Valence processing differs across stimulus modalities

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DOI: 10.1016/j.neuroimage.2018.08.059
fMRI data: https://openneuro.org/datasets/ds001491/

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Abstract

Although it is often assumed that valence processing in the prefrontal cortex (PFC) is similar for stimuli originating from different sensory modalities, evidence supporting this view is lacking. To address this, we recruited 20 male participants and used a delayed-response fMRI design to test whether perceived pleasantness of flavors and images is similarly processed in the PFC. As predicted, significant correlations were observed between image and flavor pleasantness ratings and PFC response to these stimuli; however, these responses were spatially different, with flavor pleasantness reflected in more ventrally located PFC regions than image pleasantness. These results indicate that, contrary to the general assumption of a singular circuit representing pleasantness, distinct PFC circuits are recruited depending upon stimulus modality. We argue that the ventral-dorsal distinction may be attributed to a difference in proximal versus distal stimulus representations.
1 Introduction

The ability to evaluate hedonic valence (Russell, 1980) allows us to form conscious, subjective experiences of pleasantness and unpleasantness. These subjective experiences can influence decision making and hence promote well-being and survival (Hayes et al., 2014). Consequently, the neurobiological basis of valence has been widely investigated to understand behavior in health and in disease.

Neuroimaging, electrophysiological, and neuropsychological studies indicate that the prefrontal cortex (PFC), in particular the medial part of the PFC (mPFC), plays a key role in valence processing (Hayes et al., 2014; Lindquist et al., 2015; Ongür and Price, 2000; Padoa-Schioppa and Assad, 2006; Rudenga and Small, 2013). Although it is generally assumed that subjective impressions of (un)pleasant tastes, odors, sights, sounds and touch are similarly mediated by the PFC (Hayes et al., 2014; Lindquist et al., 2015), this assumption is controversial: studies in humans and non-human primates reported that these subjective impressions are mediated by a common area in the mPFC (Chikazoe et al., 2014; Grabenhorst et al., 2010; Montague and Berns, 2002), a larger network of areas (Hayes et al., 2014; Lindquist et al., 2012), or separate areas in the PFC (Brown et al., 2011). It has been suggested that the medial orbitofrontal cortex (OFC) – the most ventral part of the mPFC – integrates multimodal sensory information and is the most likely area in the brain to mediate valence processing for stimuli originating from different sensory modalities (Kringelbach, 2005). This idea of a common neuronal brain region or network for neuronal processing of valence across stimulus modalities is shared by Montague & Berns’ predictor-valuation model (Montague and Berns, 2002) and Shizgal’ utility estimation model (Shizgal, 1997). These models argue that the value of multimodal stimuli is converted into a common scale (or currency) allowing the organism to compare their value or ‘utility’ to guide future behaviors (Grabenhorst et al., 2010; Montague and Berns, 2002).

In contrast to the view that affective processing is primarily mediated by a single area in the mPFC, more recent meta-analysis studies indicate that valence is processed in a larger scale network comprising limbic areas, such as the anterior insula, rostral and dorsal ACC, medial and lateral PFC, and amygdala, as well as thalamic and occipitotemporal regions (Hayes et al., 2014; Lindquist et al., 2015). Hayes et al., suggested that valence networks for pleasure and aversion share several, but not all, of these brain regions (Hayes et al., 2014). Conversely, Lindquist et al., argue for a general affective workspace: a functional network that acts as a flexible workspace to process both pleasure and aversion (Lindquist et al., 2015). Notably, both these meta-analyses combined studies on affective processing of several stimulus modalities but did not investigate differences between modalities.

To our knowledge only three studies directly compared the neuronal coding of hedonic valence across stimulus modalities within the same subjects (Chikazoe et al., 2014; Grabenhorst et al., 2010; Zhang et al., 2017). These studies found an overlapping representation of stimulus pleasantness across modalities. However, since these studies specifically searched for common activations or activation patterns, it remains unclear what the differences are across modalities and whether the
observed common brain areas are truly one and the same or the product of partly overlapping adjacent areas with distinct functional properties. Indeed, a meta-analysis study by Brown et al. (2011), suggests that adjacent rather than common areas in the PFC are associated with stimulus valence across stimulus modalities. Although their results still showed partial overlap, this study favored an alternative ‘adjacency’ hypothesis postulating that the brain processes hedonic valence differently between modalities.

Thus, it is unclear whether a common neuronal network in the brain processes modality-independent valence coding and/or whether different (adjacent) networks process modality-specific valence coding. A common neuronal network could for example allow comparing pleasure experienced by viewing a beautiful painting and eating a delicious pie. However, these stimuli have very different physiological consequences; a pie has a direct influence on the physiological state of the observer whereas the painting does not, which could argue for the involvement of different neuronal systems/networks. Studying the neuronal processing of valence across stimulus modalities can address whether valence is processed in similar and/or distinct neuronal networks. In the current study, we used independent component analysis (spatial ICA) combined with fMRI BOLD measurement to test the ‘common network’ versus the ‘adjacency’ hypotheses. ICA is particularly suited because it decomposes the fMRI BOLD data into networks that are functionally homogeneous across participants (Allen et al., 2012; Calhoun et al., 2001). As these functional networks (FNs) are maximally spatially segregated, ICA allowed us to investigate whether subjective experiences are processed by identical or different FNs across stimulus modalities.

2 Methods

2.1 Participants

A group of 21 Caucasian healthy young adult Dutch speaking male participants (aged 18-29, mean 24.39, SD 3.17) was recruited from the area around Groningen. Participation was based on written informed consent and this study was approved by the medical ethical committee at the University Medical Center Groningen. Participants were included when they had no self-reported history of taste, smell, neurological, or psychological disorders. Participants were right handed, non-smoker for at least three months, and had normal weight (BMI between 18 and 25) and normal or corrected to normal vision with MR-compatible lenses. Participants who had any food allergy, hypogeusia, psychiatric disorder, a history of drug abuse, non-removable metal on their body or who used any form of medication possibly affecting taste perception (i.e. gastrointestinal complaints, dry mouth, nausea, and taste disturbance) were excluded from the study. Participants received a monetary compensation for their participation.

2.2 General procedure

Participants were invited to the lab two times with a one-week interval and were instructed not to eat or drink during a 2-hour period prior to each session. During the first session, which lasted for
approximately one hour, inclusion and exclusion criteria were checked and a hypogeusia-screening was performed using taste strips (Mueller et al., 2003; Steinbach et al., 2009). Subsequently, participants engaged in a flavor tasting task in which they rated pleasantly and unpleasantly tasting beverages (see experimental design). To manipulate flavor pleasantness, we used different flavor concentrations and aimed 1) to maximize the spread in pleasantness ratings, and 2) to minimize statistical colinearity between perceived intensity and perceived pleasantness. To achieve this, we created a U-shaped relationship between intensity and pleasantness by manipulating flavor concentrations. We adjusted flavor concentrations per participant to ensure positive pleasantness ratings for a positive stimulus range and to avoid extreme disgust for a negative stimulus range. For the second session, participants were invited for a functional magnetic resonance imaging (fMRI) scan between 9:00 and 12:00 AM or between 4:00 and 7:00 PM. During the scan, participants engaged in two tasks that involved flavor and image stimuli, respectively.

### 2.3 Experimental design

#### 2.3.1 Flavor stimuli

An ‘orange’ (1250kJ/100ml) and a ‘tropical’ (1255kJ/100ml) flavored syrup (Karvan Cévitam) were chosen as stimuli. Typically, these flavors are diluted in water to create a sugar sweetened flavored beverage. Prior to the experiment, participants were asked whether they preferred orange or tropical flavored beverages. The less preferred flavor was used as the unpleasant stimulus and was mixed with fish sauce (Squid Fish Sauce, 221kJ/100gr, 77% anchovies extract, 20% salt, 3% sugar) to a 1:3 fish sauce to syrup ratio. Subsequently, a range of beverages was made for both the pleasant and the unpleasant flavors by manipulating flavor concentrations. Concentrations increased logarithmically from a 0.03:1 to 1:1 syrup to water ratio in 12 steps. As the energetic value of flavor stimuli drives their reinforcement value (de Araujo et al., 2013; Tellez et al., 2016, 2013; Veldhuizen et al., 2017), we used the tasteless carbohydrate maltodextrin (Nutricia Fantomalt) to match the caloric value of all stimuli to the maximum energy density of the pleasant beverage. This ensured that acute effects of calories did not contribute to differential response to pleasant vs. unpleasant taste.

#### 2.3.2 Flavor task

Flavor stimulus delivery was similar to the experiment described in detail previously (Dalenberg et al., 2015) with several adjustments. A schematic overview of the task is given in Figure 1. The task provides participants with visual cues and instructions in Dutch using E-prime (Psychology Software Tools Inc., Pittsburgh). The task and stimulus delivery apparatus were used in both experimental sessions. During each trial in this task, participants were warned for an upcoming taste delivery by an asterisk appearing centered on the screen (duration: 2s.). Subsequently, 2 ml of a flavor stimulus was delivered in the mouth and participants were instructed to taste this stimulus with the cue "Taste" (in Dutch: "Proeven", duration: 3s.). After tasting, participants were instructed to swallow the solution, cued as "Swallow" (in Dutch: "Slikken", duration: 3.5s.), followed by a rest period (duration: 10s.). This period minimized overlap of BOLD responses associated with rating and tasting. Finally, two consecutive discrete 9-point Likert scales appeared on the screen, ranging from "very unpleasant" to
"very pleasant" and "not intense" to "very intense", to measure perceived pleasantness and intensity, respectively. Participants were instructed to express their rating by using a button box held in their right hand. Every trial ended with a rinsing procedure, in which participants received a 2-ml bolus of tap water. At the end of every series of increasing concentrations, an extra rinsing procedure was included.

In session 1, participants were familiarized with the flavor task and received 24 flavors; 12 increasing concentrations of the pleasantly tasting beverage and 12 concentrations of the unpleasantly tasting beverage using the gustometer. All concentrations were presented once. The task lasted for about 25 minutes. Participants were explicitly instructed to stop the session if they thought that the stimulus intensity became too unpleasant as this had no consequences for the rest of the experiment and it was our goal to avoid extreme disgust. Based on the pleasantness ratings, four pleasant and four unpleasant flavor concentrations were selected for the remainder of the study. For the pleasant range, the flavor concentration with the (first) highest rating and 3 preceding concentrations was selected, whereas for the unpleasant range, the (first) minimum rating and 3 preceding concentrations was selected. If the highest or lowest rating was among the first 4 concentrations, we chose these first 4 concentrations for the remainder of the study.

In session 2, participants engaged in the flavor task inside the MR scanner. The task contained 40 stimulus trials, which were presented across four imaging runs. Every flavor stimulus was delivered 4 times balanced over all imaging runs and counterbalanced between participants. Each imaging run lasted for approximately 10 minutes (depending on reaction times) and contained two series of 5 trials (water + 4 increasing concentrations in the pleasant range and water + 4 increasing concentrations in the unpleasant range). The entire task lasted for approximately 40 minutes, in which 176 ml of liquid was consumed. As baseline, we included three 35-second periods in each imaging run, during which the participant was looking at a black screen with a white fixation cross centered in the middle.

**Figure 1. Trial structure of the flavor task.** Every flavor stimulus was delivered 4 times distributed over 4 imaging runs. Every trial started with a cue, followed by the taste. The participant was subsequently instructed to swallow, rest and then provide ratings for the stimulus on 9-point Likert type scales. The first four trials of increasing concentrations ended with one rinsing procedure. After the fifth trial, the participant was instructed to rinse twice.

**2.3.3 Visual stimuli**

40 images were used from the International Affective Picture System, IAPS. Based on reference scores, we randomly selected images that varied from high to low arousal (HA, LA) and negative to positive valence (NV, PV). The set contained 10 HA-NV, 10 LA-NV, 10 LA-PV, and 10 HA-PV images. The reference scores of the selected images are shown in Figure 4D.
2.3.4 Image task

The image task (Figure 2) was similar to the flavor task and contained 40 trials presented in a single MR imaging run with a duration of approximately 20 minutes. During each trial in this task, participants were warned for an upcoming image by an asterisk appearing centered on the screen (duration: 2s.). Subsequently, an IAPS image was shown (duration: 4s.), followed by a rest period (duration: 6s.). Finally, two consecutive discrete 9-point Likert scales appeared on the screen, ranging from "very unpleasant" to "very pleasant" and "not intense" to “very intense”, to measure perceived pleasantness and intensity, respectively. The imaging run contained 5 30-second periods of fixation cross as baseline. To adjust for offsets in mean ratings and rating variability, we normalized all ratings (z-scores) across participants and modalities.

2.4 Data acquisition

MRI scans were performed using a 3-Tesla MR scanner (Philips Intera, Best, the Netherlands) equipped with a 32-channel head coil. A T1-weighted 3D fast field echo (FFE) whole brain image was obtained in transverse orientation for anatomical reference. Acquisition parameters: FOV 256 × 232 × 170 mm (rl, ap, fh); voxel size 1 mm isotropic; TR = 9 ms; TE = 3.5 ms; flip angle 8º; SENSE factors: 2.5, 1 (ap, fh); 170 slices, scan duration = 246.3s. Functional brain images were acquired using a multi-echo EPI sequence in transverse orientation (descending). Acquisition parameters: FOV 224 × 224 × 157.5 mm³ (rl, ap, fh); 45 axial slices; voxel size 3.5 × 3.5 × 3.5 mm; matrix size 64×61; slice gap 0 mm; TE 8.02, 22.03, and 36.03 ms; flip angle 80º; SENSE factors: 3, 1 (ap, os); scan time per volume 2.45s. A total of 5 runs were acquired per participant (4 for the flavor task and 1 for the image task). As the experiment was self-paced, the total number of volumes per imaging run varied. The data set is available at https://openneuro.org as ds001491.

2.5 Data analysis

2.5.1 Behavioral data

Pleasantness and intensity ratings from MRI session (i.e., session 2) were analyzed in R (version 3.1.3, 2015-03-09) linear mixed models (LMMs, package LME4, version 1.1-7) (Pinheiro and Bates, 2000). P-values were calculated using the Satterthwaite’s approximation for the degrees of freedom, provided in the package lmerTest (version 2.0–25) (Kuznetsova et al., 2014). To investigate relationships between pleasantness and intensity ratings, with IAPS reference scores or with stimulus concentrations
we used first order polynomial predictors. To investigate whether we successfully created a U-shaped relationship between intensity and pleasantness, we z-transformed ratings per participant and used second order polynomial predictors in the regression models. In all LMMs, we used participant id as a random factor.

2.5.2 fMRI data
The data-analysis consisted of a preprocessing stage followed by two analysis pipelines: 1) a conventional SPM analysis performed on individual voxels and 2) a stimulus locked functional network time series analysis (SL FNTSA) performed on functional networks. Both pipelines were executed on the preprocessed fMRI BOLD data for the flavor and image task separately (see Figure 3).

We used both pipelines to compare our network-based analysis with a classical mass univariate analysis performed in SPM.

Figure 3. Schematic overview of the analysis pipeline. See Methods for details. Abbreviations: HRF = haemodynamic response function, ME = multi-echo, ICA = independent component analysis, FN = functional network, CSF = cerebral spinal fluid, SL FNTSA = stimulus-locked functional network time series analysis.

2.5.2.1 Preprocessing
One participant dropped out before the scanning session and we continued with all data from 20 participants. As we acquired multi-echo fMRI data (Peltier and Noll, 2002; Poser et al., 2006) using three echo times (TEs), we acquired three time-series for each functional run. These time series were denoised using the AFNI tool meica.py (version 2.5 beta11, https://bitbucket.org/prantikk/me-ica/) (Kundu et al., 2017, 2013, 2012). First, this tool realigns functional data based on the middle TE, then concatenates all three echo time-series in space (i.e., per time point) and applies an independent component analysis (ME-ICA). Subsequently, the tool identifies independent components containing BOLD and non-BOLD signals based on their TE-dependence (Kundu et al., 2017, 2013, 2012). All BOLD containing components are retained and combined into three denoised echo time series (i.e., one denoised time series per echo). Finally, these denoised echo time series are optimally combined into a denoised single time series using a T2* weighting scheme (Kundu et al., 2013, 2012; Posse et al., 1999).

The denoised single time series were coregistered to the anatomical T1 scan, normalized to MNI space, moderately smoothed with a 6 mm FWHM kernel for a stimulus locked functional network
time series analysis, and separately smoothed with an 8 mm FWHM kernel for a conventional mass
univariate fMRI analysis using SPM12 (v6906) running in Matlab R2016b.

2.5.2.2 Conventional mass univariate fMRI analysis

For the first-level statistical analysis, we performed mass-univariate regression models with a short
block design for each participant, separately for the flavor and image tasks. For the flavor task, we
included all four sessions in the first level analysis and included the regressors: 1) [Taste & Swallow]
with [pleasantness] and [intensity] ratings (z-transformed per subject) as parametric modulation, and 2)
conditions of no interest [New flavor range indicator], [New flavor indicator], [Rating screens], and
[Rinsing]. For the image task, we included: 1) [Image] with [pleasantness] and [intensity] ratings (z-
transformed per subject) as parametric modulation, and 2) conditions of no interest [New image
indicator], and [Rating screens]. As the data was already denoised during preprocessing, we did not
enter motion regressors, which may correlate with the task and, consequently, reduce sensitivity to
detect effects of interest. The task-related regressors were convolved with the canonical hemodynamic
response function (HRF) and a high-pass filter of 64 seconds was applied.

On group level, we performed mass univariate one-sample t-tests to investigate 1) group
effects of [Taste & Swallow] and [Image] as a control step to ensure we successfully measured brain
responses related to flavor tasting and watching images, 2) group effects of [pleasantness] to find brain
responses associated with pleasantness coding, separately for the flavors and images, and 3) contrasts
[flavor pleasantness – image pleasantness], [image pleasantness – flavor pleasantness] and the
conjunction [flavor pleasantness & image pleasantness] to find overlap and differences in fMRI BOLD
activity patterns for pleasantness processing between both modalities. For the main effects of stimulus
presentation, we used a family wise error corrected threshold of $P_{FWE} < 0.05$. As liking effects in taste
and flavor fMRI paradigms typically do not survive multiple comparison corrections, we thresholded
the contrasts related to stimulus pleasantness using an uncorrected threshold of $P < 0.001$. Note that
results are corrected for multiple comparisons using permutation maximum statistics in our SL FNTSA.

2.5.2.3 Stimulus locked functional network time series analysis (SL FNTSA)

The SL FNTSA identifies small FNs that are functionally homogeneous across participants and have
maximal spatial independence (Allen et al., 2012; Calhoun et al., 2001). The main benefit of this
approach is that it allows one to specifically test whether identical or different (e.g., adjacent)
functional networks correlate with pleasantness across stimulus modalities. A secondary benefit of this
approach is that it offers a significant dimensionality reduction from individual voxels (~180,000 in the
current study) to FNs (73 in the current study) and therefore less statistical tests are performed which
increases statistical sensitivity. Additionally, we do not use a haemodynamic response function (HRF)
convolution allowing for the possibility of looking at temporal BOLD changes (albeit aggregated
across similarly behaving voxels) and possible misspecifications of the HRF across brain
regions/functional networks.

In our SL FNTSA, we first parcelated the entire denoised fMRI BOLD time series of the
flavor task into FNs using spatial ICA as implemented in the Group ICA Toolbox (v2.0e) (Calhoun et
al., 2001). This data-driven technique groups fMRI BOLD signals that are synchronized over time and
over participants into FNs that are temporally coherent (Xu et al., 2013). The number of independent components (ICs) was estimated using the MDL algorithm (Li et al., 2007), which resulted in 102 ICs. Group data were first reduced to 153 principal components (PCs) on an individual level and then to 102 PCs on a group level. Spatial ICs were subsequently estimated using the Infomax algorithm (Bell and Sejnowski, 1995). As we intended to keep the fMRI data of the visual task maximally independent from the flavor task, but still spatially constrained to the same FNs, we used a spatially constrained ICA on the fMRI data of the visual task to parcelate this data into FNs with similar spatial properties to the flavor task (Lin et al., 2010). After visual inspection, 29 components were spatially located within CSF and therefore disregarded.

We chose to use the flavor task as reference in the main ICA for two reasons. First, the flavor task contained approximately twice the number of time points compared to the image task and the number of available time points is positively related to the number of components that can be estimated from the data (see e.g., Olafsson et al., 2015). Second, as the image task only contained visual stimuli while the flavor task contained flavor stimuli and visual instructions, we expected to find very little functional networks related to orally presented stimuli in the image task.

We continued with performing a stimulus-locked time series analysis on the 73 remaining FNs in R. This analysis is similar to selective averaging (Dale and Buckner, 1997). First, component time courses were filtered per subject using a high pass 64s Butterworth filter available in package Signal (version 0.7-4). Subsequently, we isolated stimulus trials per component time course and resampled the data to 1-second time bins using spline interpolation. We calculated 33 and 23 time bins for the flavor and image task, respectively. For statistical analysis, data were concatenated to datasets containing 33 or 23 time points for all 40 stimuli per component and per subject.

To investigate the spatial and temporal association between components and perceived pleasantness (adjusted for intensity), we performed LMMs per component and per time bin. A total of 2409 (33x73) and 1679 (23x73) models were performed for the flavor and image task, respectively. For each model, the time course score was entered as dependent variable, while pleasantness ratings and intensity ratings (z-transformed per participant) were entered as independent variables. The subject id constituted as a random variable to take care of repeated measures. Corrected p-values across components and time bins were calculated using permutation maximum statistics on the LMM T-values (Nichols and Holmes, 2002). Pleasantness ratings were randomized 1000 times to perform a total of 4,088,000 random LMMs. This p-value correction also accounted for temporal correlations in the data as they were preserved in each permutation.

We determined overlap by intersecting the thresholded results to determine which FN time courses were significantly associated with pleasantness across tasks in the 3-9s post-stimulus timeframe. Furthermore, direct contrasts between prefrontal FN BOLD responses across modalities were performed using area under the curve (AUC) scores. For each stimulus trial, we calculated the AUC of the FN BOLD time series 3-9s post stimulus onset. These were entered as dependent variable in LMMs while the interaction between pleasantness rating and stimulus modality was entered as independent variables. Again, subject id constituted as a random variable to take care of repeated measures.
In addition, we performed two control analyses: 1) a SL FNTSA in which we first performed an ICA on the visual task and a constrained ICA on the flavor task to evaluate whether the order would change our main results (see Figure S3, S4, and Table S4), and 2) an analysis on the rating screen time period (see Figure S5 and Table S5, S6). As the rating screens were identical across fMRI tasks, this condition allowed us to investigate how the SL FNTSA compares to an SPM conjunction analysis on a stimulus condition that is identical across the two different tasks.

3 Results

3.1 Behavioral results

Figure 4. Behavioral ratings for the flavor and image stimuli. Behavioral ratings from the MRI session are shown for the image task (A-D) and the flavor task (E-G). (A) and (B) show the relationship between image pleasantness and image intensity, with the IAPS reference scores valence and arousal, respectively. (C) shows the U-shaped relationship between the scaled image intensity and image pleasantness ratings while (D) shows the U-shaped relationship between the scaled IAPS valence reference scores and scaled IAPS arousal reference scores. The data presented in (A,B,D) corresponds to the 40 images that were used in the image task, whereas the data presented in (C) corresponds to all stimulus trials across participants. (E) and (F) show the relationship between flavor pleasantness and flavor intensity, with the selected stimulus concentration range (1-4), which was optimized across participants to maximize subjective pleasantness for the pleasant stimulus range and minimize extreme disgust for the unpleasant range. (G) shows the U-shaped relationship between the scaled flavor intensity and flavor pleasantness ratings. The flavor stimuli are grouped into water (blue), unpleasant flavor (pink), and pleasant flavor (green). For each regression line, we reported the mean $R^2$ (mean across participants in A-C and E-G) or $R^2$ (across stimuli in D). Scaled ratings refer to ratings that are z-transformed per participant. The error bars represent the 95% CI.

The results of the behavioral ratings are shown in Figure 4. We confirmed that image pleasantness strongly correlated to the IAPS valence reference scores (Fig 4A, $\beta=0.93$, $t(1,779)=52.46$, $p<0.001$) and image intensity correlated to the IAPS arousal reference ratings (Fig 4B, $\beta=0.72$, $t(1,779)=10.45$, $p<0.001$). In the flavor task, ratings for the pleasant flavor range were moderately related to selected
stimulus concentration (Fig 4E, $\beta=0.09$, $t(1,279)=2.24$, $p=0.026$) while unpleasant flavors were negatively related to selected stimulus concentrations (Fig 4E, $\beta=-0.35$, $t(1,279)=-7.43$, $p<0.001$). Intensity ratings for pleasant and unpleasant flavors were positively related to selected stimulus concentrations (Fig 4F, pleasant: $\beta=0.63$, $t(1,279)=12.02$, $p<0.001$; unpleasant: $\beta=0.58$, $t(1,279)=9.85$, $p<0.001$).

In the flavor task, we found a stronger quadratic relationship between intensity and pleasantness (Fig. 4G, linear: $\beta=-0.21$, $t(1,747)=-7.72$, $p<0.001$; quadratic: $\beta=0.73$, $t(1,747)=23.21$, $p<0.001$) than in the image task (Fig. 4C, linear: $\beta=-0.49$, $t(1,747)=-17.18$, $p<0.001$; quadratic: $\beta=0.40$, $t(1,747)=11.42$, $p<0.001$). The linear dependence between pleasantness and intensity was low for the flavor task (mean $R^2$ across participants = 0.13) and moderate for the image task (mean $R^2$ across participants = 0.32).

### 3.2 Conventional voxel-based mass univariate fMRI analysis

In our mass univariate analysis, we investigated the main effects of image viewing, flavor tasting, and pleasantness ratings and the differences between modalities on a voxel level. Results were adjusted for arousal by including intensity ratings as an additional parametric modulation. As expected, we found that fMRI BOLD in response to flavors was associated with brain areas that are typically involved in taste and flavor processing (figure 5 and Table S1). Similarly, fMRI BOLD in response to visual stimuli was associated with brain areas associated with visual processing. Flavor pleasantness ratings were associated with fMRI BOLD responses in the ventromedial PFC (vmPFC), whereas image pleasantness ratings were associated with a larger group of brain areas including a different part of the vmPFC, the precuneus, and the postcentral cingulate gyrus.

In Figure 6 (and Table S2) we show the overlap and differences between flavor and image pleasantness, on a statistical threshold ($p<0.001$ uncorrected). The results of the contrasts [flavor pleasantness – image pleasantness] and [image pleasantness – flavor pleasantness] show that flavor pleasantness is associated with BOLD responses in more ventrally located PFC regions than image pleasantness. The conjunction analysis showed that there is a very small spatial overlap ($k=32$) in a vmPFC area in which BOLD responses are associated with both flavor and image pleasantness.

Although these results suggest that stimulus pleasantness processing in the PFC largely differs across flavors and images, the voxel-based nature of this analysis is not perfectly suitable to show that either the same or adjacent networks are associated with flavor and image pleasantness processing. Therefore, we set up the SL FNTSA.
Figure 5. **Main fMRI BOLD effects for stimulus presentation and stimulus pleasantness.** Using mass univariate analyses, we acquired activation maps for (A) tasting a flavored beverage, which was associated with brain areas that are typically involved in gustatory processing such as the bilateral nucleus of solitary tract, bilateral postcentral gyrus, bilateral insula, bilateral amygdala, bilateral cerebellum, and supplementary motor area, and (B) viewing an image, which was associated with brain areas typically involved in visual processing, such as the bilateral middle occipital gyrus and superior colliculi. Parametric modulation analysis shows the activation maps associated with (C) flavor pleasantness, which correlated with vmPFC engagement, and (D) image pleasantness, which correlated with a larger group of brain areas, such as the vmPFC, precuneus, and postcentral cingulate gyrus. Main effects of flavor and image are thresholded at $P_{\text{FWE}} < 0.05$ whereas parametric modulations were thresholded at $P < 0.001$ (uncorrected). Pleasantness activation maps were adjusted for intensity ratings, $n = 20$ and color bars indicate $T$-values.


### 3.3 Stimulus locked functional network time series analysis

Figure 7 shows the stimulus locked BOLD average of a flavor and an image trial for two FNs constituting primary gustatory and primary visual areas, respectively. The visual and gustatory FN show a strong stimulus-locked HRF to their related stimulus modality, visual or flavor stimuli respectively but not to the unrelated stimulus modality. Furthermore, we show that the response in these primary sensory areas is similar across pleasant and unpleasant trials. These FNs are akin to (parts of the) statistical parametric maps acquired by the mass univariate fMRI analysis (see Figure 5).
Figure 7. Brain networks associated with flavor and image processing acquired by spatial ICA. The figure illustrates the stimulus-locked time course BOLD responses with respect to both tasks and adjusted for stimulus intensity. (A) the gustatory network comprising left and right postcentral gyrus, cerebellum, insula, amygdala, thalamus, and nucleus of solitary tract. The stimulus-locked time course of this network shows a characteristic haemodynamic response function (HRF) in response to a flavor stimulus while this HRF is non-existent for visual stimuli. (B) the visual network comprising the right and left middle occipital gyrus. The stimulus-locked time course of this visual network shows a strong HRF in response to a visual stimulus. The same network shows smaller (biphasic) HRF response in the flavor task likely related to the changes in visual cues. Trials were split into two groups associated with either pleasant (blue) and unpleasant (red) ratings to indicate that there were minimal differences in these primary sensory areas associated with differences in valence. The error bands indicate the linear mixed effect 95% confidence interval of the mean. Task labels: * = warning for upcoming stimulus; drops/rabbit = stimulus presentation; + = resting period; rating screens: 2 consecutive 9-point rating scales.

The result of the SL FNTSA is depicted in Figure 8. Here, each row represents the relation between each FN time course and pleasantness ratings. Given the slow nature of the HRF, we chose a period of 3-9 seconds post-stimulus presentation as the time-interval of interest for the stimulus-induced valence responses. Within this time interval two FNs including the ventral medial (vm)PFC (peak at 4s post-stimulus onset, T=4.52, \( P_{\text{corrected}} = 0.015 \)) and bilateral insula (peak at 8s post-stimulus onset, T=-4.87, \( P_{\text{corrected}} = 0.003 \)), respectively, were significantly associated with flavor pleasantness. In accordance with the mass univariate analysis results, a larger group of 16 FNs was associated with image pleasantness. Importantly, three of these FNs covered adjacent ventral to dorsal mPFC regions (all three peak at 5s post-stimulus onset, T=5.14; 5.40; 4.97, \( P_{\text{corrected}} < 0.001 \)). We have summarized the results of these mPFC results across modalities in Figure 9, which stresses the adjacency of these functional networks and the difference between flavor pleasantness and image pleasantness associations in their stimulus-locked time courses. Information on all FNs is available in Supplementary Table S3.

Note that although we tested 10 seconds worth of extra data in the flavor task, the critical corrected T-value only marginally differed between both analyses (flavor task critical \( T = 4.17 \); image task critical \( T = 4.12 \)) indicating that reducing the time-interval of interest only has a minimal effect on statistical power. Figure 8 furthermore illustrates the benefit of the delayed response task specifically in
the image task. In accordance to our delayed response paradigm, we found distinct FNs associated with either image perception or rating behavior. The FNs associated with pleasantness ratings during the production of a rating response to images included bilateral precentral gyrus, bilateral lingual gyrus, bilateral middle temporal gyrus (see Table S3).

As four FNs comprising the medial PFC (Figure 9) were associated with stimulus pleasantness for either flavors or viewing images, we further investigated the differences across modalities in the prefrontal cortex by directly testing the interaction between stimulus pleasantness and stimulus modality using area under the curve (AUC) scores as dependent variable in LMMs. Although, we did not find a significant interaction in the most ventral mPFC ($T(1525)=1.84$, $p = 0.066$), we did find interactions in more dorsal mPFC areas ($t(1525)=3.14$, $p = 0.0017$; $t(1525)=2.88$, $p = 0.004$; $T(1525)=3.21$, $p = 0.0014$) indicating that image pleasantness is more strongly related with BOLD responses in more dorsal mPFC areas than flavor pleasantness.

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**Figure 8. Relation between stimulus pleasantness and functional network responses across stimulus modalities.** The relation between pleasantness responses and FN time courses (adjusted for intensity) was calculated across participants and trials using linear mixed effect models. The figure shows the relation (in $T$-values) between pleasantness ratings and the response per functional network on a 1-second peristimulus timescale for flavor stimuli (A) and image stimuli (B). Horizontally, networks were grouped into larger scale network similarly to (Allen et al., 2012). Relations surviving a permutation maximum statistic multiple comparison correction are highlighted in black frames. The 3-9s time interval of interest is highlighted in red frames. The arrows indicate the four medial prefrontal cortex functional networks that were used for additional analysis. Their $T$-value time course are also shown in figure 5b. Abbreviation DMN: default mode network.
Figure 9. Relation between pleasantness ratings and functional network time courses. (A) Four adjacent medial prefrontal cortex functional networks that were associated with either flavor or image pleasantness. (B) The relation with pleasantness ratings (in T-values) graphed across the first 20 second post stimulus onset. The dashed lines indicate the multiple comparison corrected threshold. The T-value time courses are also shown in Figure 5 among the T-value time courses of all other functional networks.

4 Discussion

In the current study, we sought to investigate whether valence coding, in terms of pleasantness, is mediated by either a common or different (adjacent) neuronal networks across stimulus modalities. Our analyses revealed that multiple FNs in the mPFC are associated with stimulus pleasantness. Although, we found that very localized vmPFC circuits may be related to pleasantness across modalities, pleasantness processing was associated with modality specific mPFC regions on a larger network level. More specifically, pleasantness ratings for visual stimuli were associated with more dorsally located mPFC functional networks than pleasantness ratings for flavor stimuli.

Although several studies compared emotional states induced by stimuli stemming from different modalities (see e.g., Kragel and LaBar, 2014; Saarimäki et al., 2016), to our knowledge only a few neuroimaging studies focused on a direct within-subject comparison of stimulus-induced valence coding across stimulus modalities (Chikazoe et al., 2014; Grabenhorst et al., 2010; Zhang et al., 2017). Chikazoe et al. compared valence responses to visual and flavor stimuli using multi-voxel pattern analysis. The authors reported that fine-grained BOLD patterns in the vmPFC were predictive for pleasantness responses across these modalities (Chikazoe et al., 2014). One limitation of this study is that their results were not adjusted for arousal (or perceived stimulus intensity) ratings. Therefore, it cannot be ruled out that common voxel patterns were driven by perceived stimulus intensity rather than pleasantness. Grabenhorst et al. compared valence responses to taste stimuli and to heat stimuli presented on the hand (Grabenhorst et al., 2010). Using a conventional mass univariate fMRI analysis, they found a common area in the vmPFC correlated with pleasantness ratings across both sensory modalities. The authors furthermore showed that this result was not driven by perceived intensity
ratings. Zhang et al (2017), compared stimulus pleasantness evoked by monetary gains and losses, images of faces, and electric shocks. Using univariate and multivariate analysis, the authors show that stimulus value across modalities was represented in the vmPFC. Important differences with the current study are 1) Zhang et al. studied the anticipation of stimuli but not the perception of the stimuli themselves, and 2) in the Zhang et al. study, images of faces were only pleasant in valence while shocks were only unpleasant in valence confounding stimulus modality with stimulus valence. Although all three studies point toward a common area in the vmPFC mediating valence processing, these studies specifically searched for overlapping patterns and did not contrast pleasantness processing across modalities within the mPFC. Furthermore, as the overlapping regions presented in these studies are very small (or only survived lenient statistical thresholding), it remains unclear if and how much these findings are influenced by signal smoothing across neighboring areas with distinct functions and/or whether the overlapping area shares a similar function.

To get a more definitive answer to the question whether a singular or distinct neuronal networks mediate valence processing across stimulus modalities, we segregated our fMRI data into functional networks with maximal spatial independence to specifically investigate source signals originating from distinct brain areas. This allowed us to show that neighboring networks, rather than a singular network, in the PFC are mediating valence coding across sensory modalities. In accordance with the meta-study of Brown et al. we found a ventral-dorsal distinction within the mPFC in which flavor pleasantness was represented more ventrally than image pleasantness.

It is important to consider why a ventral-dorsal distinction in the PFC between flavor and image pleasantness may exist. In social cognition, a similar ventral-dorsal distinction in the mPFC has been observed. Social judgments about oneself predominantly engage neuronal circuits in the vmPFC whereas social judgements about others predominantly engage neuronal circuits in the dorsomedial PFC (Van Overwalle, 2009). Notably, the vPFC receives visceral input, provides output to viscerosensory structures (Critchley et al., 2007; Öngür et al., 2003; Ongür and Price, 2000; Price, 1999), and integrates the current physiological state with the perception of external stimuli and their learned physiological consequences (Critchley, 2009; Critchley and Harrison, 2013; de Araujo et al., 2008, 2006; De Araujo et al., 2012). In view of these findings, we hypothesize that the ventral-dorsal distinction between flavor and image pleasantness is related to proximal versus distal representations; pleasantness judgements for flavors can be of immediate importance to the physiological state of the observer, and therefore strongly relate to the observers’ inner world or self (i.e., a proximal representation). In contrast, pleasantness judgements for images represent judgments about the outer world and may not be directly related to our physiological state (i.e., a distal representation).

A major implication of our findings is that (meta-analytic) neuroimaging studies that integrate findings across sensory modalities to investigate affect, or related concepts such as reward and pain, may poorly represent each individual sensory modality. To address this issue, future studies should take potential differences in valence processing into account. The meta-analysis study Brown et. al. achieved this by summarizing results per sensory modality. It is important to note that they observed, in line with our current findings, an overall pattern of adjacency among modalities within the medial prefrontal cortex rather than overlap (Brown et al., 2011). Alternatively, studies investigating multiple
modalities can apply methods to ensure that study results are representative for all included stimuli. Advances in machine-learning and cross-validation techniques provided suitable methods to ensure that brain results on affective concepts are representative for all sensory modalities. In recent work, Woo et al., demonstrated that cross-validating machine learning classifiers on brain responses to different forms of mental and physical pain allowed construction of a stimulus intensity independent pain signature (SIIPS) in the brain (Woo et al., 2017). We believe that future research should focus on extending such signatures by 1) incorporating additional sensory modalities such as gustation and 2) search for a common signature across sensory modalities coding for the experience of pleasure.

In decision-making theory, value maximization is a widely used framework (Kahneman and Tversky, 1979). This framework proposes that an organism compares the subjective value of choice alternatives and chooses the alternative with the greatest value. This requires that qualitatively different stimuli are converted onto a common valuation scale. Multiple studies suggest that this process is mediated by the vmPFC (or OFC) (Bartra et al., 2013; Montague and Berns, 2002). However, these studies have two important limitations. First, they use tasks containing visual cues that represent different modalities rather than cues that are perceived by different sensory organs (Chib et al., 2009; Lim et al., 2013). Second, stimuli in most of these tasks are, by design, a predictor of money or food (Chib et al., 2009; Kennerley et al., 2009; Lim et al., 2013; Padoa-Schioppa and Assad, 2006; Sugrue et al., 2005). Subjects in primate studies, for example, compare qualitatively different visual stimuli to obtain juice rewards (Kennerley et al., 2009; Padoa-Schioppa and Assad, 2006; Sugrue et al., 2005). Consequently, these stimuli gain a physiological significance, which they may not have in a real-world environment. Although these studies do show that qualitatively different stimuli can be evaluated on a common valuation scale, these studies are insufficient in revealing a common neuronal circuit or network mediating value for stimuli perceived by different sensory organs.

The idea that the vmPFC is functionally segregated with respect to affective processing is not new. A medial to lateral distinction between the evaluation of reinforcement and punishers and an anterior to posterior segregation related to stimulus complexity has already been suggested (Elliott et al., 2000; Kringelbach and Rolls, 2004; Small et al., 2001). However, the current work shows that the vmPFC shows another level of functional segregation of affective processing driven by stimulus modality and/or physiological significance. We do note that our work is limited to the valence aspect of affect. Affective processing is comprised of more components than merely valence and studies have shown that different aspects of affective processing such as novelty, predictability, fear, anger, and surprise are associated with unique BOLD activity patterns in the brain (Saarimäki et al., 2016; Wager et al., 2015).

It is important to note that we presented flavor stimuli in a predictable order instead of a randomized order. Participants engaged in a training session prior to the MRI scan session to make them well aware of the stimulus order. We chose a predictable order for two reasons: 1) we aimed to minimize carry-over effects between the pleasant and unpleasant flavor stimuli, and 2) in a real-world environment, feeding behavior is also predictable; it usually starts with visual perception of a food followed by planning and executing motor actions to start consumption. Usually (pseudo-) randomization is used to minimize carry-over effects (Macfie et al., 1989), stimulus-specific
anticipatory effects, surprises, and/or prediction errors (den Ouden et al., 2012; García-García et al., 2017). However, we reasoned that randomization in addition to mechanically administering flavors into the mouth, conflicts with the predictable nature of flavor stimuli during real-world feeding behavior. Moreover, we did not find evidence for anticipatory effects affecting pleasantness processing, which should be reflected in early BOLD responses in the mPFC correlating with pleasantness ratings (see Figure 8 & 9).

A limitation of the current study is that we only recruited young adult male participants. Although, we found a distinction valence processing within this homogenous group, it is unclear whether these results generalize to women, children, and/or elderly.

To conclude, the current study indicates that although localized circuitry in the vmPFC may mediate valence coding across stimulus modalities, larger scale networks in the vmPFC are modality-specific unpleasantness coding.

5 Acknowledgements

This research was funded by Top Institute Food and Nutrition (TIFN, Project code SL001). Furthermore, the authors would like to thank Dr. Dana Small for important discussions about the interpretation of the results and her comments on the manuscript. We would also like to thank Luca Nanni for designing the gustometer.

6 Author contributions


7 Declaration of Interests

The authors declare no competing interests.

8 References


effects for linear mixed effect models (lmer objects of lme4 package).


