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Context matters: Neural processing of food-flavored e-cigarettes and the influence of smoking

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A B S T R A C T

E-cigarettes are harmful, addictive, and popular. In e-cigarettes, nicotine is often paired with food-flavors. How this pairing of nicotine and food cues influences neural processing warrants investigation, as in smokers, both types of cues activate similar brain regions. Additionally, while most e-cigarettes are sweet, savory e-cigarettes are seemingly absent, although savory flavors are commonly liked in food. To understand how smoking status and type of flavor modulate reactions to food-flavored e-cigarettes, in comparison to actual food, neural and subjective responses to food odors were measured in a 2 (sweet vs. savory odor) x2 (food vs. e-cigarette context) x2 (smokers vs. non-smokers) design in 22 occasional/light smokers and 25 non-smokers. During fMRI scanning, participants were exposed to sweet and savory odors and pictures creating the two contexts. Liking and wanting were repeatedly measured on a 100-unit visual-analogue-scale. Results show that sweet e-cigarettes were liked ($\Delta = 14.2 \pm 1.7$) and wanted ($\Delta = 39.5 \pm 3.1$) more than savory e-cigarettes, and their cues activated the anterior cingulate more (cluster-level qFDR = 0.003). Further, we observed context-dependent variations in insula response to odors (cluster-level qFDR = 0.023, and = 0.030). Savory odors in an e-cigarette context were wanted less than the same odors in a food-context ($\Delta = 32.8 \pm 3.1$). Smokers and non-smokers reacted similarly to flavored product cues. Our results indicate that the principles of flavor preference in food cannot directly be applied to e-cigarettes and that it is challenging to design sweet and savory e-cigarettes to appeal to smokers only.

1. Introduction

The use of e-cigarettes has been increasing dramatically worldwide since their introduction in 2007 (Tehrani et al., 2022). For established cigarette smokers, light or heavy, e-cigarettes may serve as a transitional aid towards quitting (Lindson et al., 2023), ideally leading to abstinence from both cigarettes and e-cigarettes. Even if complete abstinence is not achieved, a complete switch from smoking to vaping may be healthier, as vaping is considered less harmful than smoking (Prochaska, 2019; Chen et al., 2017; Goniewicz et al., 2017; Levy et al., 2018; Margham et al., 2016). Yet, despite a 20.6% smoking prevalence among Dutch adults in 2021, only 1.4% reported regular e-cigarette use (Boer et al., 2021). In younger populations, hardly old enough to have established a smoking habit, e-cigarettes are more popular. In the Netherlands, an alarming 14.1% of those aged 12 to 16 have experimented with e-cigarettes in 2021 (Boer et al., 2021). This trend is paralleled in the U.S., where 14.1% of high school students (Youth & Tobacco Use, 2023) and 4.5% of adults (QuickStats, 2021) reported current e-cigarette use in 2021, and where younger vapers were more likely to never have smoked. The attraction of non-smokers to e-cigarettes (Romijnders et al.; Romijnders et al., 2019; Zhong et al., 2016; Yoong et al., 2018) is concerning, as vaping is not safe (Prochaska, 2019; McRobbie, 2017), and may be a gateway to smoking (Chan et al., 2021; Khouja et al., 2021).

Flavors play a crucial role in the attractiveness of e-cigarettes (Audrain-McGovern et al., 2016) and e-cigarettes are available in a variety of different flavors. On the Dutch market alone, approximately 20,000 different e-liquid products to be used in e-cigarettes were reported to be marketed in 2017, with nearly 250 unique, frequently food-related flavor descriptions (Havermans et al., 2021). Despite this large number of available flavors, most e-liquids are marketed as sweet. Savory e-liquids are exceedingly rare, even though savory flavors are commonly liked in food. Non-sweet e-liquids are often tobacco-flavored

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(Havermans et al., 2021). Previous studies show that smokers are more interested in trying tobacco flavors (Romijnders et al., 2019), and dislike them less than non-smokers (Krüsemann et al., 2021). While this suggests that flavor perception differs between user groups, neither smokers nor non-smokers particularly like tobacco flavors. Sweet e-liquids are preferred by all user groups (Krüsemann et al., 2021; Zare et al., 2018), indicating a shared preference. However, if a specific e-cigarette flavor is found that appeals to smokers who want to quit but does not appeal to non-smokers, policymakers could consider allowing only that flavor on the market.

How a flavor is perceived may depend on the user group but also on the context of its presentation (van Bergen et al., 2021). Herz et al. showed that the pleasantness of an odor is greatly influenced by its given label (e.g. "vomit" vs. "parmesan cheese") (Herz & Von Clef, 2001). Likewise, an fMRI study showed that the same odor is liked less when labelled as "body odor" compared to "cheddar cheese". The latter label induced greater activations in reward-related brain regions and activations correlated with pleasantness ratings (De Araujo et al., 2005). Another study showed that only odors labeled according to their source ("food" and "flower") elicited brain activations in certain reward-related regions, while the same odors labelled as "body lotion" did not (Bensafi et al., 2014). While these studies suggest that flavor perception and processing differs between contexts, it is not yet elucidated whether and how they differ between the contexts of food vs. e-cigarettes. Therefore it remains unclear whether the principles of flavor preference, which are abundantly researched in food (Hoffman et al., 2016; May-Wilson et al., 2022), can be applied to e-cigarettes. Closing this knowledge gap can help to promote public health through informed product design and regulation. Hence, comparing the appeal-enhancing effects of flavors in food and e-cigarettes could be valuable, especially considering that e-cigarettes are predominantly flavored to resemble food (Havermans et al., 2021).

Comparing e-cigarette flavor preference between smokers and non-smokers is of additional interest, particularly due to the differential impact that e-cigarette use could have on their health. Notably, in smokers, nicotine cues activate brain regions associated with reward processing, such as the amygdala, orbitofrontal cortex (OFC), anterior insula and striatum (Tang et al., 2012). These regions are also active in response to food cues, in both smokers and non-smokers (Tang et al., 2012). As in smokers, nicotine cues and food cues both activate similar brain regions when presented individually (Tang et al., 2012), the pairing of nicotine cues and food flavors may influence their brain responses. One fMRI study (Kroemer et al., 2018a) investigated the pairing of nicotine and sweet flavor in e-cigarettes on e-cigarette cue reactivity in smokers. They found supra-additive increases in nucleus accumbens (striatum) activation in response to sweet-flavored e-cigarette cues, meaning that this brain region showed a stronger reward-related response to the combined nicotine and sweet flavor cue than would be expected from the sum of their individual effects (Kroemer et al., 2018a). This indicates that, in smokers, sweet flavors potentiate the rewarding effects of e-cigarettes (Kroemer et al., 2018a). How the pairing of savory flavors with e-cigarette cues influences reward, and the neural mechanism involved, is not yet understood.

Therefore, this fMRI study aimed to investigate how neural and subjective responses to food flavors in e-cigarettes correlate and differ from responses to flavors in food. Moreover, we studied whether these responses differ between user groups (smokers and non-smokers) and between flavors (sweet and savory).

We expected no differences in reward-related responses to sweet and savory flavors in the context of food, because sweet and savory foods can be equally palatable (Griffioen-Roose et al., 2009). In the context of e-cigarettes, we expected greater reward-related responses to sweet compared to savory flavors, as the dominance of sweet e-liquids and scarcity of savory ones suggests a stronger preference for sweeter e-cigarette flavors (Havermans et al., 2021). Further, we hypothesized to see similar responses in smokers and non-smokers to flavors in the context of food. In the context of e-cigarettes, we expected a stronger reward-related response to flavors in smokers compared to non-smokers, as, in light smokers, the sight of an e-cigarette might function as a nicotine cue and activate craving (Lochbuehler et al., 2018).

2. Experimental procedures

2.1. Participants

We recruited 50 international participants (25 light smokers and 25 non-smokers) in Wageningen and surroundings through posters on the university campus, flyers in the neighborhood and student Facebook groups. Respondents attended an information meeting, signed an informed consent form, and filled in a screening questionnaire assessing general demographics, lifestyle factors, vaping and smoking characteristics, health status, reward sensitivity (Behavioral Inhibition System/ Behavioral Activation System, BIS/BAS) (Carver & White, 1994), sensitivity to food cues (the Power of Food Scale, PFS) (Lowe et al., 2009), and impulsiveness (Barratt Impulsiveness Scale-11, BIS-11) (Patton et al., 1995).

Exclusion criteria were: study odor aversions (defined as rating odor liking < 40 units on a 100-unit visual analogue scale (VAS) anchored from "not at all" to "very"), dietary restrictions and/or allergies and/or hypersensitivities to food items or odors used in the study; a history of drug addiction (other than nicotine), current psychiatric, neurological, chronic metabolic, or eating disorders; pregnancy, breastfeeding, claustrophobia, the participation in other medical-scientific studies, and the use of some types of medication other than the occasional use of paracetamol and/or NSAIDS and/or the use of monophasic birth control. Participants using antihistamines were instructed to refrain from using them on the day of the test session, and reschedule the test session in case they suffered from allergies.

Participants were included if they had a BMI between 18.5 and 27 kg/m^2 and a normal sense of smell (Hummel et al., 2007). Further, included participants had to be right-handed, between 18 and 55 years old, healthy, fluent in English and/or Dutch, willing to refrain from using recreational drugs other than alcohol and nicotine in the week before the test session, and without conditions that would preclude an MRI scan.

Smokers were included if they smoked at least once a month, and not only in the weekends. Additionally, they must have consumed ≥ 100 cigarettes in their lifetime, but currently < 10 cigarettes daily. They also had to score ≤ 2 points on the Fagerström Test for Nicotine Dependency (FTND) (Heatherton et al., 1991). These criteria are in line with another fMRI study with smokers (Kroemer et al., 2018b) and match the definition of occasional to light smoking proposed by Schane et al. (Schane et al., 2010). In line with the study of Kroemer et al. (Kroemer et al., 2018b), we included light smokers as previous studies indicate that lower nicotine dependence is associated with stronger nicotine cue-reactivity and cue-induced craving (Vollstädt-Klein et al., 2011; Watson et al., 2010).

Non-smokers had smoked < 100 cigarettes in their lifetime. All participants had to be susceptible to future e-cigarette use. Susceptibility was defined in line with literature (Pierce et al., 1998) as being aware of the existence of e-cigarettes and providing a response other than "absolutely not" to at least one of the following questions: "Do you think that you will use an electronic cigarette in the next six months?", "Do you think that you will experiment with electronic cigarettes in the future?", or "If one of your best friends were to offer you an electronic cigarette, would you use it?". Previous e-cigarette use was neither required nor excluded, but recorded as never, once, or regularly.

Data from three smokers were excluded from analysis due to poor fMRI data quality. The final sample consisted of 22 smokers (10 women; mean age 24.9 years ± SD 3.9) and 25 non-smokers (13 women; mean age 22.8 years ± SD 2.5). More information on sample demographics and (e-)cigarette use is shown in Tables S1 and S2 in the supplementary material.

The study was conducted in accordance with the Declaration of Helsinki (2013) (World Medical Association, 2013), approved by the Medical Ethical Committee of Wageningen University, and registered in a public trial register (NL7963 - https://trialsearch.who.int/Trial2.aspx?TrialID=NL7963). Participants received a monetary compensation for their participation.

2.2. Design

Usually, flavor perception during eating and vaping involves retronasal olfaction, the process of smelling odors via the back of the mouth during exhalation. Additionally, eating, and possibly vaping, also stimulates taste receptors in the mouth (Rozin, 1982; Rosbrook et al., 2017). Due to methodological restrictions, we utilized only orthonasal olfaction, the direct inhalation of odors via the nostrils, to elicit flavor perceptions. We followed a 2×2×2 mixed design, measuring neural and subjective responses to sweet and savory odors in a food and an e-cigarette context, using smoking and non-smoking participants.

2.3. Odors

Per odor quality (sweet and savory), two odors were used: melon and caramel for sweet (both IFF, Hilversum, the Netherlands), and beef and potato chips for savory (IFF, Hilversum, the Netherlands, and Symrise, Holzminden, Germany, respectively).

The melon, caramel and chips odors were diluted with propylene glycol (PG) as specified in Table 1. Beef odor was diluted in demineralized water. Dilutions were stored in the fridge and renewed every week. During the test session, odors (4 L/min) were embedded in a constant non-odorous airflow (8 L/min without odor, 4 L/min with odor, relative humidity 80%, 36 °C) and presented orthonasally to both nostrils using an 8-channel olfactometer (Burghart®, Holm, Germany) and a small nasal canula. Odor release was triggered by the stimulus presentation software E-Prime® 3.0 (Psychology Software Tools, Sharpsburg, USA).

2.4. Pictures creating the context

During odor presentation, pictures creating food and e-cigarette contexts were shown using E-Prime® 3.0. Per odor, two pictures were used which were matched on size, color, background, and facial expression of the person displayed. The picture either showed a person holding a ready-to-eat food product close to the mouth (food context), or the same person exhaling vapor while holding an e-cigarette close to the mouth (e-cigarette context). In the corner of the pictures, either a plate with the corresponding food product was shown (food context), or an e-liquid bottle with a picture of the food product (e-cigarette context). A random half of the pictures were left-to-right mirrored. Examples of the pictures can be found in Fig. 1.

2.5. Experimental procedures

Participants attended an information meeting, screening, and test session. Screening and testing took place between 12:00 pm and 9:00 pm with at least one day in between.

Table 1
Overview of the used odors, their relative concentrations used during the test session and their corresponding average intensity ratings.

	Melon	Caramel	Beef	Chips
Concentration	15%	35%	0.1%	1.5%
Intensity* (± SD)	63 (± 20)	68 (± 18)	59 (± 17)	57 (± 19)

* Intensities were rated by n = 47 participants three times per odor (once per functional MRI run), on a 100-unit VAS, anchored "not at all" to "very".

2.5.1. Screening session

Participants attended a screening where their olfactory ability was tested using the Sniffin' Sticks 16-item Odor Identification task (Burghart®, Holm, Germany) in which participants are instructed to smell and identify 16 commonly known odors from a list of four alternatives/descriptors (Rumeau et al., 2016). A participant is considered normosmic and passed the test with ≥ 12 correct odor identifications (out of 16) (Oleszkiewicz et al., 2019).

Subsequently, participants were familiarized with the task in a dummy MRI scanner for about 5 min. Thereafter, participants smelled the diluted test odors from a bottle and rated them on intensity, liking, odor-label match (how much the test odors resembled their given label (e.g. *melon*)) and odor-picture match (how much the odors resembled the products seen in the corresponding pictures). All attributes were rated on a 100-unit VAS from "not at all" to "very". The data is shown in the supplementary material (Table S3).

2.5.2. Test session

Participants abstained from make-up and scented body and hair products on the day of the test. In the two hours before the test, they refrained from chewing gum, brushing teeth, and consuming anything but water. They ate 0.5 l of non-sweet, non-savory full-fat plain yoghurt (295 kcal) between 60 and 30 min before testing, to minimize hunger and potential differences in appetite for sweet and savory. To minimize potential differences in reward-related responses between the food and e-cigarette condition caused by nicotine withdrawal, smokers then also smoked a cigarette. Right before the MRI session, participants completed a questionnaire assessing adherence to the protocol and their appetite. General appetite was measured by rating hunger, fullness, prospective consumption, desire to eat, and thirst on 100-unit VAS; anchored by "not at all" to "very". Specific appetite for sweet and savory food was assessed on the same VAS scale. The following MRI session consisted of an anatomical scan (± 5 min) and three functional runs (± 15 min each).

2.5.3. fMRI task

The fMRI task consisted of 120 trials, with each of the four possible combinations of context (food and e-cigarette) and odor quality (sweet and savory) presented 30 times. To avoid expectation effects, the sequence of the 120 trials was randomized and temporally independent (orthogonal), with varied trial durations. The same sequence was used for all participants. Each trial began with a red fixation cross on a black screen for 1.5 s. Next, a picture of someone eating or vaping was shown (7 s) and the corresponding odor was released simultaneously (3 s). Participants were instructed to inhale through the nose upon seeing the picture. Thereafter, either an odor rating question was shown (7 s), followed by a black screen (1 s) and a white fixation cross (5 to 9 s), or the white fixation cross was shown immediately (11 to 16 s; see Fig. 1).

Because we used two odors per odor quality (e.g. melon and caramel for sweet), there were eight possible odor-context combinations. For each of these eight combinations, participants rated the following attributes twice in randomized order: sweetness, savoriness, liking ("*how much do you like the odor?*"), and wanting ("*how much do you want to eat/vape a product with this odor?*"). Intensity of each specific odor was rated once in each of the three functional runs. All attributes were rated with the use of a hand-held button box on a 100-unit VAS ranging from "not at all" to "very". A schematic presentation of the task structure can be found in Fig. 2.

2.5.4. MRI parameters

MRI images were acquired on a 3-Tesla MRI scanner (Elition X, Phillips, Amsterdam, the Netherlands) and a 32-channel head coil. A high-resolution T1-weighted 3D TFE anatomical scan was made (repetition time (TR) = 10 ms, echo time (TE) = 4.6 ms, flip angle = 8°, field of view = 256 × 243×180 mm, 450 sagittal slices, scanning voxel size = 0.8 × 0.8 × 0.8 mm, reconstruction voxel size 0.4 × 0.4 × 0.4 mm). For the functional scans, a T_2-weighted multiband 2D-EPI gradient echo

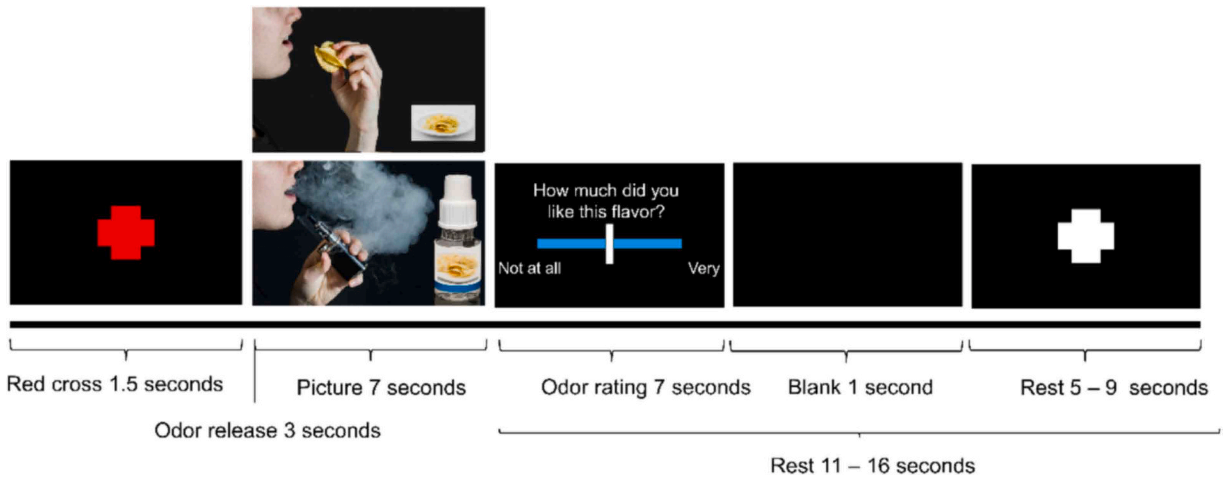

Fig. 1. fMRI trial structure and two examples of pictures creating the contexts. After showing a red cross (1.5 s), an odor was released for 3 s, and simultaneously a picture of someone eating or vaping was shown (7 s). Next, there was either an odor rating question (7 s) followed by a blank screen (1 s) and a rest period (5 to 9 s), or a rest period only (11- 16 s).

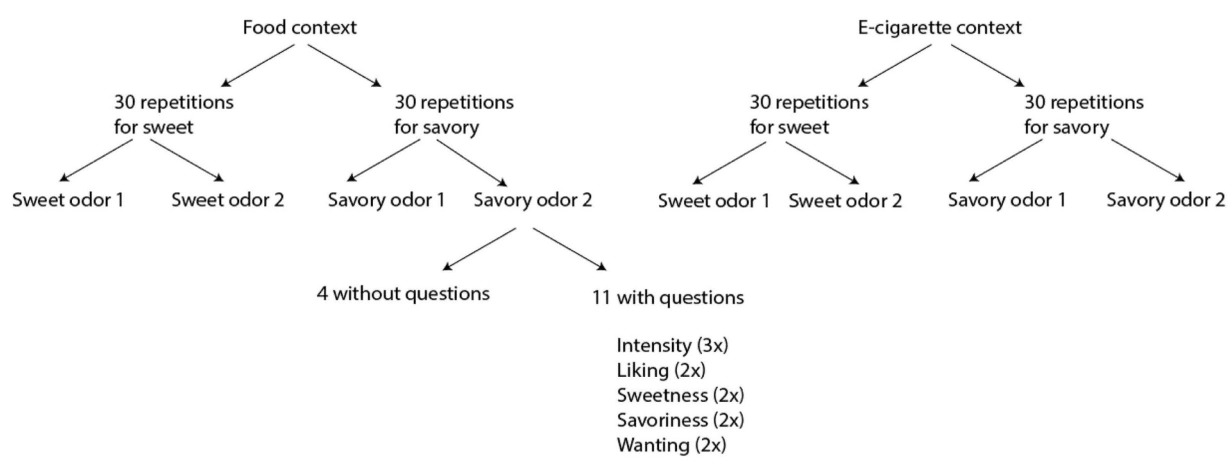

Fig. 2. Schematic representation of the fMRI task. Each context (food and e-cigarette) was presented 60 times, with 30 repetitions for sweet and 30 repetitions for savory. Per odor quality (sweet and savory), two odors were used. The odor rating questions shown for savory odor 2 (food context) were repeated for each odor in each context.

sequence was used (TR = 1152 ms, TE = 25 ms, flip angle = 57°, multiband factor 3, SENSE factor = 2.2 (AP), field of view = 230 × 230×139 mm, 63 axial slices, ascending order, scanning voxel size = 2.2 × 2.2 × 2.2 mm, reconstructed voxel size 1.8 × 1.8 × 2.2 mm).

2.6. Data analysis

Unless otherwise specified, data were analyzed using IMB SPSS Statistics 25, results with a p-value below 0.05 were regarded significant, and means are shown with standard error. Non-significant interaction terms in factorial models were removed hierarchically. For brain data, qFDR and p-values are shown at cluster level. Because we were interested in differences between odor qualities rather than individual odors, data were pooled over the two odors of the same odor quality (sweet and savory).

2.6.1. Participant characteristics and appetite ratings

To test for differences in sweet and savory appetite before the fMRI test, the scores were analyzed using a paired-sample t-test. Sweet and savory appetite did not differ from each other pre-test (mean difference= 0.92 ± 2.4, $t = 0.38$; $p = 0.71$). A 'General appetite' score was computed by averaging hunger, desire to eat, prospective consumption, and the inverse fullness score (100 − fullness). Differences between smokers and non-smokers in sweet, savory, and general appetite; and age, BMI, BIS/BAS (Carver & White, 1994), PFS (Lowe et al., 2009), and BIS-11 scores (Patton et al., 1995) were analyzed using two-sample t-tests. The data can be found in the supplementary materials, Tables S4 and S1, respectively. Differences between smokers and non-smokers in e-cigarette use and gender were analyzed with chi-square tests (Table S2). The only variables that differed between smokers vs. non-smokers were age (mean difference 2.1 years, $t = -2.28$; $p = 0.027$), BIS-11 non-planning (mean difference 0.3, $t = -2.1$; $p = 0.041$), and e-cigarette use (Cramer's V = 0.738; $\chi2(2) = 25.59$; $p < 0.001$), with smokers being older, having higher impulsiveness scores, and higher rates of previous e-cigarette use.

2.6.2. Odor perception

2.6.2.1. Analytical odor ratings. To test for potential differences in odor ratings between odor qualities and user groups, analytical odor ratings (sweetness, savoriness, and intensity) as measured during the fMRI task were analyzed individually as dependent variables in full-factorial linear mixed model analyses, with odor quality and smoking status as fixed effects and participant as random effect. We tested for differences in analytical odor perception between smokers vs. non-smokers as differences in analytical odor perception could drive differences in hedonic odor perception.

2.6.2.2. Hedonic odor ratings. To test for differences in hedonic odor ratings between odor qualities, contexts, and user groups, liking and wanting ratings as measured during the fMRI task were first averaged per participant. Ratings were then analyzed individually as dependent variables in full-factorial linear mixed model analyses, with flavor quality, context and smoking status as fixed effects and participant as random effect. Potential confounders were entered individually into the basic models (with non-significant interaction terms removed) to test for their significance one-by-one. We tested the following covariates/factors: personal characteristics (age, gender, BMI, BIS/BAS, BIS-11, PFS scores), odor intensity ratings, general appetite, and prior e-cigarette use. Odor intensity was significant when predicting liking ($\beta = 0.191$; $F(1,134) = 4.2$; $p = 0.043$). When predicting wanting, only gender was found to be significant ($\beta = 6.2$; $F(1,44) = 4.3$; $p = 0.045$). The results of other covariates/factors can be found in the supplementary materials (Tables S5 and S6 for liking and wanting, respectively). The final models were corrected for the covariate odor intensity (evaluated at mean value 61.6) because odor intensity differed between sweet vs. savory odors and influenced liking. Final models were also corrected for the factor e-cigarette use (evaluated at "used once") as e-cigarette use differed between smokers vs. non-smokers.

2.6.3. fMRI data preprocessing

The imaging data were preprocessed and analyzed with the SPM12 software package (Wellcome Department of Imaging Neuroscience, London, UK) run with MATLAB R2021a (The Mathworks, Inc., Natick, MA, USA). Functional images were realigned and slice-time corrected. Anatomical images were coregistered to the mean functional images and normalized into MNI space. Normalization was then applied to the functional data before smoothing using a 3D Gaussian smoothing kernel ([3.6, 3.6, 4.4] mm full width at half-maximum). A volume-wise check for motion was conducted using ArtRepair toolbox (Mazaika et al., 2023). For two participants head motion of more than 0.5 mm / TR affected more than 20% of the total volumes. These two participants were not included in any analysis.

2.6.4. fMRI model specification and estimation

2.6.4.1. Subject level analysis. The four conditions of interest (the four possible combinations of odor quality and context (each 4 s)), red crosses (1.5 s) and odor ratings (7 s) were modelled. Red crosses and odor ratings were ignored in further analysis as conditions of no interest. To account for motion-related variance, the six motion parameters assessed during realignment were added as regressors. For each subject parameter estimated, 10 contrasts were calculated: each of the four conditions (individually) vs. rest, food cues vs. rest, e-cigarette cues vs. rest, sweet food vs. savory food cues (Food Sweet vs. Food Savory), sweet e-cigarette vs. savory e-cigarette cues (Ecig Sweet vs. Ecig Savory), sweet food vs. sweet e-cigarette cues (Food Sweet vs. Ecig Sweet), and savory food vs. savory e-cigarette cues (Food Savory vs. Ecig Savory). As an additional quality check, whole brain-analysis was performed using a t-contrast of the combined four conditions vs. rest (any condition vs. rest) to check for visual cortex responses to the picture cues. One participant showed no visual cortex activation and was not included in any analysis.

2.6.4.2. Group level analysis

2.6.4.2.1. Sweet vs. Savory odors. To test our a priori hypothesis of no difference in reward-related brain responses to sweet compared to savory food cues, and greater reward-related response to sweet compared to savory e-cigarette cues, we entered individual t-contrasts into one-sample t-tests using the Sweet Food vs. Savory Food contrasts, and Sweet Ecig vs. Savory Ecig contrasts, respectively. In line with the analysis of hedonic odor ratings, we included e-cigarette use and differences in intensity ratings between odors as covariates. Then, we conducted a region-of-interest (ROI) analysis using an anatomical mask that is described in detail elsewhere (Smeets & de Graaf, 2019) and includes regions implicated in reward processing (Knutson et al., 2000, 2001): the bilateral insula, anterior and middle cingulum, supplementary motor area (SMA), OFC, thalamus, and striatum (caudate, putamen, palladium). We set the cluster-forming threshold of ROI-masked contrasts at $p < 0.001$ (uncorrected) with a cluster extent of $k = 20$ voxels. We regarded clusters as significant when (cluster-level) quantitative false-discovery rate (q_{FDR}) < 0.05. In addition, we performed exploratory whole-brain analyses using a threshold of $p < 0.05$ (family-wise error (FWE)-corrected; $k = 20$), and regarded clusters as significant when (cluster-level) $p_{FWE} < 0.05$. Note that compared to whole-brain analysis, for ROI analysis we chose a less stringent correction for multiple comparison to avoid missing relevant neural landmarks for further investigations (Lieberman & Cunningham, 2009).

2.6.4.2.2. Food vs. E-cigarette context. To test for differences in neural response to the same odor in different contexts, we analyzed sweet food vs. sweet e-cigarette contrasts, and savory food vs. savory e-cigarette contrasts using one-sample t-tests in ROI and whole-brain analyses as indicated above, with e-cigarette use as a covariate.

2.6.4.2.3. Smokers vs. Non-smokers. To test our a priori hypothesis of no difference in brain activation between smokers vs. non-smokers in response to food cues, but greater activation in reward-related brain areas in smokers compared to non-smokers in response to e-cigarette cues, we conducted two-sample t-tests using food vs. rest and e-cigarette vs. rest contrasts, respectively. To further explore differences between the two groups, we tested all other contrasts calculated during subject level analysis using two-sample t-tests. ROI and whole-brain analyses were performed as indicated above, with odor intensity and e-cigarette use as covariates.

2.6.5. Correlations between neural and subjective responses

To test for correlations between hedonic odor ratings and brain activations in reward-related regions, for several brain regions we exported mean parameter estimates from each individual condition vs. rest contrast (e.g. food sweet vs. rest, food savory vs. rest, etc.) from SPM12 to SPSS using MarsBaR (version 0.44). To avoid double-dipping, for the main analysis we extracted parameter estimates from eight brain regions that were significant in a ROI analysis of the any condition vs. rest contrast on group level (all conditions combined vs. rest). These regions included clusters in the amygdala, anterior insula, caudate, middle cingulate, supplementary motor cortex, and thalamus. We then calculated the mean ratings for liking and wanting for each participant, along with the mean parameter estimates for each brain region, all of which were collapsed across all conditions. Subsequently, we conducted Spearman correlation analyses to associate the mean brain parameter estimates with the mean liking ratings, and then, with the mean wanting ratings. Because the clusters obtained from the any condition vs. rest contrast did not cover all relevant areas, we conducted further exploratory analysis. This involved extracting mean parameter estimates from brain regions that were significant in our analyses-of-interest to investigate potential correlations between hedonic odor ratings and brain activation in these specific areas.

3. Results

3.1. Odor perception

3.1.1. Analytical odor ratings

Sweet odors were perceived as more sweet than savory odors. Likewise, savory odors were perceived as more savory compared to sweet odors. Sweet odors were rated as more intense compared to savory odors. There were no differences in analytical odor ratings between smokers vs. non-smokers (sweetness F(1, 45) = 0.01; p = 0.94, savoriness F(1, 45) = 1.4; p = 0.25, intensity F(1, 45) = 0.2; p = 0.67). Mean ratings per odor quality and F-values for main effects can be found in Table 2.

3.1.2. Hedonic odor ratings

Sweet odors were liked more than savory odors ($\Delta = 14.2 \pm 1.7$, $p < 0.001$), independent of user group and context. Liking ratings did not differ between contexts. There was an interaction between odor quality and user group [F(1, 137) = 7.3; p = 0.008], however, post-hoc comparisons showed that neither sweet nor savory odor liking differed between user groups ($\Delta = 3.4 \pm 4.6$; p = 0.23, and $\Delta = -5.1 \pm 4.6$; p = 0.47, respectively).

Sweet odors were wanted more than savory odors in both contexts (food context $\Delta = 7.1 \pm 3.3$; p = 0.031, and e-cigarette context $\Delta = 39.5 \pm 3.1$; $p < 0.001$). There was an interaction between odor quality and context. Post-hoc tests showed that savory odors were wanted more in the food compared to the e-cigarette context ($\Delta = 32.8 \pm 3.1$; $p < 0.001$), while sweet odors wanting did not differ between contexts ($\Delta = 0.396 \pm 3.1$; p = 0.90). Further, an interaction was found between odor quality and user group [F(1, 137) = 9.8; p = 0.002], however, post-hoc comparisons showed that wanting ratings of neither sweet nor savory odors differed between smokers and non-smokers [$\Delta = 6.4 \pm 5.2$; p = 0.227, and $\Delta = -7.3 \pm 5.2$; p = 0.17, respectively).

Table 3 shows the mean ratings of liking and wanting per odor-context combination and user group, together with information on the fixed effects included in the model. Because these ratings did not differ between smokers and non-smokers, Fig. 3 shows mean values of liking and wanting per odor quality - context combination collapsed across user groups.

3.2. Brain activation

We tested if brain responses to sweet odors varied from those to savory odors, and if brain responses to the same odors differ, depending on the context of their presentation. We also tested for differences in brain response between smokers and non-smokers. Significant brain activation differences per comparison can be found in Table 4. Figure S 1 in the supplementary materials shows coronal, sagittal, and axial slices of color-coded T-maps of these comparisons in ROIs. Unthresholded T-maps can be found at neurovault.org with the identifier https://identifiers.org/neurovault.collection:15844.

3.2.1. Sweet vs. Savory odors

In the food condition, we found that responses to sweet vs. savory cues did not differ in the ROI analysis, however, exploratory whole-brain analysis revealed stronger activation in the bilateral lingual gyrus in response to savory cues [$p_{FWE} < 0.001$; see Fig. 4A]. In the e-cigarette condition, using ROI analysis, we found stronger brain activation in response to sweet compared to savory cues in the anterior cingulate [qFDR = 0.003; see Fig. 5A]. Whole-brain analysis revealed no differences.

3.2.2. Food vs. E-cigarette context

In response to sweet odors, we found stronger activation in the right anterior insula in the e-cigarette compared to food context [ROI analysis, qFDR = 0.030; see Figure 5_B]. Exploratory whole-brain analysis of the same contrast showed that e-cigarette cues activated large regions of the visual cortex more, including regions in the lingual gyrus and middle occipital gyrus [$p_{FWE} < 0.001$; see Fig. 4B].

In response to savory odors, we found more activation in the posterior insula in the food compared to e-cigarette context [ROI analysis, qFDR = 0.023, Fig. 5C]. Exploratory whole-brain analysis showed large clusters in the left and right lingual gyrus to be more active in the e-cigarette condition ($p_{FWE} < 0.001$; see Fig. 4C).

3.2.3. Smokers vs. Non-Smokers

Smokers and non-smokers showed no differences in brain responses to e-cigarette cues or any of the contrasts tested.

3.3. Correlations between neural and subjective responses

Out of the eight clusters that were significantly activated by the any condition vs. rest contrast, one cluster in the left amygdala correlated positively with liking and wanting. Additionally, parameter estimates of clusters in the right anterior insula, caudate, middle cingulate, and supplementary motor cortex correlated positively with wanting. The exploratory analysis showed that activations in the ACC and anterior insula (Fig. 5A and B, respectively) also correlated positively with wanting.

Details on correlations, including brain coordinates, voxel sizes, correlation coefficients, and p-values, are provided in Table 5.

4. Discussion

This study examined differences in reward-related responses to food flavors between the contexts of food and e-cigarettes, sweet and savory flavor qualities, and smokers and non-smokers. In line with literature, the context in which flavors were presented influenced their ratings (van Bergen et al., 2021; Herz & Von Clef, 2001; Bensafi et al., 2014) as well as associated activations in the insula (Bensafi et al., 2014). Savory flavors presented in a food context were wanted substantially more than savory flavors presented in an e-cigarette context. Liking did not differ between contexts. In both contexts, sweet flavors were liked and wanted more than savory flavors. Notably, the difference between sweet vs. savory flavor wanting was much greater in the e-cigarette than in the food context, and, in the e-cigarette context, sweet vs. savory flavors activated the ACC more. There were no differences in responses to flavored e-cigarette or food cues between smokers and non-smokers. Additionally, we explored neural correlates of liking and wanting and

Table 2
Odor attribute ratings per odor quality shown as mean and SE.

	Sweet odors	Savory odors	F-test of odor quality effects*
Sweetness	79.0 ± 1.2	21.0 ± 1.2	F(1,704) = 2899.5; p < 0.001
Savoriness	17.4 ± 1.5	73.6 ± 1.5	F(1,704) = 1984.1; p < 0.001
Intensity	65.1 ± 1.7	58.0 ± 1.7	F(1,1082) = 64.0; p < 0.001

* The F-test tested for main effects of odor quality in mixed model analyses

Table 3
Liking and wanting ratings per odor quality - context combination and user group, shown as mean and SE. N (smokers) = 22; N (non-smokers) = 25.

	Liking[a] (Smokers)	Liking[a] (Non-smokers)	Wanting[b] (Smokers)	Wanting[b] (Non-smokers)
Sweet Food	78.5 ± 3.0	75.1 ± 3.0	78.8 ± 3.6	72.4 ± 3.7
Savory Food	60.0 ± 3.0	65.1 ± 3.0	64.8 ± 3.6	72.1 ± 3.7
Sweet E-cigarette	77.1 ± 3.0	73.7 ± 3.0	78.4 ± 3.6	72.0 ± 3.7
Savory E-cigarette	58.6 ± 3.0	63.7 ± 3.0	32.0 ± 3.6	39.3 ± 3.6

[a] model included Intercept [F(1,123) = 89.7; p < 0.001], User group [F(1,42) = 0.04; p = 0.84], Odor quality [F(1,158) = 70.0; p < 0.001], Context [F(1,137) = 0.85; p = 0.36], User group By Odor quality [F(1,137) = 7.3; p = 0.008], E-cigarette use [F(2,42)= 0.707; p = 0.45], Odor intensity [F(1,132) = 4.1; p = 0.044].

[b] model included Intercept [F(1,93) = 60.5; p < 0.001], User group [F(1,42) = 0.010; p = 0.922], Odor quality [F(1,158) = 99.5; p < 0.001], Context [F(1,137) = 58.0; p < 0.001], User group By Odor quality [F(1,137)= 9.8; p = 0.002], Context By Odor quality [F(1,137) = 54.5; p < 0.001], E-cigarette use [F(2,42)= 0.4; p = 0.67], Odor intensity [F(1,97.3)= 0.8; p = 0.36].

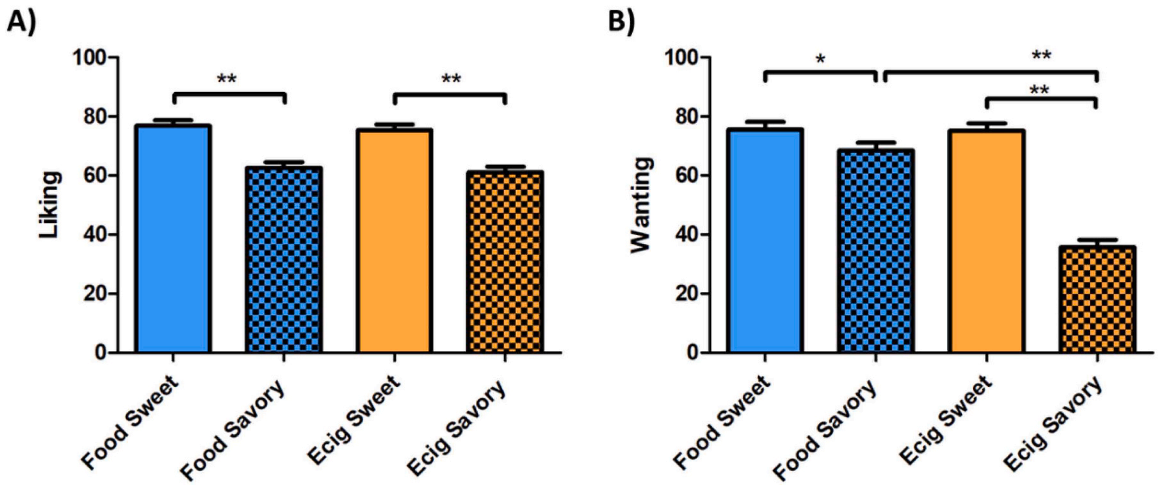

Fig. 3. A) Liking and B) Wanting ratings for each combination of odor quality and context. Data is collapsed across user groups and presented as mean and SE ($n = 47$). * $p < 0.05$; * * $p < 0.001$; blue = food context; orange = e-cigarette context; solid = sweet flavor; checked = savory flavor.

observed those in the left amygdala, which is in line with a previous study using odors (De Araujo et al., 2005) and highlights the role of the amygdala in reward processing (Paton et al., 2006; Berridge & Kringelbach, 2008). Wanting ratings correlated also with activations in several other regions known for reward processing (Knutson et al., 2000, 2001), including the anterior insula, caudate, middle cingulate, and supplementary motor cortex.

As we discuss our findings in the following paragraphs, it is crucial to approach our interpretations of the fMRI results with caution. Both the ACC and the insula are multifunctional brain regions involved in a wide variety of processes. Therefore, attributing specific cognitive or emotional states to activations in these areas can be challenging and may lead to oversimplified conclusions. Any conclusions drawn should consider the limitations of reverse inference, as the same brain region's activation could have multiple explanations.

4.1. *Sweet versus savory flavors*

We compared responses to sweet vs. savory odors in the context of food and in the context of e-cigarettes. The differences we found in reaction to sweet vs. savory flavors are unlikely to be driven by differences in flavor intensity, as we corrected for these in the analysis of brain and subjective data.

4.1.1. *Food context*

In the context of food there was no difference in response to sweet vs. savory odors in reward-related brain areas, as expected. Yet, sweet flavors were liked and wanted more than savory flavors. This was contrary to our hypothesis. However, considering that our participants were satiated, the finding aligns with literature suggesting that liking and wanting for sweet, unlike for savory, is independent of hunger (Finlayson et al., 2007; de Graaf et al., 2023). The divergence between neural and subjective responses in our study is consistent with the results of Griffoen-Roose et al., who observed differing brain reactions to sweet vs. savory food cues in reward-related areas, without corresponding differences in subjective liking (Griffioen-Roose et al., 2014). This suggests a dissociation between neural responses and subjective experiences. The implications of this dissociation on product appeal requires further investigation.

In the exploratory whole brain analysis we found stronger activation in the visual cortex in response to savory, compared to sweet food cues. Stronger visual cortex activation in response to food cues has been attributed to the enhanced attention towards - and salience of - these cues (van der Laan et al., 2011; Smeets et al., 2013). This suggests that the savory food cues in our study were more salient compared to sweet food cues and attracted more visual attention. Differences in the pictures shown are less likely to explain variations in visual activity, as we carefully matched the visual features of the pictures creating the contexts.

4.1.2. *E-cigarette context*

In the context of e-cigarettes, we found stronger activations in reward-related brain areas in response to sweet flavors, as expected. Specifically, a cluster in the middle ACC activated more in the sweet compared to savory e-cigarette condition. In a meta-analysis, activation of this part of the ACC has been associated with the processing of unpleasant and non-food odors. Specifically, this middle ACC region activates more in response to unpleasant compared to pleasant odors (Torske et al., 2022). In our study however, ACC activation was accompanied by, and – in exploratory analysis - correlated with, higher liking and wanting ratings. This suggests that the ACC activation is unlikely to reflect higher unpleasantness of the sweet compared to savory e-cigarette flavor.

The middle part of the ACC also activates more in response to nonfood compared to food odors (Torske et al., 2022). The heightened ACC activation in response to sweet compared to savory e-cigarette cues in our study could therefore indicate that sweet flavors in e-cigarettes are less strongly associated with their food-origin, whereas savory flavors are more closely associated with food. This distinction could also be explained by the common use of sweet food odors in non-food products such as body care items or room fragrances (e.g. cherry, vanilla), while savory food odors are typically only encountered in food.

For savory-flavored e-cigarettes we found an interesting discrepancy in that they were liked, but not wanted. Liking and wanting are neurally distinct components of reward that, in drug use, can be distinguished depending on addiction state or health beliefs. For example, one may like the acute effect of drugs, but have no motivation to consume them due to their harmful nature. In contrast, an addicted person may want to consume a drug even though it no longer results in a pleasurable effect, or liking of that drug (Berridge & Robinson, 2016). That wanting did not differ between smokers and non-smokers in our study may be due to the inclusion of light smokers for whom liking and wanting might not have dissociated (yet).

In food, liking and wanting for savory (but not sweet) qualities may be distinguished based on hunger states (Finlayson et al., 2007). Whether this likewise applies to e-cigarettes is not understood, and further studies should look into that. In our study, hunger ratings did not correlate with liking and wanting, however, participants in our study

Table 4
Differential brain activation per contrast in whole-brain exploratory analysis and ROI main analysis, with differences in odor intensity and e-cigarette use added as covariate where applicable.

Brain region	Side	Analysis	k	Peak voxel MNI coordinates			Peak Z-score
				X	Y	Z	
Food Savory > Food Sweet							
lingual gyrus	L	WB* *	87	− 14	− 74	− 13	6.44
lingual gyrus	R	WB* *	45	11	− 76	− 8	6.22
Ecig Sweet > Ecig Savory							
middle cingulum	R	ROI*	155	6	25	38	4.50
anterior cingulate cortex	L			− 8	39	22	4.31
middle cingulum	L			− 3	28	33	4.19
Ecig Sweet > Food Sweet							
anterior insula	R	ROI*	61	42	18	-11	4.08
anterior insula	R			37	27	− 4	3.81
calcarine cortex	R	WB* *	2688	2	− 80	− 4	> 8.00
lingual gyrus	L			− 26	− 63	− 11	> 8.00
lingual gyrus	L			− 7	− 80	0	> 8.00
middle occipital gyrus	L	WB* *	132	− 26	− 83	18	6.49
middle occipital gyrus	L			− 21	98	11	6.12
middle occipital gyrus	L			− 25	− 89	9	5.87
middle occipital gyrus	R	WB* *	98	35	− 78	20	6.47
middle occipital gyrus	R			29	− 87	14	5.78
superior occipital gyrus	R			22	− 94	14	5.15
Ecig Savory > Food Savory							
lingual gyrus	R	WB* *	1505	4	− 83	− 6	> 8.00
lingual gyrus	L			− 1	− 81	0	> 8.00
lingual gyrus	L			− 5	− 80	− 11	7.8
Food Savory > Ecig Savory							
posterior insula	R	ROI*	68	38	− 17	7	4.08
posterior insula	R			42	− 9	9	4.03
anterior insula	R			38	− 4	3	3.53

* *Exploratory WB analysis significant at cluster level $p_{FWE} < 0.05$
*ROI analysis significant at cluster level $q_{FDR} < 0.05$
R = right, L = left, WB = whole-brain, ROI = region-of-interest, k = cluster extent

were satiated. Another explanation for the difference found between liking and wanting lies in the way liking and wanting were measured. While the question assessing wanting was clearly linked to the combination of flavor and context ("*how much do you want to eat/vape a product with this odor?*"), liking was measured by asking "*how much do you like this odor?*" (not: "*how much do you like this odor in food (e-cigarettes)?*"), which may have allowed for a dissociation of the odor rating from the context. This potential dissociation could also explain why brain activation in reward-related areas in our study usually correlated with wanting, but not with liking.

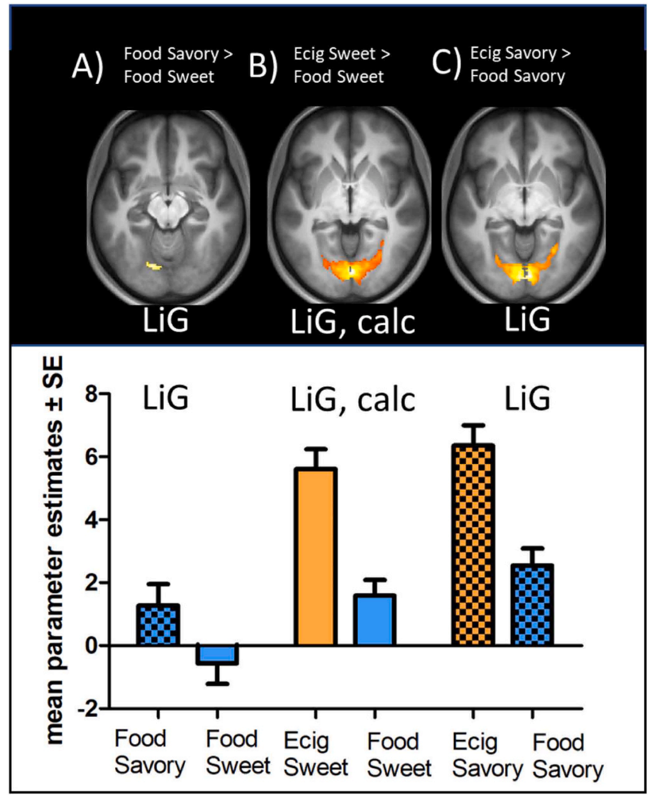

Fig. 4. Color-coded T-maps showing differences in whole brain activation from exploratory analysis, overlaid on mean anatomical image (top) and with associated parameter estimates presented as mean and SE (bottom). Shown are the largest clusters per contrast A) Greater activation of the LiG in response to savory compared to sweet food cues (k = 87, $p_{FWE} < 0.001$; peak voxel MNI (−14, −74, −13); differences in odor intensity added as covariate). B) Greater activation of the LiG and calc in response to sweet e-cigarettes compared to sweet food cues (k = 2688, $p_{FWE} < 0.001$; peak voxel MNI(2, −80, −4); differences in e-cigarette use added as covariate). C) Greater activation of the LiG in response to savory e-cigarette compared to savory food cues (k = 1505, $p_{FWE} < 0.001$; peak voxel MNI(4, −83, −6); differences in e-cigarette use added as covariate.) LiG = lingual gyrus; calc= calcarine cortex; blue = food context; orange = e-cigarette context; solid = sweet flavor; checked = savory flavor.

4.2. Food vs. E-cigarette context

We further investigated how the brain reacted to the same odor in a food vs. e-cigarette context, revealing differences in flavor perception and processing between the two contexts. Sweet flavors activated the right anterior insula more in the e-cigarette compared to the food context. Although there were no significant differences in liking and wanting of the sweet flavor between the two contexts, across conditions, wanting ratings correlated with right anterior insula activations, in both the main and exploratory analyses. This finding contrasts with previous research suggesting that the right anterior insula is generally activated by unpleasant odors (Torske et al., 2022), as in our study, participants did not report the flavor as unpleasant.

The right anterior insula is also known to activate more in response to non-food odors compared to food odors (Torske et al., 2022). In line with that, in our study sweet food-flavors activated the same part of the anterior insula more when presented in an e-cigarette, compared to a food-context. This might mean that the sweet food-flavor presented in a (non-food) e-cigarette context is perceived as non-food. Interestingly, this greater activation was not seen for the savory flavor condition, possibly indicating that in a non-food context, the association between savory food-flavors and food is stronger than for sweet food-flavors and food.

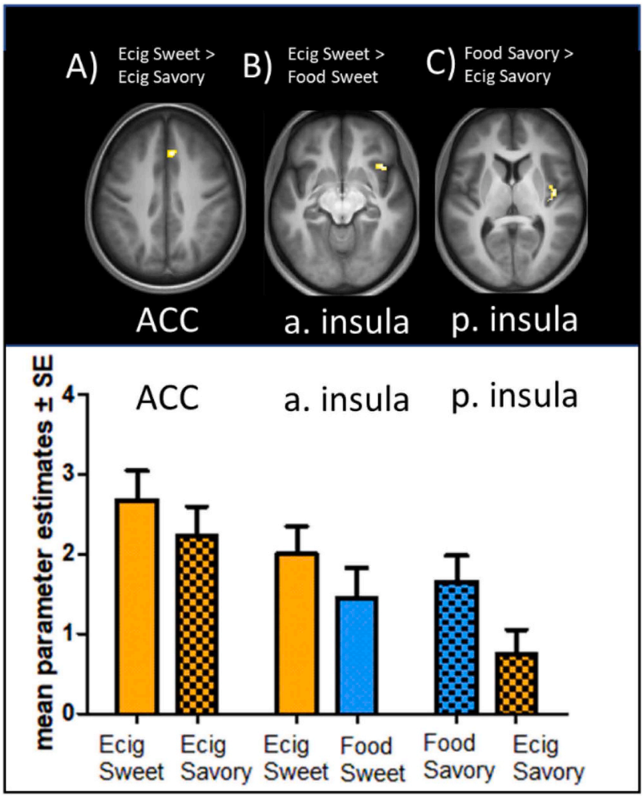

Fig. 5. Color-coded T-maps showing differences in brain activation in reward-related areas overlayed on mean anatomical image (top) and with associated mean parameter estimates presented as mean and SE (bottom). A) Greater activation of the anterior cingulate cortex in response to sweet compared to savory e-cigarette cues (k = 155, $q_{FDR} < 0.003$; peak voxel MNI(6,25,38); differences in odor intensity added as covariate.) B) Greater activation of the anterior insula in response to sweet e-cigarettes compared to sweet food cues (k = 61, $q_{FDR} = 0.030$; MNI(42, 18, −11); differences in e-cigarette use added as covariate). C) Greater activation of the posterior insula in response to savory food compared to savory e-cigarette cues (k = 68, $q_{FDR} = 0.023$; MNI(38, −17, 7) differences in e-cigarette use added as covariate). ACC = anterior cingulate cortex; a. insula = anterior insula; p. insula = posterior insula; blue = food context; orange = e-cigarette context; solid = sweet flavor; checked = savory flavor.

A striking finding of this study is that sweet flavors in e-cigarettes were liked and wanted as much as sweet flavors in food. Food as a primary reinforcer is universally liked and needed to satisfy basic survival needs. High liking and wanting ratings for food were to be expected; however, it is worrisome that sweet flavors in e-cigarettes were equally wanted. Additionally, in exploratory whole brain analysis we found stronger responses of the visual cortex to e-cigarette cues (both sweet and savory) compared to food cues (also sweet and savory). Again, this could be explained by greater attention to - and salience of - the e-cigarette cues (van der Laan et al., 2011; Smeets et al., 2013). Collectively, these findings underscore the risk posed by e-cigarettes, as e-cigarette appeal and salience are closely linked to e-cigarette use (Pacek et al., 2019).

4.3. Smokers vs. Non-smokers

Surprisingly, smokers and non-smokers did not differ in their response to e-cigarette cues. This contradicts a previous study, which showed stronger brain responses to nicotine cues in light smokers (Vollstädt-Klein et al., 2011). We included light smokers due to this responsivity to environmental nicotine cues (Vollstädt-Klein et al., 2011; Watson et al., 2010), their willingness to quit (Rahmani et al., 2021), and the significant health risks associated with even occasional smoking (Hackshaw et al., 2018). Excluding heavy smokers also improved the food context's suitability as a control condition, as heavy smoking reduces taste sensitivity (Chéruel et al., 2017) and potentially alters food preference (Ma & Lee, 2023; Grunberg, 1982). In line with this, we expected and observed similar responses between light smokers and non-smokers in the context of food. In the context of e-cigarettes, the observed similarity in brain response between smokers and non-smokers would have been expected if we had included heavy smokers, who are known to be less reactive to environmental nicotine cues than light smokers (Vollstädt-Klein et al., 2011; Watson et al., 2010).

In a previous study, heavier smokers and non-smokers reported similar liking for sweet e-cigarette flavors (Krüsemann et al., 2021). This aligns with our finding of no difference between light smokers and non-smokers and suggests that sweet e-cigarette flavors are universally liked, independent of nicotine dependency. As higher nicotine dependency is often linked with stronger cravings, we would have expected higher wanting ratings in heavier smokers. However, these cravings in heavy smokers may not be triggered by specific cues or depend on e-cigarette flavors; they could be a result of nicotine withdrawal. In our study, sweet e-cigarettes were highly wanted, by smokers and non-smokers alike. Implementing a ban specifically on sweet flavors would reduce the appeal of e-cigarettes to non-smokers, aligning with the Dutch National Prevention Agreement's objective to discourage e-cigarette use among non-smokers and youth (Blockhuis, 2021). Simultaneously, such a ban could diminish the attractiveness of e-cigarettes for light smokers who might consider them for harm reduction or as a quitting aid. However, the effectiveness of e-cigarettes as a cessation tool, particularly the role of flavors, remains uncertain (Liber et al., 2023). Consequently, we advocate for stricter regulations on sweet e-cigarettes to safeguard the health of non-smokers.

The similarity in how smokers vs. non-smokers reacted to sweet and savory e-cigarette cues in our study implies that it is difficult to use these flavors qualities to simultaneously attract smokers and repel non-smokers. However, it is worth considering that the similar responses of smokers vs. non-smokers in our study could be due to minimal group differences. We included non-smokers who were susceptible to e-cigarette use as a comparison of sweet vs. savory flavor liking and food vs. e-cigarettes would be futile if participants are aversive to e-cigarettes per se, independent of flavor. Additionally, this group is at risk for vaping and smoking (Chan et al., 2021; Khouja et al., 2021) and is therefore of interest for policy. Participants with a history of vaping were not excluded from our study. All smokers in our sample had used an e-cigarette at least once. Additionally, 32% of the non-smokers had tried e-cigarettes, with one non-smoking participant having used them more regularly. Removing that participant from a supplementary analysis had no meaningful impact on the outcomes and did not change the overall conclusion of the study. Yet, the inclusion of non-smokers unsusceptible to e-cigarette use may have led to different results.

4.4. Strengths and limitations

Our study has noteworthy strengths. Foremost, it bridges a gap between applied and fundamental research by simultaneously addressing practical concerns of public health and fundamental questions in the field of flavor processing. This dual focus enhances the impact and relevance of our study, making it valuable for both applied and foundational research. Further, we recruited a sufficient sample size with balanced gender distribution.

A limitation of this study is that the exposure to pictures and orthonasal odors only approximates the actual experience of eating and vaping. Prior studies have shown similar evaluations of non-savory e-liquids through smelling vs. vaping, supporting the validity of smelling for their assessment (Krüsemann et al., 2020). However, the evaluations of savory flavors in food may differ between orthonasal and retronasal delivery (Rozin, 1982). Whether this applies to e-cigarettes is, again,

Table 5
Neural correlates of odor liking and wanting in reward-related ROIs. Correlated were mean liking and mean wanting ratings collapsed across conditions with mean parameter estimates extracted from significant clusters in the any condition vs. rest contrast (main analysis) and clusters found to be significant in the contrasts-of-interest (e.g. Ecig Sweet vs. Ecig Savory; exploratory analysis), collapsed across all conditions. Shown are cluster location, size and coordinates as well as correlation coefficients with liking and wanting together with associated p-values.

Brain Region		k	Peak voxel MNI coordinates			Liking		Wanting	
	Side		X	Y	Z	ρ	p-value	ρ	p-value
Main analysis									
amygdala	L	86	-21	1	− 15	**0.298**	0.042	**0.412**	0.004
amygdala	R	94	24	1	− 13	0.027	0.855	0.166	0.264
			31	− 6	− 6				
anterior insula	L	28	− 44	14	− 6	0.120	0.423	0.223	0.132
anterior insula	R	172	49	14	− 6	0.231	0.118	**0.322**	0.027
			46	5	− 6				
caudate	R	46	11	− 4	16	0.196	0.187	**0.314**	0.032
			17	− 11	18				
middle cingulate	R	22	1	− 26	31	0.205	0.168	**0.288**	0.050
sup motor cortex	R	547	2	19	38	0.256	0.083	**0.350**	0.016
			1	25	53				
			1	34	29				
thalamus	R	46	2	− 20	11	0.019	0.899	0.020	0.894
			2	− 8	9				
Exploratory analysis									
anterior/ mid cingulate	R/L	155	6	25	38	0.278	0.059	**0.377**	0.009
			− 8	39	22				
			− 3	28	33				
anterior insula	R	61	42	18	-11	0.227	0.125	**0.367**	0.011
			37	27	− 4				
posterior insula	R	68	38	− 17	7	0.068	0.351	0.240	0.104
			42	− 9	9				
			38	− 4	3				

L = left, R = right, k = cluster extent, ρ = spearman's correlation coefficient (N = 47)

unknown. Future studies should assess the relationship of savory e-liquid assessments between smelling vs. vaping.

4.5. Recommendations for future research

While we adjusted for the influence of prior e-cigarette use in the analysis, future research could match the number of e-cigarette users and their vaping frequency across groups to control for the influence of nicotine and flavor conditioning. We further advise future studies to assess how e-cigarette flavor preferences, nicotine dependency, and hunger influence the perception and processing of food-flavored e-cigarette cues. Future studies should also assess liking differently, with a clearer connection between the flavor and the product. Additionally, the predictive value of reward-related responses for product appeal remains to be assessed, especially considering the inconsistencies found between neural vs. subjective responses. Lastly, the inclusion of nicotine in future studies could be valuable. Nicotine enhances dopamine function in reward-related brain regions (Brody et al., 2004), influencing their response to rewards (Wang et al., 2020). Specifically, nicotine may amplify the reinforcement of drug (Tizabi et al., 2002) and non-drug (Perkins et al., 2017) rewards by increasing nucleus accumbens activation (Tizabi et al., 2002). However, this enhancement may be specific to certain types of rewards (Perkins et al., 2017). While it has been shown that nicotine supra-additively increases nucleus accumbens reactivity to sweet flavors in e-cigarettes (Kroemer et al., 2018a), it is unknown whether nicotine does the same for savory flavors. Researching how the brain reacts to savory-flavored, nicotine containing e-cigarettes may therefore inform us about the specificity of the reinforcement-enhancing effects of nicotine and enhance our understanding of the complexity of reward-related flavor processing in the context e-cigarettes.

5. Conclusion

We showed that flavor processing differs between the context of food and e-cigarettes, meaning that the principles of flavor preference in food cannot easily be applied to e-cigarettes. In the context of e-cigarettes, we observed a meaningful difference in the perception of sweet vs. savory flavor qualities, suggesting that sweet flavors motivate e-cigarette use more than savory flavors. Moreover, the specific differences in neural processing between sweet vs. savory flavors in the context of e-cigarettes suggest that sweet e-cigarette flavors may be less strongly associated with their food origin. This suggestion is further supported by the observed differences in processing when directly comparing neural reactions to flavors in a food vs. e-cigarette context. We additionally showed that smokers and non-smokers did not differ in their reaction to sweet and savory e-cigarette cues, suggesting that these flavor qualities cannot be applied in product re-design with the aim to appeal to smokers only.

Overall, this study contributes to our understanding of flavor perception, shedding light on the complex interplay between flavors, contexts, and reward processing in the context of food and e-cigarettes. The findings have implications for public health, emphasizing the need to address the appeal and attractiveness of e-cigarettes, particularly among non-smokers.

CRediT authorship contribution statement

Hellmich Ina M.: Data curation, Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing. **Krüsemann Erna J.Z.:** Conceptualization, Methodology, Writing – review & editing. **van der Hart Joris R.H.:** Data curation, Investigation, Writing – review & editing. **Smeets Paul A.M.:** Formal analysis, Methodology, Supervision, Writing – review & editing. **Talhout Reinskje:** Funding acquisition, Supervision, Writing – review & editing. **Boesveldt Sanne:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the writing process the authors used ChatGTP in order to improve readability and language. After this, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2024.108754.

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