Superadditive Opercular Activation to Food Flavor is Mediated by Enhanced Temporal and Limbic Coupling

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Abstract: Food perception is characterized by a transition from initially separate sensations of the olfactory and gustatory properties of the object toward their combined sensory experience during consumption. The holistic flavor experience, which occurs as the smell and taste merge, extends beyond the mere addition of the two chemosensory modalities, being usually perceived as more object-like, intense and rewarding. To explore the cortical mechanisms which give rise to olfactory–gustatory binding during natural food consumption, brain activation during consumption of a pleasant familiar beverage was contrasted with presentation of its taste and orthonasal smell alone. Convergent activation to all presentation modes was observed in executive and chemosensory association areas. Flavor, but not orthonasal smell or taste alone, stimulated the frontal operculum, supporting previous accounts of its central role in the formation of the flavor percept. A functional dissociation was observed in the insula: the anterior portion was characterized by sensory convergence, while mid-dorsal sections activated exclusively to the combined flavor stimulus. psycho-physiological interaction analyses demonstrated increased neural coupling between the frontal operculum and the anterior insula during flavor presentation. Connectivity was also increased with the lateral entorhinal cortex, a relay to memory networks and central node for contextual modulation of olfactory processing. These findings suggest a

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central role of the insular cortex in the transition from mere detection of chemosensory convergence to a superadditive flavor representation. The increased connections between the frontal operculum and medial temporal memory structures during combined olfactory–gustatory stimulation point to a potential mechanism underlying the acquisition and modification of flavor preferences. *Hum Brain Mapp* 36:1662–1676, 2015. © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Chemosensory perception of food is commonly separated into an anticipatory and a consummatory phase [Small et al., 2008], which are characterized by a transition from separate sensations of smell and taste toward the merged sensory experience of a flavor. For example, approaching a grilled chicken truck, the first chemosensory impression we encounter is typically a familiar delicious barbecue smell which drives the decision to make a purchase. As we take our first bite, the olfactory sensation gives way to the familiar combination of the saltiness and savory taste on our tongue. Only after we swallow this first bite, and thus engage in the actual consumption, do the odorous volatiles from the food in the mouth reach the olfactory epithelium through the pharynx [Murphy et al., 1977]. The smell and the taste of the grilled meat are then perceived simultaneously, eliciting the familiar and intensely rewarding sensation of grilled chicken flavor.

Although mainly a combination of unisensory smell and taste signals, food flavor creates a more pleasant and intense holistic experience than predicted by the mere summation of its preceding sensory elements. Reinforced by associative learning and multisensory perception mechanisms [Auvray and Spence, 2008], perceptual binding between the object's smell and taste is hereby usually so complete that the joint percept is erroneously perceived to originate from one common sensory source in the mouth and not from the multisensory integration process that it truly is [Lim and Green, 2008; Small and Prescott, 2005; Todrank and Bartoshuk, 1991]. Although the anatomical separation of olfactory and gustatory receptor organs in the periphery clearly points toward a cortical basis for the emergence of the unique perceptual properties of food flavors [Lundstrom et al., 2011], the neural processing cascade which gives rise to the privileged processing of combined olfactory–gustatory input relative to its parts presented in isolation remains to be fully understood [Small and Green, 2012].

A number of brain areas are characterized by tight anatomical connections with both the primary gustatory and olfactory cortex [Rolls and Baylis, 1994; Shepherd, 2006], and as such are thought to contribute to the emergence of a flavor percept. Neuroimaging studies have most frequently reported activation to both smell and taste in the orbitofrontal cortex (OFC) [O'Doherty et al., 2001;

Poellinger et al., 2001; Savic and Gulyas, 2000; Small et al., 1997a, 1997b; Sobel et al., 1998; Zald et al., 1998; Zald and Pardo, 1997; Zatorre et al., 1992], the anterior insula, and frontal and parietal sections of the operculum [Cerf-Ducastel and Murphy, 2001; Cerf-Ducastel et al., 2001; Poellinger et al., 2001; Savic and Gulyas, 2000; Small et al., 1999].

The unique functional correlates of integrated flavor perception within this chemosensory network have mainly been explored through the detection of localized increases in MRI signal that superadditively exceed the observed activation in the same region to smell or taste alone. Such direct comparisons of activity associated with unisensory and multisensory input have consistently yielded activity in the rolandic operculum (the section of the operculum frontally and parietally bordering the central gyrus) and dorsal midinsular cortex [Green and Hayes, 2003; Lim and Green, 2008; Small and Prescott, 2005; Stevenson, 2013; Todrank and Bartoshuk, 1991]. Although this work has been influential to the idea that these areas constitute primary sites of olfactory–gustatory integration, the view of superadditivity as the sole underlying criterion for sensory integration in functional MRI has increasingly been challenged in the nonchemosensory-based multisensory literature [Angelaki et al., 2009; Stanford and Stein, 2007]. In line with emerging behavioral evidence that suggests a Bayesian optimization of weight assignment to cues from multiple sources, it has been proposed that sensory integration may more appropriately be reflected by modulations within a larger sensory processing network, including subadditive activation changes occurring in regions of sensory convergence [Beauchamp, 2005]. Superadditivity, within this framework, would then represent only the final result of perceptual evaluation: a value-added response to multisensory input, evoked by integration of the merged sensory information with cognitive and affective associations linked to the emergent supramodal object. Although large portions of secondary chemosensory cortex are known to be activated by both olfactory and gustatory stimuli [Seubert et al., 2013; Veldhuizen et al., 2011], subadditive convergent brain responses to odors and tastes have not been consistently described or related to the observed superadditive effects. Combining a classical framework for the assessment of multisensory integration with exploratory analyses of flavor-dependent changes in effective connectivity, the present study

therefore pursued two aims: first, we aimed to dissociate convergent subadditive from superadditive responses to familiar olfactory and gustatory stimuli within a single experiment. Second, these results were used to inform seed-based connectivity analyses in an effort to elucidate the pathways by which superadditive flavor areas interface with these sensory networks and higher order cognitive-affective processing during the formation of a holistic representation of a food stimulus.

MATERIALS AND METHODS

Participants

Thirty-six healthy individuals provided written informed consent to participate. Of these, one participant did not complete the study and three subjects were excluded for excess motion during the neuroimaging portion (>4 mm), resulting in a final sample of 32 participants (16 female, mean age 27 years, SD 4.4 years). Participants with metal implants, past or current neurological and psychiatric illness, smell or taste impairment, or alcohol abuse were not included. The study protocol conformed to the revised version of the Declaration of Helsinki and was approved by the local Institutional Review Board.

Stimuli and Stimulus Delivery

The stimulus material consisted of a target beverage: orange juice (Tropicana Original, Purchase, NY), which was chosen to represent a food item characterized by both high familiarity and high perceived pleasantness. The orange juice was presented along one of three pathways, representing the different phases of food consumption: as an orthonasal odorant (volatile components presented to the nose), as a tastant (presented to the tongue while maintaining a closed soft palate) and as a flavor stimulus (combined odor- and taste-stimulation after swallowing the liquid, resulting in opening of the soft palate). The unisensory smell stimulus was hereby presented via the orthonasal route to maintain ecological validity, as it represents the stimulation pathway by which a food smell would typically be encountered in a naturalistic setting (from orthonasal through gustatory, to combined gustatory-retronasal; see Small et al. [2005] for a discussion of differences between unisensory orthonasal and retronasal odor stimulation).

To limit habituation/adaptation and maintain alertness, target trials were pseudorandomly mixed with a distractor beverage, which was optimized to answer a separate research question and is therefore, not included in the present analyses. Water activates taste cortex [Frey and Petrides, 1999] and has a discernable taste [Bartoshuk et al., 1964]. To minimize the effect of baseline activity on our results, we therefore included artificial saliva as a tasteless stimulus by means of a double deion-

ized water-based stock solution of 2.5 mM sodium bicarbonate and 25 mM potassium chloride (Sigma-Aldrich Corporation, St Louis, MO; see O'Doherty et al [2001] for a similar procedure). During their first day of testing, participants were presented with a 25, 50, 75, and 100% concentration of this solution and asked to select the one that was closest to tasteless and odorless in quality; this concentration was then used as the control stimulus and for rinsing during all further testing. Subjects were trained to maintain similar levels of tongue movement for taste and control stimulus presentation to limit the potential confound of differences in motor activity between conditions.

Odor stimuli were presented orthonasally by a custom-designed, computer-controlled, 16-channel olfactometer suitable for an event-related functional imaging study. A similar olfactometer design has been described in detail elsewhere [Lundstrom et al., 2010]. In short, a valve control unit regulates the state of the olfactometer's pilot-air solenoid valves that, in turn, control odor-onset valves located at the odor canisters next to the scanner bore via individual high pressure pilot air. Each of these directs a continuous airstream of 3.0 liters per minute (lpm) into an odor glass reservoir containing 10 ml of the odor in question when triggered by the valve control unit. The odorized headspace is transported to a birhinal nosepiece where one channel serves as a conduit for the odorless control flow. This control flow is directed to the nosepiece between odor presentations. In the nosepiece, the flow from the activated channel (odor or control) mixes with a continuous, low-flow airstream (0.5 lpm), adding up to a total airflow of 1.75 lpm per nostril. This continuous airstream masks the tactile cues that might otherwise alert the subject to channel-switching [Boesveldt et al., 2010; Miller et al., 2013]. The olfactometer produces near-rectangular olfactory stimuli with fast stimulus rise time and a minimal odor concentration loss over time [Lundstrom et al., 2010]. A custom-designed gustometer, nearly identical to previously used setups [Haase et al., 2007; Veldhuizen et al., 2007] delivered taste and control solutions in 0.5ml aliquots over 3s. Four programmable syringe pumps, each holding a filled 60ml syringe, were placed outside in the console room and separately connected to a mouthpiece by means of Tygon tubing [Saint-Gobain, France, 31ft (9.4 m), 1/16 in. (1.6 mm) ID, 1/8 in. (3.2 mm) OD]. The mouthpiece merged the gustatory stimuli into a final 1.5 in. (38 mm) long piece of tubing which served as the common outlet for all stimuli. Participants were instructed to hold the final piece of tubing between their teeth so that the opening would rest comfortably on the anterior third of the tongue. Both the olfactometer and gustometer were operated by trigger pulses sent through the E-Prime software package (Psychology Software Tools, Sharpsburg, PA), which also controlled the visual projection of instructions to the participants and collected their responses.

Figure 1.

Illustration of the experimental procedure. The top row shows an example of a "Taste" trial, the bottom shows an example of an "Odor" trial. For both odor and taste trials, a third of trials each presented the target beverage, the distractor beverage, and the odor/tasteless control stimulus. At the end of each trial,

participants performed a three alternative forced-choice response task during which they were asked to identify the presented beverage using an MRI-compatible button box. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Procedures

Study procedures consisted of three separate testing sessions: an initial screening, a mock scanner training, and an fMRI session. The screening procedure served to detect any impairment in participants' ability to taste and smell, using the cued odor quality identification subtest of the Sniffin Sticks battery [Hummel et al., 1997] as well as a taste quality identification task [Landis et al., 2009]. Participants identified on average 13.3 (SD 1.1) out of 16 odors correctly, and all participants performed above the cutoff for hyposmia (11 correct responses, Hummel et al. [2007]). All participants were able to identify the four different taste qualities.

The mock scanner training session allowed participants to get acquainted with the experimental procedures used during the MRI session. In addition to practicing, the task and familiarizing themselves with the stimulus material, participants were asked to rate the pleasantness and intensity of the orange juice stimuli when presented separately as odor, taste, and flavor using a computerized visual analog scale. The scale endpoints were labeled "Extremely unpleasant" and "Extremely pleasant"; intensity was rated from "No sensation" to "Strongest imaginable sensation."

The experimental design used during functional MRI testing consisted of pseudorandomized events, half of

which were "taste" trials (oral stimulation) and half of which were "odor" trials (nasal stimulation). As illustrated in Figure 1, "taste" trials were further divided into a pre swallow and postswallow time period, corresponding to the experience of taste alone, and flavor, respectively.

In brief, trials started with the visual presentation of a black fixation cross, which was followed by the word "odor" or "taste" to alert the participant to the stimulation route (oral or nasal) together with a 3 s presentation of a corresponding odor, taste, or a tasteless and odorless control stimulus. The stimulation period was followed by a variable "hold" period for 4–10 s during which the tongue was to be held still and swallowing was to be avoided. For taste trials, this hold period was followed by a cue to swallow the liquid, which remained on the screen for 3 s, and then by another hold period of 4–10 s. Then, a tasteless solution was presented to rinse the taste off the tongue, followed by another swallow. Odor trials consisted of a single 3 s presentation of an odor stimulus, followed by a variable hold period. For both odor and taste trials, a third of trials each presented the target beverage, the distractor beverage, and the odor/tasteless control stimulus. At the end of each trial, participants performed a three alternative forced-choice response task during which they were asked to identify the presented beverage using an MRI-compatible button box. Mean task accuracy was at 90.4% (SD = 7), with no significant difference between

stimulation routes (paired Student's *t*-test between oral and nasal stimulus presentations, $t(31) = 1.74$, $p = \text{ns}$). The main purpose of this task was to maintain and monitor alertness over the course of the experiment; it did not constitute an experimental variable of interest per se and as such, the few trials labeled as incorrect were not excluded from neuroimaging analyses.

Data Acquisition

The BOLD imaging sequence was divided into three sessions with a total duration of 45 min. Data were acquired on a 3T TIM Trio Siemens MRI scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel head coil. First, structural images were acquired by means of a three-dimensional T1-weighted MPRAGE sequence (160 slices, TR: 1810 ms, TE: 3.51 ms, 9° flip angle, matrix size 96×96 , FOV $240 \times 180 \text{ mm}^2$, voxel size of $0.9 \times 0.9 \times 1 \text{ mm}^3$). Then, whole brain functional images were collected during three separate runs with a T2*-weighted interleaved EPI sequence (TR: 2,500 ms, TE: 22 ms, 90° flip angle, matrix size: 96×96 , FOV: $240 \times 240 \text{ mm}^2$, voxel size: $2.5 \times 2.5 \times 2.5 \text{ mm}^3$, 0.5 mm slice gap, 40 slices). Images were acquired obliquely, at an approximate rotation of 20° axial/coronal from the anterior commissure (AC)-posterior commissure (PC) line. At the beginning of each of the three sessions, the MR signal was allowed to equilibrate over three scans, which were then excluded from analysis.

fMRI Data Analyses

Preprocessing and Univariate Analysis. Data were processed using SPM8 (www.fil.ion.ucl.ac.uk/SPM) running under MATLAB R2008a (The Mathworks, Sherborn, MA). We realigned the functional time series by a two-pass procedure, using the first image (first pass) and then the mean image (second pass) as references. Anatomical scans were coregistered to their respective mean EPI scans; they were then used to determine spatial normalization parameters by means of the unified segmentation approach [Ashburner and Friston, 2005]. The resulting normalization parameters were applied to the functional scans, transforming the time-series into MNI space [Evans et al., 1993]. Finally, the functional images were smoothed with a 9 mm FWHM isotropic Gaussian kernel to accommodate intersubject variation in anatomy.

Analyses of the time series were performed within the framework of the general linear model (GLM), removing low-frequency noise with a high pass filter (128 ms cutoff period). Events were separated into onsets of odor, taste, and flavor. Odor and taste events were specified as the onsets of the respective oral or nasal stimulus presentation, while flavor events were defined as the onset of the "swallow" cue after oral stimulus presentation, when the

soft palate was open and the retronasal odor could reach the nasal cavity.

For single-subject statistics, odor, taste, and flavor events were modeled separately for each beverage and for the odorless and tasteless solution. Two additional regressors modelled the rinse periods after oral beverage administration. The regressors were convolved with the hemodynamic response function and then used as predictors in the GLM. The six realignment parameters of each scan (translations and rotations) were used as covariates to remove residual artifacts due to head movement. Examinations of the response function to the different stimulus types indicated a slower onset of the taste response relative to the odor response; thus, the onsets of the taste and flavor trials were convolved with a 3 s boxcar function while odor trials were treated as singular events. Subtraction contrasts between the target beverage and the odorless and tasteless solution were calculated on the subject level for the odor, taste, and flavor conditions. This was done to remove activation that was assumed to be identical across conditions and thus not accounted for by chemosensory stimulation (eg. sniffing, swallowing, somatosensation) from subsequent analyses. These three first level subtraction contrasts (odor-baseline, taste-baseline, flavor-baseline) entered a one-way ANOVA at the second level.

Modality-specific activations were assessed by conjunction analyses of odor and flavor, and taste and flavor ($O \cap F$ and $T \cap F$), masked by an exclusive mask of the respective other sensory modality at a threshold of 0.05 uncorrected (note that a more liberal threshold of the exclusive mask reflects a more conservative approach in this context, see e.g., Uncapher and Rugg [2009] for a similar procedure). For assessment of convergent activations, a conjunction of odor, taste and flavor was computed ($O \cap T \cap F$). Due to the conservative inclusion of three contrasts, the conjunction here was thresholded at $P < 0.001$ uncorrected, rather than < 0.05 using family-wise error correction (FWE), to reduce the occurrence of false negative results. All conjunction analyses were computed using the minimum statistic to assess the conjunction null hypothesis, which thus was rejected solely when an effect was found in all conditions [Nichols et al., 2005]. Superadditive effects for Flavor over Odor and Taste combined were assessed by the contrast $F > (O + T)$, and decomposed extracting individual subject's percent signal change relative to the odorless and tasteless baseline using the *rfxplot* toolbox [Glascher, 2009]. All activations are reported at $p_{\text{Peak}} < 0.05$ using FWE correction unless otherwise noted. A priori regions of interest included the insula, frontal and parietal operculum, orbitofrontal cortex, piriform and entorhinal cortex as core regions constituting primary and secondary olfactory and gustatory areas according to recent functional anatomical meta-analyses [Seubert et al., 2013; Veldhuizen et al., 2011], as well as the structural neuroanatomy of the olfactory system [Carmichael et al., 1994]. Given that the precise localization of subregions within anatomical areas are still under debate, especially for gustatory cortex, [Iannilli et al., 2014], regions of interest were defined on the basis of coordinates derived from a stereotaxic brain

atlas [Mai et al., 2008], rather than specific coordinates from previous findings; in these regions a small volume correction (SVC) was applied (9 mm sphere, $P < 0.05$ FWE).

Analysis of Psycho-Physiological Interactions: Analyses of psycho-physiological interactions (PPIs) are used to determine changes in effective connectivity with a predefined seed-region; this method permits the identification of unique contributions to task-related processes in this region which may occur in absence of super-threshold changes in activation captured by the GLM in the connected clusters themselves [Friston et al., 1997]. To identify cortical areas providing unique contributions to enhanced responses to olfactory–gustatory stimulation, we therefore extracted BOLD signal over the time course of the experiment from the cortical areas showing maximal superadditive responses to combined olfactory–gustatory information. This permitted identification of a network of areas which may not respond superadditively, but show an increased exchange of information with flavor-sensitive areas during simultaneous olfactory and gustatory stimulation.

To maximize our signal-to-noise ratio, seeds were defined for each subject individual as a 6 mm sphere around the closest peak ($P < 0.05$ uncorr.) located within the operculum within a 10 mm radius of the second level peak. After high-pass filtering and subtraction of the effects of the intercept and realignment parameters, the first eigenvariate was calculated to represent the adjusted time-course within the region.

The resulting vectors were deconvolved, multiplied element-wise with a delta function representing the difference between the respective modality and its specific null event baseline, and reconvolved with the canonical HRF. The resulting PPI regressors then entered the psycho-physiological analyses on the first level [Friston et al., 1997]. The two main effects of this interaction (i.e., the deconvolved time course of the seed-region and the convolved difference between beverage administration and baseline), as well as the motion parameters, were included in the analysis as covariates of no interest. Parameter estimates of the PPI regressors for Odor, Taste and Flavor then entered a second level GLM. The contrast $F > O+T$ was used to identify any regions of enhanced effective connectivity with the operculum during flavor presentation relative to the unisensory conditions. Again, activations were reported at $p_{\text{Peak}} < 0.05$ using FWE correction, and a priori regions of interest were reported using a small volume correction (9 mm sphere, 0.05 FWE).

RESULTS

Perceptual Ratings

Perceptual ratings of the stimuli demonstrated significant differences in perceived intensity between the three modalities [ANOVA, main effect of modality; $F(2,62) = 4.82$, $P = 0.029$]. Moreover, there was a statistical

tendency for participants to rate the modalities differently with respect to their perceived pleasantness [$F(2,62) = 2.66$, $P = 0.078$]. Decomposing these effects by paired t-tests, we found that orange juice flavor was perceived as more intense than its taste [$t(31) = 3.31$, $P < 0.01$] or odor [$t(31) = 2.44$, $P = 0.020$] alone, while no significant difference between the two unimodal conditions, odor and taste, was observed ($P > 0.7$). In addition, orange juice flavor was considered more pleasant than its taste alone [$t(31) = 2.39$, $P = 0.023$] and marginally more pleasant than its odor alone [$t(31) = 2.00$, $P = 0.054$]. The difference in pleasantness ratings between odor and taste of orange juice was not significant ($P > 0.40$).

Unique cortical contributions to olfactory and gustatory processing unisensory representation

We initially assessed whether our imaging paradigm reliably captured responses to each experimental condition by the respective main effects. These demonstrated robust activations for each of the odor, taste, and flavor conditions against their respective baseline (see Supporting Information Table). To identify cortical areas which uniquely contributed to one, but not the other sensory modality, we separately identified joint activations for each of the unisensory (odor and taste) conditions with flavor, while masking out any variance explained by the respective other modality. This demonstrated that odor-related activity, in absence of taste-related activity, dominated in areas commonly considered to comprise primary olfactory cortex [Seubert et al., 2013], including the temporal piriform cortex and amygdala (see Fig. 2 and Table I). In addition, clusters in the thalamus and temporal pole showed distinct activations associated with olfactory stimulation. Conversely, taste, but not odor-associated activity, was observed in bilateral clusters within the postcentral gyrus (see Fig. 2 and Table I), which extended dorsally from the primary gustatory area [Veldhuizen et al., 2011] into primary somatosensory cortex and the parietal operculum. Anterior insula activity typically reported in gustatory neuroimaging studies was masked out due to its structural overlap with olfactory-induced activity. The remaining posterior part of the insular cortex, which was active to taste alone, corresponds more closely to an area which has been suggested to show a secondary gustatory response linked to subjective interpretations of the stimulus' personal relevance [Iannilli et al., 2014].

Identification of chemosensory convergent areas

As a next step, we investigated conjunctions of odor, taste, and flavor perception in an effort to identify cerebral areas characterized by activation across all chemosensory stimulus types. As illustrated in Figure 3 and Table II, convergent, but subadditive activation across smell, taste and flavor stimulation was predominantly found in the

Figure 2.

Modality-specific activity, represented by conjunctions of each unimodal with the bimodal condition, and masking out the respective other unimodal condition at a threshold of 0.05 uncorrected. Clusters meeting a statistical threshold of $P < 0.05$ FWE are depicted, but thresholded at 0.001 uncorrected for

illustration purposes. Bar charts depict percent signal change relative to modality-specific baseline. Error bars indicate $\pm$ standard error of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I. Unimodal activations

Peak P	Peak T	Peak Z	Cluster Size	MNI-Coordinates(mm)			Hemisphere	Area
				x	y	Z		
Conjunction Odor $\cap$ Flavor, masked with Taste								
<0.001	6.82	5.87	22	24	-1	-16	R	Temporal Piriform Cortex/Amygdala
0.001	6.10	5.38	36	-3	-19	11	L	Thalamus
0.003	5.79	5.16	9	-24	-4	-16	L	Temporal piriform Cortex/amygdala
0.007	5.56	4.99	5	-18	-22	-10	L	Amygdala/hippocampus
0.008	5.54	4.97	7	3	-1	65	R	Superior frontal gyrus
0.021	5.23	4.74	5	57	11	-7	R	Lateral temporal pole
Conjunction Taste $\cap$ Flavor, masked with Odor								
<0.001	7.16	6.09	130	57	-19	38	R	Parietal operculum/postcentral gyrus
<0.001	7.12	6.06	111	-60	-22	38	L	Parietal operculum/postcentral gyrus
0.009	5.48	4.93		-57	-19	23	L	Parietal operculum/postcentral gyrus
0.011	5.43	4.89	7	-57	2	32	L	Frontal operculum/precentral gyrus

Activation peaks and cluster extent for the separate conjunctions of each unimodal with the bimodal condition. Activation to the respective other unimodal condition was masked out at a threshold of 0.05 uncorrected. Peak voxels of each cluster are reported at $P < 0.05$ using family-wise error correction.

Figure 3.

Depiction of convergent, but subadditive activation to all presentation modes (right) and superadditive activity to flavors (left). Images are thresholded at 0.001 uncorrected for illustration purposes; the orbitofrontal cluster is thresholded at 0.05 uncorrected.

Bar charts depict percent signal change relative to modality-specific baseline. Error bars indicate $\pm$ standard error of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

orbitofrontal cortex, and other regions known to be involved in cognitive-affective food evaluation and appetite, including the superior frontal gyrus and the lateral hypothalamus, bilaterally [Grabenhorst et al., 2008; Petrides, 2005; Petrovich et al., 2005; Volkow et al., 2011]. In the bilateral insular cortex, a cluster of convergent, but subadditive activation emerged in its anterior portion (Fig. 4).

Identification of chemosensory areas with superadditive responses to combined olfactory-gustatory stimulation

Sensory convergence in combination with superadditive activation for flavor processing relative to the sum of unimodal odor and unimodal taste combined (superadditive flavor activation), included large clusters in the frontal

operculum. Areas commonly associated with multisensory integration, such as the superior temporal and middle frontal gyri and the intraparietal sulcus [Driver and Noeselt, 2008], also showed superadditive responses to flavor; signal change extraction showed that these were mainly driven by deactivations for the unimodal conditions (see Fig. 3 and Table II). In the dorsal midinsula, superadditive activation in absence of convergent activity was observed, indicating a functional dissociation between the anterior and dorsal midinsula with respect to flavor processing (Fig. 4, significantly larger difference between the summed signal change of the olfactory and gustatory activation relative to the flavor condition [$t(31) = 5.26$, $P < 0.001$]).

To delineate flavor-specific functional connectivity patterns associated with superadditive activation to combined

TABLE II. Chemosensory integration

Peak P	Peak T	Peak Z	Cluster Size	MNI-Coordinates (mm)				Hemisphere	Area
				x	Y	z			
Convergence (conjunction of Odor $\cap$ Taste $\cap$ Flavor)									
<0.001 (unc.)	5.87	5.22	138	3	5	53	R	Superior frontal gyrus	
<0.001 (unc.)	3.46	3.29		12	-1	65	R	Superior frontal gyrus	
<0.001 (unc.)	4.25	3.97	45	39	17	-1	R	Anterior insula	
<0.001 (unc.)	3.73	3.53	26	-36	17	-1	L	Anterior insula	
<0.001 (unc.)	3.75	3.55	13	12	-4	-10	R	Lateral hypothalamus	
<0.001 (unc.)	3.58	3.40	3	-12	-4	-10	L	Lateral hypothalamus	
0.05(SVC)	2.96	2.85	67	-24	32	-16	L	Orbitofrontal cortex	
0.041(SVC)	3.05	2.94	37	18	26	-22	R	Orbitofrontal cortex	
0.015(SVC)	3.48	3.31	59	54	-31	29	R	Parietal operculum	
Superadditivity (Flavor > Odor +Taste)									
<0.001	10.35	>8	1072	-51	-10	32	L	Frontal operculum/precentral gyrus	
<0.001	7.34	6.20		-36	-10	11	L	Dorsal midinsula	
<0.001	6.62	5.73		-48	-31	-1	L	Superior temporal gyrus	
<0.001	9.96	7.67	780	57	-7	32	R	Frontal operculum/Precentral gyrus	
0.001	6.28	5.51		39	-10	14	R	Dorsal midInsula	
<0.001	6.57	5.70	137	66	-37	-7	R	Superior temporal gyrus	
0.004	5.71	5.10	25	60	-49	23	R	Superior temporal gyrus	
0.001	6.22	5.46	23	-15	-61	-22	L	Cerebellum, anterior lobe	
0.004	5.77	5.14	24	18	-64	-22	R	Cerebellum, anterior lobe	
0.002	5.89	5.23	88	33	-67	47	R	Intraparietal sulcus	
0.003	5.87	5.22	93	42	17	35	R	Middle frontal gyrus	
0.003	5.80	5.16	42	-36	11	38	L	Middle frontal gyrus	
0.019	5.27	4.77	18	-54	20	14	L	Frontal operculum	
0.020	5.24	4.75	4	18	-19	-4	R	Thalamus	
0.021	5.23	4.74	8	30	-13	56	R	Postcentral gyrus	

Activation peaks and cluster extent for chemosensory convergence (top) and superadditive responses to flavor (bottom). Unless otherwise noted, peak voxels of each cluster are reported at $P < 0.05$ using family-wise error correction.

olfactory-gustatory stimulation, time-courses were extracted from subject-wise peak coordinates within 10 mm of the group level peak coordinates in the left and right frontal operculum. Psychophysiological interaction analysis indicated enhanced neuronal coupling with the right entorhinal cortex, bilaterally, during the flavor condition relative to unimodal stimulus presentation. Enhanced neuronal coupling was also found between the right operculum seed and the left anterior insula (see Fig. 5 and Table III).

DISCUSSION

Previous studies have demonstrated extensive overlap between the cortical networks involved in gustatory and olfactory processing, but the mechanisms by which sensory information from these two modalities is merged to create holistic experiences of food flavors with enhanced perceptual properties remains unclear. To address this question, the present study compared cortical processing of unisensory olfactory and gustatory stimulation of a familiar beverage, orange juice, to the combined olfactory-

gustatory stimulation that emerges during its consumption. Contrasting these different presentation modes, we pursued two aims: we first dissociated sites demonstrating convergent, but subadditive activation from areas showing superadditive responses to flavor. Then, we explored the cortical information flow between areas associated with the emergence of a superadditive flavor experience.

As expected, we observed convergent activation for chemosensory stimulation (odor alone, taste alone, combined flavor of orange juice) in all key areas implicated in higher order chemosensory processing [Gottfried and Zald, 2005; Seubert et al., 2013; Veldhuizen et al., 2011], including the medial orbitofrontal cortex, the anterior insula, the superior frontal gyrus, and the parietal operculum. All three types of sensory stimuli also activated the lateral hypothalamus significantly more than the taste- and odorless control conditions, likely reflecting the appetitive value associated with these stimuli [Petrovich et al., 2005; Volkow et al., 2011].

Among these regions of chemosensory convergence, privileged processing of a combined flavor stimulus, as determined by signal superadditivity, was only found in the frontal operculum. Located at the intersection of

Figure 4.

Depiction of dissociable response patterns to chemosensory stimulation in the insular cortex: the anterior insula cluster (yellow) activated equally to all types of chemosensory stimulation, while the dorsal midinsula cluster (green) activated predominantly to flavor in absence of unisensory activation. Images are

thresholded at 0.001 uncorrected and masking out other cortical activity for illustration purposes. Bar charts depict percent signal change relative to modality-specific baseline; error bars indicate $\pm$ standard error of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

somatosensory and gustatory systems [Cerf-Ducastel et al., 2001; Veldhuizen et al., 2011], this cortical region has frequently been proposed to be of key importance for food perception, responding not only to perceptual stimulus properties, but also encoding knowledge about the reward value of the consumed item [Small et al., 2001; Stice et al., 2011]. The opercular activation site extended into a section of the dorsal midinsula that was activated by flavor, but not taste or smell, when presented separately. This area was clearly separable from the subadditive convergence site located more anteriorly, indicating a functional dissociation within insular cortex. Corresponding to cytoarchitectonically distinct subsections [Mesulam and Mufson, 1982], anterior portions of the insula are closely connected to the anterior cingulate and the piriform lobe while

medial portions show stronger orbitofrontal connectivity [Deen et al., 2011]. Evidence from functional neuroimaging supports separate roles of these regions, with the anterior insula frequently being implicated in gustatory–olfactory convergence [Shepherd, 2006; Small and Prescott, 2005; Yaxley et al., 1990], while the dorsal midinsula usually lacks activation to odor perception [Kurth et al., 2010; Seubert et al., 2013]. The view of the anterior insula as a key site of convergent chemosensory processing is further supported by our seed-based connectivity analyses, where its coupling with the frontal operculum increased during presentation of the combined flavor percept. Our data thus support the idea brought forward by others that the anterior insula serves as a convergence detector, likely acting as an interface linking sensory input to associated

Figure 5.

Psychophysiological interaction analyses for a seed regions placed in the right operculum (right side) and left operculum (left side). Depicted increases in functional connectivity are based on a second level contrast of Flavor>Odor+Taste, excluding variation explained by the no-stimulus baseline. Images are thresholded at 0.001 uncorrected for illustration purposes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

emotional states [Adolphs et al., 2003; Calvert et al., 1999; Rolls, 2010; Seubert et al., 2010; Wicker et al., 2003].

The role of dorsal midinsula, in contrast, remains more elusive, as a number of previous studies have demonstrated activation of the dorsal midinsula by the consumption of taste alone [de Araujo and Simon, 2009; Kurth et al., 2010; Veldhuizen et al., 2011], a finding which we do not replicate here. An important aspect of our experimental design might explain this divergence. In contrast to other studies, which presented pure tastants, consumption in our study was dissociated in time from the presentation of taste to the mouth; instead, consumption was coupled with the flavor condition, where dorsal-mid insular activity was observed in the present study. In line with previous work suggesting an important role of this area for self-referential emotional evaluation, such as positive and

negative oral temperature stimuli [Guest et al., 2007], water taste when subjects were thirsty [de Araujo et al., 2003], nonoral thermal stimulation of the hand [Craig et al., 2000], and painful touch [Rolls et al., 2003], the dorsal midinsular activity we find here may thus reflect interoceptive changes resulting from food ingestion.

Increased connectivity when both gustatory and olfactory information was available was further observed with the lateral entorhinal cortex, a subsection of the anterior temporal lobe [Nakamura and Kubota, 1996]. Consistent with the emerging idea of the anterior temporal lobe as an amodal hub linking distributed modality-selective regions to support the formation and retrieval of semantic knowledge [Baxter, 2009; Patterson et al., 2007; Suzuki and Baxter, 2009], this area is characterized by dense bulbar and piriform projections on the one hand [Room et al., 1984] and

TABLE III. PPIs during flavor perception

Peak P	Peak T	Peak Z	Cluster size	MNI-coordinates (mm)			Hemisphere	Area
				<i>x</i>	<i>y</i>	<i>z</i>		
Right frontal operculum								
Flavor>Odor+Taste								
0.028	5.08	4.63	2	30	8	−31	R	Entorhinal cortex
0.014 (SVC)	3.46	3.29	5	−39	14	−1	L	Anterior insula
Left frontal operculum								
Flavor>Odor+Taste								
0.011 (SVC)	3.56	3.38	7	27	2	−31	R	Entorhinal cortex

Activation peaks and cluster extent for cluster characterized by connectivity increases for flavor relative to odor or taste alone. See regions were selected based on a sphere around the subjects individual peak closest to the second-level peak for superadditive activation in the operculum (R: 51, -10, 32, L: 57, -7, 32). Unless otherwise noted, peak voxels of each cluster are reported at $P < 0.05$ using family-wise error correction.

connections to the hippocampal formation conversely. As such, it has been suggested to form a key relay for the retrieval of olfactory memories, and may support recognition of complex perceptual configurations [Biella et al., 2007; Chapuis et al., 2013; Kerr et al., 2007]. This view is additionally supported by recent neuroimaging work in individuals suffering from primary progressive aphasia, which has emphasized the role of neural integrity in the anterior temporal lobes for the identification of odor identity [Olofsson et al., 2013]. The observed enhanced connectivity between the operculum and the lateral entorhinal cortex as an access node to memory networks is of key interest given that the olfactory, but not the gustatory system, has the necessary discriminatory power to form synthetic codes for distinct objects [Lundstrom et al., 2011]. Although this has commonly lead to the assumption that food object identity is encoded through the olfactory modality alone, our findings suggest facilitated access to temporolimbic circuits elicited by joint olfactory–gustatory sensory stimulation. Combined with reports that damage to the anterior temporal lobe can result in changes in food preferences in primates [Horel et al., 1975; Kling et al., 1993], these findings highlight a potential functional anatomical basis for crossmodal appetitive and aversive learning during the acquisition of flavor preferences [Dalton et al., 2000; Yeomans et al., 2006]. These mechanisms could be central to the formation of maladaptive eating patterns and warrant future investigations. The only distinct activations to gustatory over olfactory input in the present study were found at the intersection of the post-central gyrus and parietal operculum, areas which have frequently been implicated in neuroimaging studies of gustation [Cerf-Ducastel et al., 2001; de Araujo et al., 2003; Haase et al., 2007; Haase et al., 2009; McCabe and Rolls, 2007; Veldhuizen et al., 2007]. Activation of this anatomical area has repeatedly been linked to sensations arising from the oral cavity in general given the close spatial proximity of neurons sensitive to somatosensation and gustation [Kadohisa et al., 2005; Smith-Swintosky et al., 1991; Yamamoto et al., 1985]. This area has also been shown to respond to olfactory stimulation when administered through the mouth [Small and Prescott, 2005].

Given that we chose to administer the unisensory odor orthonasally to maintain ecological validity of the odor presentation in the absence of a taste stimulus, it remains open to further investigation whether the differential activation observed for olfaction relative to gustation is modality-specific or rather, a result of the different presentation pathways associated with the two modalities. In the present study, gustatory stimulation alone produced cortical activations which overlapped with those previously observed for retronasal odor [Small et al., 2005]; this may be viewed as an indication for the presence of modality-independent responses to motivational aspects of food consumption. Conversely, given the dominant role of smell perception in the formation of the flavor percept, one might speculate that some of the observed effects, particularly the enhanced connectivity with the entorhinal

cortex, might persist in a weakened form to an orally presented stimulus without gustatory properties. Future studies should aim to further separate the motivational from the purely sensory aspects, including a more detailed description of the temporal flow of activity, in an effort to fully understand their contribution to appetite regulation.

It should further be noted that privileged processing of combined olfactory–gustatory stimulation was observed in a number of regions that are commonly implicated in multisensory integration, such as the temporoparietal and intraparietal junction, as well as the middle frontal gyrus [Beauchamp, 2005]. Activation of these supramodal associative areas suggests that, despite the preattentive and complete perceptual nature of the binding process into a food flavor, chemosensory convergence should be considered a multisensory phenomenon. Whether these areas are crucial to the occurrence of flavor binding or just provide hubs for the integration of additional sensory modalities, such as somatosensation or audition, into the food consumption experience, remains to be determined.

In the evaluation of our findings, a few limitations should be considered. Foremost, our choice to only compare different stimulation routes within one stimulus type, orange juice, means that generalizability, as well as factors which may influence opercular connectivity during consumption of a combined olfactory–gustatory stimulus, need to be expanded upon and rigorously tested by future studies. Although the considerable overlap with previous studies observed in both unisensory and superadditive activity patterns strengthens our confidence in the reported findings, direct comparisons to other food stimuli of similar familiarity and pleasantness, as well as systematic variations of these attributes are required to obtain a more complete picture of the relevance of the delineated cortical pathways for the experience and formation of flavor preferences over the life course.

Breathing and tongue movement are potential confounds in any experiment studying smell and taste perception. The approach taken in the present study was to remove motor activity from the results by computing difference contrasts against a high-level control condition, which we assumed to be identical in all but the smell and taste components of the task. It should be noted, however, that this procedure rests on the assumption that the presence of chemosensory stimulation itself does not systematically influence these physiological parameters. Future studies should directly compare motor activity and breathing rates between odorless and tasteless conditions and the target stimuli to estimate their effects on cortical areas known to be affected by these parameters, such as the supplementary motor area (SMA), insular cortex, and primary olfactory cortex.

In conclusion, our results highlight the relevance of a distributed subadditive network that supports the generation of a flavor representation from a combined olfactory–gustatory object. We propose a functional division within insular cortex during flavor processing with a central role

of the anterior insula as a chemosensory convergence zone and a midinsular area encoding motivational aspects of consumption. Our data provides evidence for privileged access to semantic memory circuits via the entorhinal cortex during combined olfactory–gustatory perception. This increased neural coupling may underlie the formation of flavor preferences and should be explored with respect to its relevance for the formation of maladaptive eating habits.

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