sensory-specific satiety between mixture and component, a mechanism known to involve the reward network [31,32], which may likely modulate the basic configural/elemental learning rules. Furthermore, whether for single odorants or mixtures, some of the above literature targeted with *a priori* a subset of brain regions among which (OFC, PC, amygdala) and did not further investigated other brain structures such as frontal and temporal areas known to be involved in memory and high cognitive processing [27].

Habituation or mere-exposure designs can be used to induce olfactory perceptual learning. Habituation paradigms have been more widely employed in neurosciences, likely due to its widespread use in animal studies. The resulting behavioral responses, or more precisely the absence of response, is indeed an easily observable behavior. Habituation is also defined as the most primary and ancient form of learning [33] and may occur in a food context during sensory-specific satiation procedures. The mere-exposure procedure also appears as an ecological paradigm, as food perception is modified following repeated exposures. With repeated exposures, food becomes more familiar and, consequently, more pleasant. Habituation relates to the sensory or behavioral response decrease following repeated exposure to stimulation, and adaptation is one neuronal mechanism by which habituation may occur. While habituation involves exposing participants to an odorant repeatedly delivered at a high frequency until the participant does not respond or detect the odor [34], the mere-exposure consists of low frequency repeated exposures that do not induce habituation but may induce associative learning [35]. These two procedures likely involve different brain mechanisms. While habituation necessitates recovery after exposure, modulating the odorants' salience, mere-exposure favors associations and requires consolidation [36–38].

While the studies to date appear to show that OFC and piriform cortices are key brain areas underlying the processing of odor mixtures elementally or configurally, several questions remain unanswered. In the present study, we investigated the neurophysiological correlates of the configural learning processing of an AB odor mixture in humans using a mere-exposure implicit learning task based on our previous study [20], since this could be seen as a "natural" process that might occur during food choices. Our hypotheses are based on our previous sensory study [20] where a group of subjects repeatedly exposed to an AB pineapple mixture (Gmix) would perceive AB as more configural, while a group of subjects exposed repeatedly to A and B separately (Gcomp) would perceive AB as more elemental. Because typicality scales were not adequate to highlight the higher configural processing [20], we decided to use on top a scale of the “number of odors” perceived. Therefore, the group with configural perception, Gmix, would perceive the AB mixture as more typical of pineapple and less complex than Gcomp. Our hypotheses about brain areas involved in mixture processing mostly address the AB mixture's configural processing as, to the best of our knowledge, no studies explored the

elemental processing with a mere-exposure design in humans. Therefore, we expect a higher brain activity in Gmix vs Gcomp group in response to AB in the OFC, following Boyle et al. [29] procedure, which approach is the closest to our design. We do not have hypotheses for brain areas dealing with elemental processing since the mere-exposure design had not been previously tested in humans. We decided to investigate whole-brain activity to increase the investigation's breadth on the brain mechanisms involved in the configural and elemental processing of blending odor mixtures. However, to restrain the investigations into the configural/elemental processes, we used stringent group contrasts where participants were exposed to the same A and B odorants but either mixed or separated during the mere-exposure phase.

II. MATERIAL AND METHOD

1. Participants

The study was conducted in Germany, at the Smell & Taste Clinic, Dresden. The participants were 31 right-handed volunteers, mostly German medical students (16 males, mean age: 25.0 ± 2.3 years). Fifteen participants were randomly assigned to a Gmix group that was exposed to the AB mixture, and sixteen participants to a Gcomp group that was exposed to the A and B components separately. Following fMRI images' pre-processing, 6 participants (2 in Gmix group and 4 in Gcomp group) were not included in the analysis's next steps because of bad realignment or failed segmentation. Therefore, the analysis was performed on 13 participants for Gmix and 12 participants in Gcomp. Participants received a moderate financial reward for the time spent in the laboratory. The exposure procedure was explained in detail apart from the aim of the exposure and the odor qualities tested. Participants were explained a false-pretext that we were studying emotional state variation following odor stimulation (aromatherapy). The fMRI recording procedure was explained in detail to the participants, who provided written consent before participation. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the Technical University of Dresden Medical Scool (EK number EK12003201). A detailed medical history, combined with an odor perception assessment by the "Sniffin' Sticks" test [20], ascertained that participants were in good health and had a functional sense of smell.

2. Stimulus delivery

Four food grade (Sigma Aldrich, St. Quentin Fallavier, France) olfactory stimuli were used: the two components A (ethyl isobutyrate, CAS#97-62-1) and B (ethyl maltol, CAS# 4940-11-8), the AB mixture, and a supplementary odorant PEA (phenyl ethyl alcohol, CAS#60-12-8) used to equilibrate the

total time of exposure between groups. Gcomp was exposed 11 times to A, and 11 times to B, so 22 stimulations in total during each exposure session; therefore, to equilibrate the total time of exposure between the two groups during the exposure sessions, Gmix was exposed 11times to AB and 11 times to a dummy odor PEA, which was not further studied. The odorants were prepared in propylene glycol (PG, Cooper Pharmacia, Melun, France). A, B and PEA were respectively prepared at 50, 20, and 50 % w/w in PG and delivered with a Burghart OM4b olfactometer (Burghart Medical Technology; Wedel, Germany). Mechanical stimulation of the nasal mucosa associated with stimulus delivery was avoided by embedding stimuli in a constant flow of odorless, humidified air of controlled temperature (80% relative humidity; total flow 4 L/min; 37°C) [39]. A Teflon™ cannula inserted either in the right or in the left nostril of participants (counterbalanced across participants) directed the gaseous stimulus from the olfactometer to the participant's nose. The odorants' final concentrations of mixture and components were fixed by an aroma expert to achieve a blending pineapple quality for the AB mixture. Furthermore, the intensities were equilibrated between odorants and mixture at 8.27% for A, 11.14% for B, 6.66% for A in the mixture AB, 11.25% for B in the mixture AB and 2.43% for PEA.

3. Experimental procedure

The study consisted of 3 sessions, each spaced by 1-3 days. The first two sessions served to pre-expose the participants to the odorants; the last session was the fMRI recording. The mere-exposure procedure was strictly similar in both groups, apart from the A and B components being mixed or not. One group of participants (Gmix) was exposed to the AB mixture, while the other group (Gcomp) was exposed to the A and B components separately. A false pretext was used to explain the study without revealing its overall aim, the exposure goal, the type of odors (mixture vs. components), or their qualities. The participants were told that they were participating in an aromatherapy study and that emotions would be evaluated following exposure to odors. Participants were not aware that two groups were exposed to different types of odors. As participants were exposed individually, they could not exchange information on the study and were asked to not do so until after the three sessions.

3.1. Mere-exposure procedure

To ensure adequate learning, we reproduced our previous design of exposure [20]. The exposures consisted of two half an hour sessions, spaced by 1 to 3 days. Participants were exposed 11 times per session to each stimulus (22 in total). Gmix was exposed to the target mixture AB and a dummy odorant PEA to equilibrate the total exposures between groups. In contrast, Gcomp was exposed separately to the target components of the mixture, A and B. Stimulations were performed with the olfactometer, and participants were asked to breathe through the mouth during the whole exposure to avoid disturbances in the olfactometer's airflow. Each stimulation lasted 1.5 s, and the interstimulus interval was 30 ± 5 s

of stimulus onset asynchrony. A 2 min break was made in the middle of each session. The order of presentation of the stimuli was counterbalanced between participants. The long interstimulus interval, the onset asynchrony, the break in the middle of the session, and the counterbalancing between the two odors ensured the mere exposure design by avoiding habituation. Participants rated different emotions on visual analog scales between stimulations to ascertain the aromatherapy false pretext and keep the participants focused during the session. Eleven questions were adapted from the Self-Assessment Manikin [40] and the Differential Emotion Scale questionnaires [41]. Participants evaluated their anxiety, satisfaction, relaxation, stress, sadness, happiness, calm, confidence, and odor pleasantness and intensity. These data were not analyzed.

3.2. fMRI procedure

The two groups followed the same protocol of stimulation and recording in the scanner. This last session took place two days after the last exposure and lasted for one hour. Participants were presented with the 4 odors (AB, A, B, and PEA) in a block design via the olfactometer. The session consisted of 4 blocks, one for each stimulus. The AB mixture was always delivered first to prevent participants from adopting default analytical processing induced by previous exposure to the components separately [15,23]. After this, A, B, and PEA odors were presented in a counterbalanced order between participants. All participants had previously undertaken fMRI scans with the same experimental paradigm, so the scanner's novelty effect was avoided. The sequence of the olfactometer consisted of 5 repetitions where the target stimulus was delivered during 20 s. (ON periods), each followed by an OFF period of 20 s., where an odorless airflow was delivered to the participant. To avoid habituation to the odors, the ON periods' stimulations were not strictly continuous but rather were released during 1 s and spaced by 2 s (Figure 1). Participants were instructed to breathe through the mouth and not to sniff the odors.

After each block, participants were asked (via intercom) to rate the typicality of the pineapple odor they just received (i.e., "Is this odor a good or a bad example of pineapple?") using a 9 point scale (1: bad example, 9: good example). Before entering the MRI, participants were trained on the typicality test with two Sniffin' Sticks (Burghart Medical Technology), one a relatively bad example (carvi odor, mint quality evaluated), and one a relatively good example (citrus-grapefruit odor, grapefruit quality evaluated). At the end of all blocks, while still in the magnet, participants evaluated intensity, pleasantness, and the number of components perceived. Stimuli were presented before each question in a counterbalanced order. The scales for "intensity" and "pleasantness" were similar to that used for "typicality", with endpoint anchors of 1 (not intense, not pleasant) and 9 (intense, pleasant). The scale for the "number of odors" contained five categories: 1, 2, 3, 4, and "more than 4 odors". After this psychophysical testing, an anatomical MRI recording was performed.

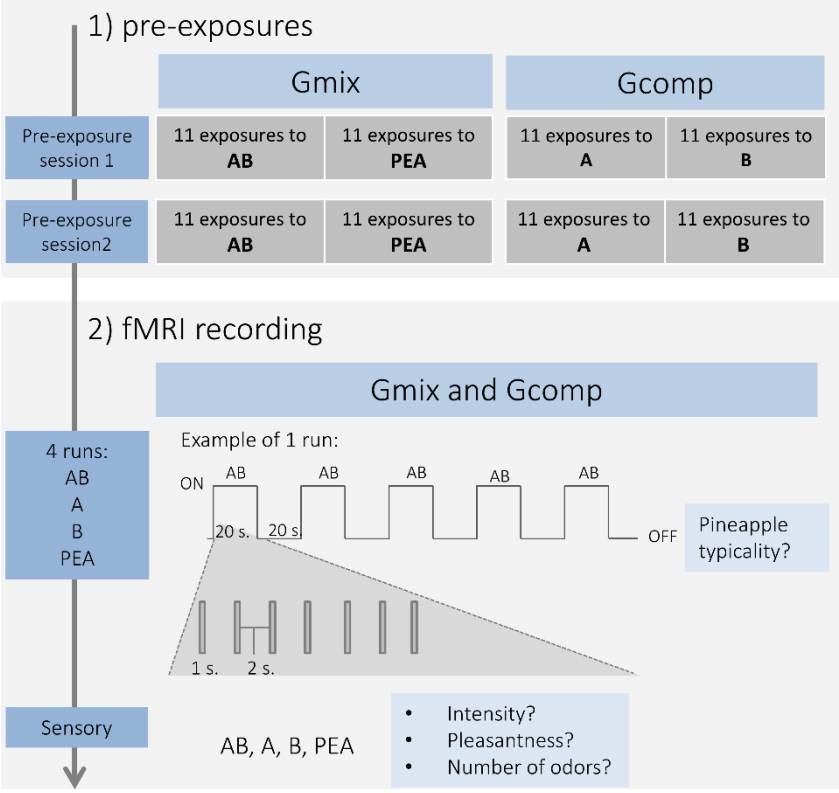


Figure 1: study design of the pre-exposure sessions and the fMRI recording. Pre-exposure differed between both group Gmix and Gcomp. fMRI session was identical for both groups, and participants received first the AB mixture and then in a counterbalanced order A, B, and PEA odorants (4 runs, one per odor condition). Each run consisted of 5 odorant repetitions (ON, 20 s) followed by an OFF stimulation (odorless air, 20 s). Sensory attributes were evaluated in a dedicated session at the end of the recording.

3.3. fMRI parameters

The study was performed on a 1.5 Tesla MR-scanner (Magnetom Sonata; Siemens Medical, Erlangen, Germany). The fMRI data were collected in 96 volumes per session using a 2D gradient Echo Planar Imaging (GE-EPI) sequence with 38 axial slices (Imaging Matrix: 64x64; TR: 2500ms; TE: 40ms; FA: 90°; voxel size: 3x3x3.75mm). The high-resolution T1-weighted sequence of the brain (3D IR/GR sequence: TR=2180ms / TE=3.93ms) was acquired for subsequent superimposition of functional data and to exclude any incidental brain pathology.

3.4. fMRI data analysis

fMRI data analysis used SPM8 software (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7 (MathWorks Inc., Natick, MA, USA). After a manual origin correction, data were pre-processed (registering, realignment, co-registration between functional and structural images, segmentation, normalization in a stereotaxic space, and smoothing using a 5*5*5 mm^3 FWHM Gaussian kernel), first-level statistical analysis was implemented

with canonical hemodynamic response functions. Smoothing at 5*5*5 mm^3 was chosen regarding our hypothesis of activation in pyriform and limbic regions, which are relatively small regions involved in odor processing and odor memory. This low smoothing also reduces false-positive results. Activation coordinates were presented in MNI space. A whole-brain analysis was performed, and functional regions associated with loci of activations were identified using the Mai Atlas [42].

At the individual level, the baseline signal of each OFF session was suppressed from its respective ON session. The realignment parameters were used as a covariate to exclude the variance linked to movements'. The resulting contrasts were used in a group level analysis. T-tests were computed to compare both groups (independent, unequal variance) for each odorant and mixture. An explicit mask containing left and right olfactory, gustatory, somatosensory, limbic, and temporal areas was created from the *aal* atlas and used in the factorial designs (WFU pick atlas) (precentral and postcentral regions, frontal region (sup, mid, medial, inf), rolandic operculum, olfactory, rectus, insula, hippocampus, and hippocampal regions, amygdala, cingulum (and, mid and post) and the temporal regions (sup, mid, inf, pole sup and pole mid). Results were thresholded at $p < 0.001$ without family-wise error (FWE) correction but with a cluster-level threshold at $k = 10$ voxels to have significant values at $p<0.05$ to limit false-positive results. MNI coordinates [x, y, z] of activated brain areas and cluster level *t* and *p-values* are presented. Kendall correlations were computed between the mean observed activity in the cluster of interest and the sensory variables; $p < 0.05$ was considered significant.

3.5. Sensory data analysis

Because of the low number of participants, the Kruskal-Wallis test was used for each variable corresponding to the perceptual dimensions evaluated during the fMRI session (typicality, intensity, pleasantness, number of odors) to compare groups (Gmix, Gcomp) and odorants (AB, A and B). Tests were considered significant when $p < 0.05$. For the multilevel comparisons between odorants, a False Discovery Rate correction (FDR) was used based on the Benjamini-Yekutieli correction, which determined that only those comparisons different at $p < 0.025$ were considered significant. In the pleasantness ratings, two values were missing and were replaced by the median value of available data.

III. RESULTS

Notable differences were found for the variable “number of odors perceived” (Figure 2). Between group comparisons for each odorant showed that Gcomp perceived AB mixture as more complex than did Gmix (medians mGcomp = 3, mGmix = 2; $\chi^2 = 5.85$, df = 1, $p = 0.02$). No differences were found for A or B odorants between groups ($\chi^2<0.7$, df=1, $p>0.43$). Within group comparisons showed that Gmix did not perceived AB as more complex than A and B (mAB = 2, mA = 2, mB = 1.77, $\chi^2 = 1.44$, df = 3, p-

value = 0.70). Conversely, Gcomp perceived AB as more complex than A and B, compared with the component A (mAB = 3, mA = 2, mB = 1.5; χ^2 = 9.98, df = 3, p-value = 0.02; AB-A = 2.93, pcorr = 0.01; AB-B = 2.43, pcorr = 0.02). No sex effects were found for any of these comparisons (p > 0.09). These results are in line with our hypothesis that configural learning of the AB mixture took place in Gmix and elemental learning of the AB mixture in Gcomp.

There was no effect of the exposure group on the pineapple typicality of the AB mixture compared either to its components in each group (χ^2 < 0.65, df = 2, p > 0.70) or in the group comparisons for each odorant (χ^2 < 0.13, df = 1, p > 0.70). Therefore, typicality did not show the configural or elemental learning effects expected.

Gmix rated odor B as lower in intensity compared with AB and A (mAB = 5, mA = 5, mB = 3, χ^2 = 10.6, df = 3, p-value = 0.01; B-AB = -3.05, pcorr = 0.007; B-A = -2.48, pcorr = 0.02). No differences of intensity between odorants were found within Gcomp (χ^2 = 3.58, df = 3, p = 0.31) and no between groups differences in intensity were found (χ^2 = 2.76, df = 1, p = 0.096). The mixture and its components were rated as being similarly mild in pleasantness in the two groups (pcorr > 0.11).

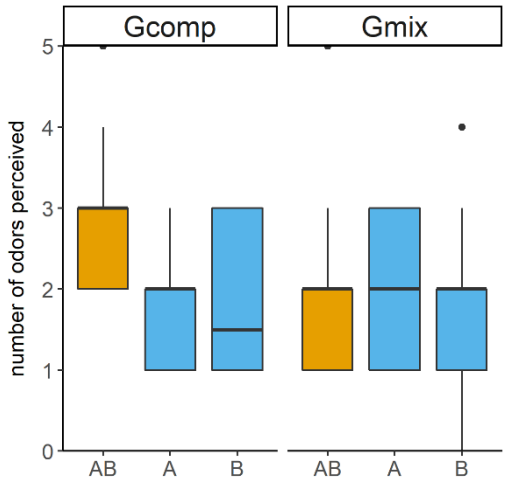


Figure 2: Median number of odors perceived at the end of the fMRI recording session. Error bars represent the 25% and 75% percent quartiles. AB: blending mixture of A (ethyl acetate) and B (ethyl maltol) odorants. Gcomp is the group of participants mere-exposed to the A and B odorants, and Gmix is the group mere-exposed to the AB mixture. The exposure occurred the week before fMRI recording.

In the group pre-exposed to the mixture (Gmix), one cluster, localised in the left inferior frontal gyrus ([-36, 24, -12], k = 15, t = 5.46, p-cluster = 0.04), was significantly more activated activated after stimulation with AB, than in Gcomp (Figure 3). The reverse contrast (Gcomp vs. Gmix) for AB did not show significant activations for AB. Finally, the contrasts between Gmix vs. Gcomp or Gcomp vs. Gmix did not show differences of activation in the responses to the A or B components.

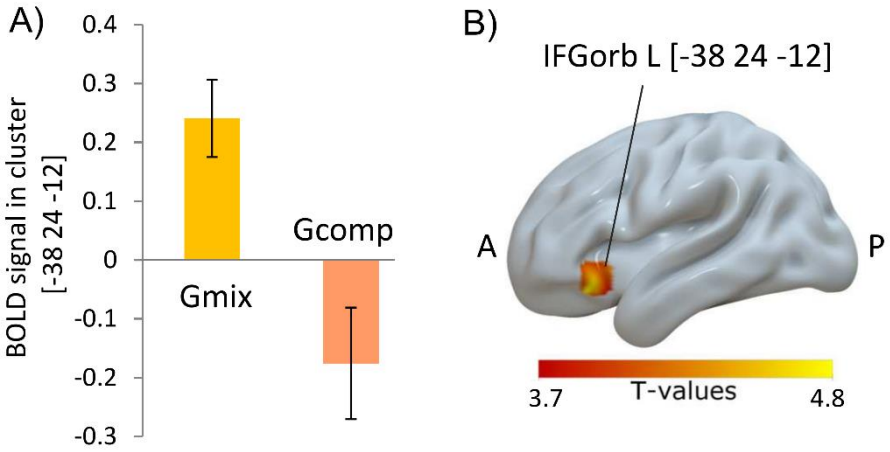


Figure 3: Brain responses to AB in Gmix vs. Gcomp. A) mean BOLD signal (±SEM) in the two groups and the cluster around the peak at [-38 24 -12], B) surface representation on an inflated brain to localize the cluster in the inferior frontal gyrus orbital part. Coloration represents the whole cluster's T-value from lower activation in red to the highest peak in yellow. Gmix: group pre-exposed to the AB mixture, Gcomp: group pre-exposed to the A and B components, AB: blending mixture of the odorants A (ethyl acetate) and B (ethyl maltol), A: anterior, P: posterior. T-values presented correspond to uncorrected values, t = 4.8 corresponds to a $p < 0.0003$ (yellow colors), and t = 3.7 to a $p < 0.002$ (red colors).

Finally, the BOLD signal in the IFGorb L in response to the AB mixture tended to be correlated with the number of odors perceived (Figure 4). While the correlation was not significant (T = 119, p = 0.16, tau = -0.21), two outliers, one in each group, rated more than four odors perceived in AB, a value not used by any other participants. When these two participants were removed from the analysis, the correlation was very close to significance (T = 90, p = 0.056, tau = -0.29) and clearly showed a separation between the two exposure groups. Although this marginal effect should be viewed with caution, it perhaps reflects low statistical power and suggests that the role of IFGorb L in the configural learning of the AB mixture deserves further investigation.

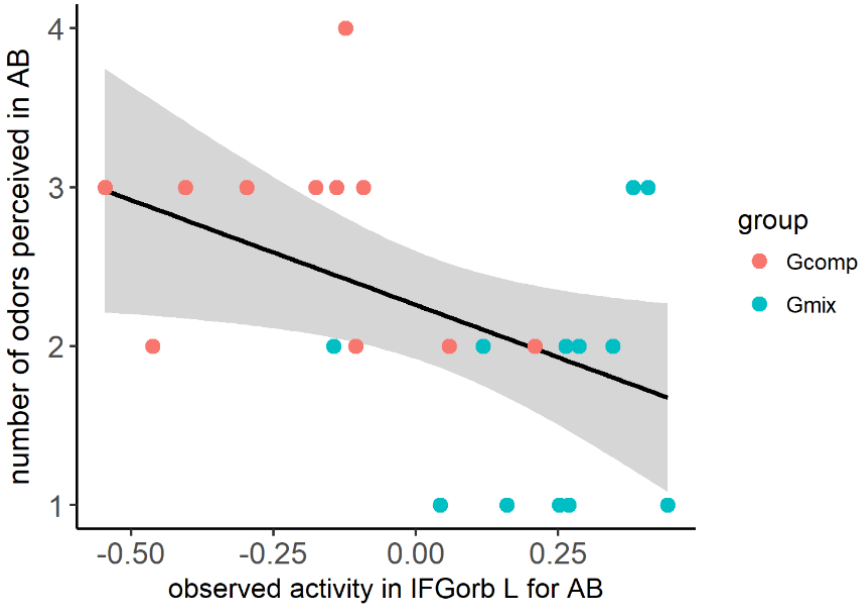


Figure 4: Correlation between the number of odors perceived and the observed brain activity (BOLD signal) in the inferior orbital part of the left inferior frontal gyrus (IFGorb L) cluster previously highlighted for the AB mixture. After removal of two outliers participants, a very close to significant correlation was found (T = 90, p = 0.056, tau = -0.29). The higher the activation in the IFGorb L, the lower the number of odors perceived in the AB mixture. Gmix: group pre-exposed to the AB mixture, Gcomp: group pre-exposed to the A and B components, AB: blending mixture of the odorants A (ethyl acetate) and B (ethyl maltol).

IV. Discussion

In this study, two groups of participants were either pre-exposed to a binary AB blending mixture (Gmix) to favor the mixture's configural processing or separate A and B components (Gcomp) favoring the mixture's elemental processing. Therefore, depending on the group, we expected to find the brain correlates of either configural or elemental learning and memory. At a sensory level, Gmix rated the AB mixture as less complex than Gcomp. Furthermore, Gcomp perceived the mixture as more complex than the components. Both results show that the configural and elemental implicit learning strategies efficiently increased the configural perception in Gmix and the elemental perception in Gcomp.

In parallel fMRI data highlighted, we found a cluster in the orbital part of the left inferior frontal gyrus (IFGorb L) that showed increased activity in response to AB in Gmix compared with Gcomp. The brain activity for AB tended to correlate with the number of components perceived in the AB mixture. Although this marginal effect should be viewed with caution, it perhaps reflects low statistical power and suggests that the role of IFGorb L in the configural learning of the AB mixture deserves further investigation. However, the comparison between AB vs. A+B in Gmix did not yield any significant cluster of activated voxels. Therefore, the differential processing between the mixture and its components might be too subtle to be highlighted with our statistical thresholds. Concerning Gcomp, no

significant differences in activity were found compared to Gmix, and no within-group differences were found between the odorants. Therefore, with our design, we did not highlight a difference in activation between Gcomp and Gmix following elemental learning in Gcomp. This result might suggest that Gmix also performed elemental learning in parallel with configural learning. As suggested by Howard & Gottfried [30], this result might show that configural learning in Gmix is also accompanied by elemental learning of the components. We might also be underpowered to highlight these areas; however, the fact we highlighted changes in Gmix is not in favor of this explanation. This result should be further investigated with other binary and more complex mixtures to ascertain this explanation.

1. Role of the IFGorb L in the processing of the AB mixture

The contrast we performed, comparing AB in the two groups, was challenging in terms of statistical power as we compared groups trained to the same odors, either mixed or separated. We, therefore, expected and obtained a few statistically significant differences. The only significant, cluster-thresholded difference was found for the contrast between both groups in response to the AB mixture. The corresponding brain area is the orbital part of the left frontal gyrus (IFGorb L) and is of particular interest. IFGorb L is often found activated but not always discussed as an area of interest. Studies discussing this area's functionality are mainly identification, recognition, and odor-naming studies [43–47]. All these tasks involve high cognitive processing, which likely requires semantic processing. Therefore, IFGorb L has been attributed to semantic functionality due to its proximity and potential connectivity with Broca's area.

Other studies suggested that the IFG L, especially the orbital part, is also involved in tasks that do not require semantic processing, such as familiarity judgments or passive perceptual tasks [47–50]. Of particular interest, Plailly et al. [48] investigated odor familiarity in schizophrenic patients with deficits in familiarity judgments. An extensive set of 28 familiar or unfamiliar odors were tested, and patients and controls had to judge their familiarity during PET imaging. Patients indeed rated more odors as unfamiliar than controls. While the control group had a significant increase in IFGorb L activity during familiarity judgments compared to baseline conditions (i.e., odorless and random yes/no ratings), the patient group did show a different activity between familiarity judgments and baseline. Savic and Berglund [50] also found that the left IFG correlated with familiarity judgments. Therefore, we could have good reasons to think that IFGorb L has a role in familiarity processing.

The question is whether our design may have involved semantic processing. It is possible as participants were asked at the end of the run to rate the pineapple typicality. This explanation could reconcile both previously established functions of IFGorb L about familiarity and semantic. It would

also explain why this area was less activated in the elemental learning for Gcomp because, in this group, the pineapple odor is sparsely associated with the qualities of A or B when perceived elementally (A: strawberry-like odor, B: caramel-like odor). Although the typicality results do not support this hypothesis, it has to be noticed that the fMRI context is not suitable for typicality measures. Measures of typicality are assumed to reflect an odor's congruency and a brain representation associated with an odor-object (e.g., pineapple). The difference of typicality between a mixture and its components informs the configural vs. elemental processes, i.e., the higher the difference between mixture and components, the highest the configural perception. If one component has the same typicality as the mixture for a target odor, then the mixture is perceived elementally. In the present study, variations in judgments of typicality were not reflected in the fMRI data. One issue with typicality ratings is that they are highly cognitively demanding as they require odor evaluation, odor recognition, and comparison with a mental reference, e.g., pineapple-like odor. This mental reference may vary across participants, resulting in high variability and low confidence in the rating, especially in small groups. Furthermore, participants had to directly evaluate the pineapple typicality after each run without actually receiving the odor, which further increased the task's memory demands.

In contrast, we have greater confidence in measures of “the number of odors perceived”, particularly since when participants evaluated the number of odors perceived, they were simultaneously stimulated with the odor. The number of odors perceived relates to the mixture perception's unicity, as defined by the unique cue theory [3,51]. The unique cue theory assumes that a mixture AB might be the sum of the single elements A and B, plus a U percept that is unique to the mixture and results from the conjunction of A and B. This theory was further developed; when the configuration is robust, A and B salience is reduced in favor of U [2,8]. The components' information can even disappear entirely in complete configural mixtures (some blending mixtures [20]) or highly complex mixtures [6,52,53]. Therefore, the elemental/configural perceptions can be understood as a continuum from exclusively elemental perceptions (only A and B percepts and no U percept) to exclusively configural perceptions (no A and B but only U percept). The in-between perceptions contain different degrees of A, B, and U perceptions that extend from weak to robust configural perceptions (i.e., the components' information regularly fade at the expense of the U percept) [54]. The shift along this continuum may depend on several factors, such as the type of mixture (blending, non-blending), the mixture's complexity, and the level of experience with the components separately or mixed [55]. Here, we combined two of these factors that likely favor a strong configural perception: the blending mixture and a relatively high level of experience with the mixture. The blending mixture can be understood as an ambiguous odor (similarly to ambiguous images, which, at a given time, is either perceived as U or as A + B [13,55]. However, with increased experience with the mixture, the U configuration is favored at the expense of A and B. Therefore, the “number of odors perceived” scale used here might reflect this continuum of perceptions from strong configuration" (i.e., "one odor") to elemental perception (i.e., "more than 4 odors"). Therefore, the IFGorb L might be a mediating memory area that gives access to the U percept in Gmix.

If the correlation between this sensory evaluation and the activity in this brain area is further confirmed, this result would also support this explanation.

This explanation is supported by a recent human anatomical study showing that the IFGorb L has very high functional connectivity with the lateral and posterior orbitofrontal cortex, insula, anterior and mid-cingulate gyrus, and other temporal and frontal regions [56]. These regions are involved in odor integration and memory construction associated with odor and taste [57,58], suggesting a central role for IFG in mediating memories between high-level areas (e.g., OFC, insula, and other temporal regions). In support of this view, a recent study highlighted structural changes of the IFG following daily olfactory training [59]. Before and after six weeks of daily training with different tasks and odor presentation (i.e., intensity ranking, odor quality ranking, and odor recognition), participants had a structural brain recording. Notably, the IFGorb L showed a significant increase of grey matter density compared to a group exposed to visual training, confirming the critical role of the IFGorb L in odor memory. The present data also suggest that this area could be more dedicated to a configural memory than an elemental one, as IFGorb L was not more activated in response to A and B components in the Gcomp group.

2. Absence of significant activations in piriform and orbitofrontal cortices

Previous fMRI studies showed the piriform cortex and OFC's central role in configural odor mixture learning [29,30]. However, these studies did not indicate a role for the IFGorb L in these processes. Several differences might account for these results.

Boyle et al. [29], for example, studied the brain processing of a mixture compared to its components, finding that the OFC response to the mixtures is supra-additive compared with components. Our failure to reproduce this finding, and the fact that Boyle et al. [29] did not show involvement of IFG, may be due to our use of prior exposure to the mixture or its elements to modulate configural/elemental processing. Hence, IFGorb L's role in processing the AB mixture in our study seems to be linked to configural implicit learning. Secondly, our statistical parameters were more stringent than those used in the Boyle study. Boyle et al. [29] used uncorrected p-values at 0.004, while we used cluster threshold p-values at 0.05 with at least 10 voxels. This cluster threshold restrains the number of false positives but also increases the number of false negatives. Therefore, we might be underpowered to show OFC activations and cannot draw definitive conclusions regarding the OFC's involvement in configural mixture perception.

Howard & Gottfried [30] used a sensory-specific satiety task to highlight areas that process configurally and elementally a complex peanut butter mixture. They hypothesized that some brain areas

would present differential activity before and after sensory-specific satiety. When the brain activity correlates with a decrease in pleasantness, it is associated with the sensory-specific satiety process. The areas that correlate with reduced pleasantness for some mixture's components, after satiation, are likely involved in the mixture elemental processing (i.e., the information on the components is preserved). Conversely, the areas that do not correlate with a decrease in pleasantness for some components, revealing no generalization of the sensory-specific satiety to the components, and a conclusion that the area processes the mixture configurally is supported (i.e., the information on the components is not processed in this area). The authors showed that PPC processes the mixture configurally, while the components' qualities are processed in parallel in the OFC-amygdala cortices. Here, we did not reproduce these results, and methodological differences may account for that. We used a mere-exposure paradigm that differs from the habituation paradigm used in Howard's study regarding brain mechanisms involved. While habituation necessitates recovery after exposure, modulating the odorants' salience, the mere-exposure procedure favors associations and requires consolidation [36,37]. Therefore, sensory-specific satiety may have induced dedicated reward mechanisms that may involve the amygdala and OFC regions. Finally, Howard and Gottfried [30] did not show the IFG involvement as they had *a priori* selection of seven brain areas involved in odor and reward value processing, and IFG was not part of them.

Nevertheless, these results show the olfactory system's remarkable plasticity and highlight early mechanisms that we may not have been able to highlight with our fMRI paradigms. Indeed, signal losses and image distortions due to susceptibility artifacts are not rare in OFC and PC cortices (cf. for review [60]). Finally, the piriform cortex generally presents a high susceptibility, and its activity is highly modulated by attentional processes and breathing [61,62]. Therefore, our recording parameters may have hindered the recording of both areas, and we cannot exclude these areas in the configural implicit learning, perception, and memory of the AB mixture.

3. Conclusions

Our study shows the involvement of the left orbital part of the inferior frontal gyrus in the reminiscence of a configurally learned blending binary mixture in humans. This area seems to have a central role in mediating robust configural memory processes in odor perception, which configural learning promotes. Functional connectivity with a mere-exposure olfactory paradigm would permit us to confirm this function. Furthermore, testing of an initially non-blending mixture would allow us to discriminate between the configural mechanisms favored by the blending properties of the "pineapple" mixture (blending configuration) and the configural learning that induces configural perception in any binary mixture (learned configuration). These perceptual learning processes are essential in dealing with unfamiliar odors and reducing the complexity of the odor mixture to memorize. In the food context, quick decisions are taken, which directly impact health and pleasure. In this context, familiarity with food is often considered as a critical decisional factor. Although our results should be replicated with

other aromatic binary and more complex blending mixtures, they bring forward our comprehension of the brain mechanisms behind complex food odor perception. These results might be of interest in the food industry, aroma formulation, and clinical research to understand the food representation and possibly the modulation of food perception in human eating disorders.

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Author Statement

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Configural memory of a blending aromatic mixture reflected in activation of the left orbital part of the inferior frontal gyrus

Sample CRediT author statement:

Charlotte Sinding: conceptualization, methodology, investigation, formal analysis, writing- original draft; **Thomas Hummel**: conceptualization, methodology, resources, supervision, project administration, writing - review & editing; **Noëlle Béno**: methodology, investigation; **John Prescott**: writing - review & editing; **Moustafa Bensafi**: formal analysis, writing - review & editing; **Gérard Coureaud**: conceptualization, methodology, investigation, supervision, project administration, funding acquisition, writing - review & editing; **Thierry Thomas-Danguin:** conceptualization, methodology, investigation, supervision, project administration, funding acquisition, writing - review & editing