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An fMRI Study of the Interactions Between the Attention and the Gustatory Networks

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Abstract

In a prior study, we showed that trying to detect a taste in a tasteless solution results in enhanced activity in the gustatory and attention networks. The aim of the current study was to use connectivity analyses to test if and how these networks interact during directed attention to taste. We predicted that the attention network modulates taste cortex, reflecting top-down enhancement of incoming sensory signals that are relevant to goal-directed behavior. fMRI was used to measure brain responses in 14 subjects as they performed two different tasks: (1) trying to detect a taste in a solution or (2) passively perceiving the same solution. We used psychophysiological interaction analysis to identify regions demonstrating increased connectivity during a taste attention task compared to passive tasting. We observed greater connectivity between the anterior cingulate cortex and the frontal eye fields, posterior parietal cortex, and parietal operculum and between the anterior cingulate cortex and the right anterior insula and frontal operculum. These results suggested that selective attention to taste is mediated by a hierarchical circuit in which signals are first sent from the frontal eye fields, posterior parietal cortex, and parietal operculum to the anterior cingulate cortex, which in turn modulates responses in the anterior insula and frontal operculum. We then tested this prediction using dynamic causal modeling. This analysis confirmed a model of indirect modulation of the gustatory cortex, with the strongest influence coming from the frontal eye fields via the anterior cingulate cortex. In summary, the results indicate that the attention network modulates the gustatory cortex during attention to taste and that the anterior cingulate cortex acts as an intermediary processing hub between the attention network and the gustatory cortex.

Keywords

Taste; Insula; Connectivity; Attention; fMRI; Humans

Introduction

Imagine you are in a café eating chocolate cake. It is absolutely heavenly and you want to know the ingredients. Maybe a pinch of salt was added? You ask your friend to taste the cake to see if she can detect the salt. Such directed attention towards the salty taste can increase sensitivity and enhance perception. For example, in the visual modality, it is well known that individuals respond more accurately and faster to visual stimuli if its location is cued in advance (Posner et al. 1980). Such top-down influences on perception are thought to be accomplished by higher order attention networks acting upon the sensory cortex to induce baseline shifts in the firing rate of relevant populations of neurons (Luck et al. 1997; Driver and Frith 2000; Kanwisher and Wojciulik 2000). Similar attentional influences are also thought to operate in other modalities; for example, listening for a sound in silence (Voisin et al. 2006), sniffing odorless air for an aroma (Zelano et al. 2005; Veldhuizen and Small 2011; Veldhuizen et al. 2011), or looking for an item in an empty visual scene (Kastner et al. 1999; Hopfinger et al. 2000) all result in increased activation of the respective primary sensory cortical region.

Behavioral studies have also documented perceptual benefits during directed attention to taste. Marks and colleagues demonstrated that detection thresholds to sucrose were lower in sessions in which the subject had been informed that they were likely to receive a sweet taste compared to sessions in which they were told they were likely to receive sour taste (Marks and Wheeler 1998; Marks 2002). Accordingly, neuroimaging work has shown that searching for taste in a tasteless solution results in enhanced gustatory cortex activation compared to passive sampling of the tasteless solution (Veldhuizen and Small 2011; Veldhuizen et al. 2007, 2011).

In addition to enhanced responses in the sensory cortex, neuroimaging studies consistently show engagement of a large-scale heteromodal network including the posterior parietal cortex, frontal eye fields, and the anterior and posterior cingulate cortex (Posner 1980; Posner et al. 1980; Pugh et al. 1996; Kanwisher and Wojciulik 2000; Chun and Marois 2002; Corbetta and Shulman 2002; Pessoa et al. 2003; Mesulam et al. 2005) during directed attention tasks. Likewise, directed attention to taste results not only in enhanced responses in the gustatory cortex but also in activations in the canonical attention network (Veldhuizen et al. 2007). Although this finding suggests that the canonical attention and gustatory networks interact, co-activation by itself does not provide direct evidence of modulation. Another complicating issue is that the gustatory cortex in the insula and operculum has also been implicated in attentional processes not involving the gustatory modality. For example, the parietal operculum has been suggested to play a role in spatial attention (Corbetta and Shulman 2002), and the anterior insula and frontal operculum in general directed attention (Kurth et al. 2010; Menon and Uddin 2010) and selfawareness (Craig 2009). Consequently,

areas within the insula and operculum are not necessarily the target of topdown modulation by the attention network, but may (also) be part of the attention network itself.

The aim of the present study was to use connectivity analyses to examine whether the attention network modulates neural response in the gustatory cortex. First, we used psychophysiological interaction (PPI) analyses (Friston et al. 1997) to explore *whether* and *where* there is evidence for increased functional connectivity between regions co-activated during baseline shifts associated with attention to taste. Next, since PPI models cannot include more than one pre-specified region and since they do not allow inferences to be made about the directionality of influences, we employed dynamic causal modeling (DCM). Using DCM, we specified models that included regions that the PPI analyses identified as showing connectivity and tested for various configurations of possible influences between these regions. We predicted a hierarchical model in which topdown influences from the attention network preferentially modulate the anterior insula and frontal operculum during directed attention to taste.

Methods and Materials

The general methods for this study have been previously described by Veldhuizen et al. (2007). These methods are reproduced in brief below in conjunction with two new sections on the connectivity analyses: PPI analysis and DCM analysis.

Subjects

Fourteen right-handed subjects (11 women, 3 men, mean age 26.2 ± 3.0 years with a mean Edinburgh Handedness inventory score of 89; Oldfield 1971) gave informed consent to participate in our study that was approved by Yale University School of Medicine Human Investigation Committee. All subjects reported having no known taste, smell, neurological, or psychiatric disorder.

Taste Stimuli and Delivery

Taste stimuli were sweet (5.6×10^{-1} M sucrose), salty (1.8×10^{-1} M sodium chloride), or sour (1.0×10^{-2} M citric acid). A tasteless solution was created from 2.5 mM sodium bicarbonate (Sigma, grade) and 25 mM potassium chloride (O'Doherty et al. 2001) at concentrations of 100%, 75%, 50%, and 25%, of which the one that “tasted most like nothing” was selected for each individual subject. Stimuli were all delivered as 0.4 ml of solution over 4 s from syringe pumps with a gustometer system that has been described in detail previously (Veldhuizen et al. 2007).

Experimental Design

All subjects first performed a single run of the task in a training session in a mock scanner, to ensure comfort during swallowing in a supine position. We used a long event-related design. Trials were 26 s in duration and included an instruction, receipt of a solution, a response, a swallow, receipt of a rinse, and a final swallow (Fig. 1a). Taste and tasteless solutions were delivered during three different conditions: (1) taste detection, (2) passive tasting while uninformed about the taste identity, and (3) passive tasting, but correctly

informed about the taste identity. Our previous analyses showed greater differential responses between conditions 1 and 2 (taste detection and passive tasting when not knowing the taste identity). Therefore, we focus on the responses during these conditions here (Veldhuizen et al. 2007) and refer to them as DETECT and PASSIVE.

During training, subjects learned that for condition DETECT they would hear a verbal cue “detect” at the beginning of a block of trials (condition DETECT) indicating that they should probe the subsequent stimuli for taste. Each trial within condition DETECT began with the word “liquid”, which alerted subjects that the solution was about to be administered. They were then required to probe the solution for a taste and to press button A if it contained a taste and button B if it was perceived to be tasteless (assignment of button/response combination was counterbalanced across subjects). In control condition PASSIVE, the instruction at the beginning of the block was “randomly press”. Subjects were instructed that they should not probe solutions for a taste during these blocks and that they should make a random button press during the response period. In condition PASSIVE, subjects were accurately informed about the identity of the stimulus (i.e., they heard “sweet”, “salty”, “sour”, or “tasteless” just prior to delivery rather than “liquid”) and were told to make a random button response (Fig. 1b). For further details of the procedure, see Veldhuizen et al. (2007).

fMRI Scanner

The images were acquired on a Siemens 3-T Trio scanner. Echoplanar imaging was used to measure the blood oxygenation-level dependent (BOLD) signal as an indication of cerebral brain activation. A susceptibility-weighted single-shot echoplanar method was used to image the regional distribution of the BOLD signal with TR, 2,000 ms; TE, 20 ms; flip angle, 90°; FOV, 220 mm; matrix, 64×64; slice thickness, 3 mm; and acquisition of 40 contiguous slices. Slices were acquired in an interleaved mode to reduce the crosstalk of the slice selection pulse. At the beginning of each functional run, the MR signal was allowed to equilibrate over six scans for a total of 12 s, which were then excluded from analysis. The anatomical scan used a T1-weighted 3D FLASH sequence (TR/TE, 2,530/3.66 ms; flip angle, 20°; matrix, 256 × 256; 1-mm-thick slices; FOV, 256; 176 slices).

fMRI Analysis and Statistics

Data were analyzed on Linux workstations under the Matlab software environment (MathWorks, Inc., Sherborn, MA, USA) using SPM2 (Wellcome Trust Centre for Neuroimaging, London, UK). Functional images were time acquisition-corrected to the slice obtained at 50% of the TR. All functional images were then realigned to the scan immediately preceding the anatomical T1 image. After segmentation, the images (anatomical and functional) were then normalized to the Montreal Neurological Institute template of gray matter, which approximates the anatomical space delineated by Talairach and Tournoux (1998). Functional images were smoothed with a 10-mm FWHM isotropic Gaussian kernel. For time-series analysis on all subjects, a high-pass filter (128) was included in the filtering matrix (according to convention in SPM2) in order to remove low-frequency noise and slow drifts in the signal, which could bias the estimates of the error. Condition-specific effects at each voxel were estimated using the general linear model. The

response to events was modeled by a canonical hemodynamic response function, consisting of a mixture of 2 gamma functions that emulate the early peak at 5 s and the subsequent undershoot. The temporal derivative of the hemodynamic function was also included to account for slight variations in the timing of event onsets (Henson et al. 2002). We defined our events of interest as mini-blocks of 12.5 s duration from taste onset to swallow. The swallow and the rinse were modeled as events of no interest. There were four events of interest in total: (1) DETECT_{taste}, (2) DETECT_{tasteless}, (3) PASSIVE_{taste}, and (4) PASSIVE_{tasteless}.

Main Effect of Attention

To isolate baseline shifts, we focus this analysis on tasteless events only, since attentional effects are not confounded by the presence of a taste stimulus. A within-subjects comparison of DETECT_{tasteless}–PASSIVE_{tasteless} was performed using a random effects model in order to account for inter-subject variability. Parameter estimate images from the contrast were entered into a one-way ANOVA group analysis. SPM assigns significance to *T* fields using the theory of Gaussian random fields (Friston et al. 1995; Worsley and Friston 1995). Activations of a cluster size >3 in. were reported at $p_{\text{uncorrected}} = 0.001$.

PPI Analyses

PPI analyses (Friston et al. 1997; Gitelman et al. 2003) were performed with SPM2. PPIs provide a way to examine how neural activity from a source or *seed* region interacts with a psychological state (e.g., attention vs. no attention) to produce differential neural activity in other parts of the brain. The seed region is pre-specified, and the PPI analysis results in a whole-brain map that displays voxels whose activity correlates with the interaction term between the source signal and the psychological variable. This may result in a significantly activated cluster, providing evidence for a PPI between the seed region and that *target region* under the specified behavioral state. The presence of a PPI indicates that the psychological variable modulates the output from the seed region or the responsiveness of the target region to the seed signal (Friston et al. 1997). PPI analyses go beyond simple correlations because both the activity from the source region and the psychological state itself are included as nuisance variables, which means that activity in the observed target regions explicitly do *not simply* correlate with activity in the seed region.

Seed regions were defined as all areas that showed activity in the comparison of DETECT_{tasteless}–PASSIVE_{tasteless} at the group level. Regions included the right frontal eye fields, posterior cingulate cortex, anterior cingulate cortex, left posterior parietal cortex, left parietal operculum, bilateral anterior insula, right frontal operculum, and the left mid insula (Table 1 and Fig. 2) (Veldhuizen et al. 2007). The first eigenvariate of the time-series data was extracted from a 15-mm sphere, for which each subjects' peak voxel formed the centroid. Subject-specific peak voxels were determined by searching each individual subject's contrast of DETECT_{tasteless}–PASSIVE_{tasteless} (displayed at $p < 0.1$) for a peak within 10 mm of the group activation maxima shown in Table 1. The eigenvariate from the 15-mm sphere was then deconvolved (Gitelman et al. 2003), multiplied with the psychological variable (DETECT_{tasteless} vs. PASSIVE_{tasteless}) and reconvolved with a hemodynamic response function to form the PPI term. For each subject, we computed new

PPI parameter estimate images with the interaction as a regressor-of-interest and the time-series eigenvariate and psychological variable as nuisance regressors. These images were then entered into a one-way ANOVA group analysis to examine which areas displayed increased connectivity with the seed regions under the DETECT condition compared to the PASSIVE condition. T-maps of contrasts were thresholded for display at $p_{\text{uncorrected}} = 0.001$, with a cluster size threshold of 3 voxels. Voxels were considered significant at $p < 0.05$ corrected for multiple comparisons using the false discovery rate across small volumes defined using coordinates from Table 1 as the centroid of a 15-mm radius sphere for predicted peaks (all areas that showed activity in the comparison of DETECT $_{\text{tasteless}}$ –PASSIVE $_{\text{tasteless}}$ at the group level; Veldhuizen et al. 2007).

DCM Analysis

We used the DCM tool in SPM5 (Wellcome Trust Centre for Neuroimaging) to determine whether responses in the significantly functionally connected areas from the PPI analyses modulated the anterior insula and frontal operculum directly, indirectly, or both (Friston et al. 2003). As opposed to PPI, which only examines the connectivity from single seed regions, DCM allows the examination and comparison of multiple network models containing multiple prespecified regions. DCM requires the specification of intrinsic connectivity between the chosen regions (i.e., “steady-state” connectivity) and driving inputs into at least one region in order to cause network activity. Additional modulatory inputs affect the strength of the intrinsic coupling in a context-sensitive manner. Models were compared with group level fixed effects Bayesian model selection (Stephan et al. 2009; Penny et al. 2010), which uses the free energy approximation to the log evidence for each model (Stephan et al. 2009). The free energy formulation contains terms for both model accuracy and complexity (Stephan et al. 2009). Thus, more complex models are not necessarily better. The log model evidence is also used to compute the conditional probability for each model across all three models, which is the probability of obtaining the observed fMRI data given a particular configuration of the multiple regions in the model compared to other models. A fixed effects analysis assumes that all subjects are using the same model architecture. This assumption is considered to be appropriate when the subjects are relatively homogenous and the processes being studied are attentional mechanisms that are unlikely to vary across the subject group (Penny et al. 2010; Stephan et al. 2010; Desseilles et al. 2011). Additionally, we extract the estimated modulation parameter of each condition (DETECT and PASSIVE) on the connection strength and then test for significant effects of condition with an ANOVA in SPSS (PASW statistics version 18.0). Further details of the DCM models are specified below.

Results

Baseline Shifts in the Gustatory Cortex and Co-activations in the Attention Network

To determine if trying to taste in the absence of taste activates the gustatory cortex, we contrasted responses during DETECT $_{\text{tasteless}}$ with those during PASSIVE $_{\text{tasteless}}$ and reported the findings in a previous manuscript (Veldhuizen et al. 2007). Importantly, the analysis was restricted to tasteless events and was inclusively masked with an ROI we built from the taste–tasteless contrast from individual subjects. This ensured that regions

responding to trying to taste reflected attentional modulation in the taste-responsive cortex. The analysis revealed several peaks in bilateral insula and overlying operculum (Table 1 and Fig. 2a). In the left hemisphere, we observed peaks in the two regions of the dorsal mid insula and the overlying Rolandic operculum, a peak in the anterior insula that extended into the overlying frontal operculum, and one in the parietal operculum. In the right hemisphere, we observed one peak at the junction of the anterior insula and frontal operculum and one in the frontal operculum proper. We performed the same analysis without inclusive masking of the taste–tasteless contrast to identify non-sensory regions that respond while trying to taste. As predicted, this produced responses in the canonical attention network including the posterior parietal cortex, frontal eye fields, dorsal anterior cingulate cortex, posterior cingulate cortex (Table 1 and Fig. 2b), and left middle frontal gyrus (not displayed).

Psychophysiological Interactions Between the Attention Network and the Gustatory Cortex

To test our prediction that the canonical attention network influences responses in the gustatory cortex during the attention task, we used each peak from Table 1 as a seed region for a PPI analysis (frontal eye fields, middle frontal gyrus, anterior cingulate cortex, posterior cingulate cortex, posterior parietal cortex, parietal operculum, mid insula, left anterior insula, right anterior insula, right frontal operculum). Significant PPIs were observed between (1) the seed region in the frontal eye fields and anterior cingulate cortex and (2) between the seed region in the posterior parietal cortex and the anterior cingulate cortex (Table 2 and Fig. 3), such that greater connectivity was observed during taste detection vs. passive tasting. In addition, we observed a trend for a similar PPI between the seed region in the parietal operculum and the anterior cingulate cortex (Table 2 and Fig. 3). We also found significant PPIs between the seed region in the anterior cingulate cortex and the right anterior insula and right frontal operculum (Table 2 and Fig. 3), with greater connectivity observed during taste detection vs. passive tasting. These results raise the possibility that the anterior cingulate cortex acts a mediator between the attention network and the gustatory cortex in the anterior insula and frontal operculum. No other significant PPIs were observed.

Dynamic Causal Modeling Analysis

The PPI analysis confirmed that attention modulates connectivity between regions previously implicated in attention and the gustatory cortex. Next, to determine the direction of the influences and interactions between these regions, we used DCM to test three possible models of information flow through this network. It has been recommended to let the DCM model space be informed by prior knowledge if possible (Stephan et al. 2010). We therefore elected to limit our parameters by first requiring that candidates show an effect of attention and then requiring evidence of the presence of connectivity as indicated by PPIs, thereby avoiding the danger of selecting based on anatomical data alone, which has been shown to be detrimental to network estimation (Smith et al. 2011). We realize this may not be the definitive model for all taste–attention interactions but it is informed by empirical criteria from the current dataset. Thus, based on the regions identified in the PPI analysis, we specified an across-hemisphere network of the following regions: left posterior parietal cortex, left parietal operculum, right frontal eye fields, and right anterior insula. We included

only the most significantly activated area of the anterior insula and frontal operculum in the DCM: the anterior insula (and left the frontal operculum out). Taste and tasteless events (collapsed across condition) were used as driving inputs and entered all models through the anterior insula (Fig. 4a). All models were specified to have bidirectional “steady-state” connectivity (intrinsic connections) between all five areas (Fig. 4a). Here we let the models be informed by anatomical data, for example, tractography studies in humans for anatomical connections between posterior parietal cortex and anterior cingulate cortex and insula (van den Heuvel et al. 2009; Uddin et al. 2010). However, one need not assume that monosynaptic connections are necessary for modeling in DCM (Grefkes et al. 2010), for example, evidence of functional connectivity would also point to the possibility of influences. We have no awareness of evidence for an anatomical connection between frontal eye fields or parietal operculum and insula; however, there is evidence of resting state functional connectivity between the frontal eye fields and insula (Deen et al. 2011), and work in nonhuman primates has shown extensive anatomical connections between these areas (Mesulam and Mufson 1982).

Responses from DETECT and PASSIVE events (collapsed across taste and tasteless to obtain more power) were used as modulatory inputs on the top-down connections between areas (anterior insula being downstream) to create three possible models (Fig. 4b) to evaluate our hypothesis that the anterior cingulate cortex acts a mediator between the attention network and gustatory cortex in the anterior insula and frontal operculum. One model specified indirect top-down modulation of the anterior insula by the attention network; the frontal eye fields, posterior parietal cortex, and parietal operculum modulate anterior cingulate cortex; and the anterior cingulate cortex modulates the anterior insula (model A). One model specified direct top-down modulation of the anterior insula by the attention network; the frontal eye fields, posterior parietal cortex, parietal operculum, and anterior cingulate cortex all modulate anterior insula directly (model B). Lastly, we specified a model with direct and indirect top-down modulation of the anterior insula; the frontal eye fields, posterior parietal cortex, and parietal operculum modulate the anterior cingulate cortex and anterior insula; and the anterior cingulate cortex modulates the anterior insula (model C).

Note that all these models specify only modulations of top-down connections (i.e., they are not bidirectional). As mentioned above, this was based on our a priori hypothesis of top-down attentional modulation and the PPI results. However, it is conceivable that connections between regions could also be bidirectional. To test for this possibility, we performed Bayesian model selection to determine if bidirectional modulations should be included in the models as a first step. We compared a family of models with top-down modulations only (models A and B, we excluded model C for the many possible permutations) with variations of model A and B that have one or more bidirectional modulations. Note that for the purpose of this analysis only, we disregard the differences between A and B and regard them as exemplars of the same family. That is, we want to determine whether a certain direction of modulation is implied regardless of whether modulations via the anterior cingulate cortex perform better than direct modulations on the anterior insula. Bayesian model selection demonstrated that there was strong evidence in favor of all modulations being bidirectional. The family of only unidirectional modulations showed a posterior probability of 2.92×10^{-41} ,

families of one bidirectional modulation showed a posterior probability of 4.67×10^{-22} on average, families of two bidirectional modulations showed a posterior probability of 7.18×10^{-8} on average, families of three bidirectional modulations showed a posterior probability of 2.80×10^{-13} on average, and lastly, the family of full bidirectional modulations showed a posterior probability of ~ 1 . We therefore chose to proceed with our model space as informed by the PPI analyses, with all modulatory influences being bidirectional.

Next, we used the Bayesian model selection to compare models A, B, and C and demonstrated that there was strong evidence (posterior probability ~ 1) in favor of model A (indirect modulation of the anterior insula via ACC) (Fig. 4c). For each subject, we extracted estimates of modulation parameters per condition within model A (averages in Fig. 4d). A within-subjects 2 (DETECT vs. PASSIVE) $\times$ 8 (connections: parietal operculum to anterior cingulate cortex, posterior parietal cortex to anterior cingulate cortex, frontal eye fields to anterior cingulate cortex, anterior insula to anterior cingulate cortex, anterior cingulate cortex to parietal operculum, anterior cingulate cortex to frontal eye fields, anterior cingulate cortex to posterior parietal cortex, and anterior cingulate cortex to anterior insula) ANOVA confirmed a significant effect of attention on the connections in the model ($F(1, 13) = 0.035$, $p < 0.001$). Post hoc t tests of the connection strengths showed that the difference between the detection task and the passive task was significant for the connection from the frontal eye fields to the anterior cingulate cortex ($p = 0.028$, Bonferroni-corrected for multiple comparisons) and from the anterior cingulate cortex to the anterior insula ($p < 0.002$, Bonferroni-corrected), but not in any of the other connections (all p 's > 0.27). One-sample t tests on the estimated parameters for the inputs confirmed that both the taste and tasteless (regardless of attention) driving inputs into the anterior insula were significant ($t = 4.720$, $p < 0.001$ and $t = 4.810$, $p < 0.001$, respectively). Thus, these results support our hypothesis that there is top-down modulation of the gustatory cortex in an indirect fashion, with modulation of the anterior insula via the anterior cingulate cortex.

Discussion

In a previous study, we reported that directing attention to taste results in co-activation of the gustatory and attention networks (Veldhuizen et al. 2007). Here we used connectivity analyses to demonstrate that these networks are not only co-activated, but that they also interact with each other. More specifically, we show that there is an indirect modulation of the taste cortex by the attention network during taste attention.

First, using PPI analyses, we found that activity in the frontal eye fields, parietal operculum, and posterior parietal cortex influenced responses in the anterior cingulate cortex, which in turn influenced responses in the anterior insula and frontal operculum. This suggests the existence of a hierarchical model in which the anterior cingulate cortex acts as a mediator between the gustatory and attention networks. Although not typically considered as part of the gustatory cortex, the anterior cingulate cortex is consistently activated in response to taste stimulation (Zald et al. 1998; O'Doherty et al. 2001; De Araujo et al. 2003; Small et al. 2003, 2004; Marciari et al. 2006). It is also part of the canonical attention network (Mesulam et al. 2005). More critically, however, is the fact that this region of the anterior cingulate cortex shows supra-additive responses to taste stimulation and attention to taste

(Veldhuizen et al. 2007) and very strong responses to breaches of taste expectation (Veldhuizen et al. 2011), supporting the possibility that taste and attention signals are integrated here.

Based upon the PPI findings, as well as prior literature indicating that the anterior cingulate cortex may integrate taste and attention signals, we next employed DCM to test whether information flow through the taste and attention network is best described by direct, indirect (via anterior cingulate cortex), or indirect plus direct models of information flow (Fig. 4). Comparison of Bayesian model estimation strongly supported indirect influences of the attention network upon the taste cortex via the anterior cingulate cortex (which receives from the frontal eye fields, posterior parietal cortex, and parietal operculum). The strongest influence upon gustatory taste cortex during the attention task came from the anterior cingulate cortex, which was in turn modulated most strongly by the frontal eye fields. Indirect modulation via the anterior cingulate cortex (Posner et al. 2006) has been reported by studies of attention in other modalities, and this has been interpreted as suggesting the involvement of both goal-directed (or executive control) and stimulus-driven (or salience detection) attention (Posner et al. 2006; Corbetta et al. 2008). The current study suggests that the dominant pathway of modulation during attention to taste comes from the anterior cingulate cortex and frontal eye fields, highlighting the role for these regions in acting to optimize sensory coding of taste in the insular gustatory cortex in the service of goal-directed behaviors.

We also found a trend for a PPI between the parietal operculum and the anterior cingulate cortex. Like the anterior cingulate cortex, this region of the brain has been postulated to play a role in taste perception (Kobayakawa et al. 1996, 1999; Ogawa et al. 2005) and attention (Corbetta and Shulman 2002). It is also known to code for oral somatosensation (Penfield and Boldrey 1937; Boling et al. 2002). As there are no known projections from the taste thalamus to this region (Mesulam and Mufson 1985; Pritchard et al. 1986), we have argued that the neural response in this area during taste perception reflects somatosensory perceptual processing or attention to the mouth (Small et al. 2003; Veldhuizen et al. 2007). Interestingly, oral somatosensory stimulation “captures” taste, in the sense that taste is perceived at the locus of somatosensory stimulation, even in the absence of gustatory receptors being stimulated at that locus (Todrank and Bartoshuk 1991; Green 2003). The parietal operculum has been hypothesized to play a central role in the binding of multimodal information into a single object in flavor perception (Small et al. 2005; Small 2008). It may be that attention to taste requires attention to the mouth. Indeed, the findings in the current study show that the parietal operculum itself is not modulated by the canonical attention network during attention to taste but that it does exert a modulatory force upon processing in the region of the anterior insula and frontal operculum, which is consistent with the proposition that attention to taste is dependent upon attention to the mouth. Future studies may test this hypothesis directly. Finally, the current results suggest that although the anterior insula and frontal operculum are implicated in non-gustatory attentional orienting (Shulman et al. 1999; Corbetta et al. 2005; Kincade et al. 2005) and interoceptive awareness (Critchley et al. 2004), local processing within the insula and operculum alone cannot account for the upregulation in activity that is observed in the insular cortex during taste attention.

Various recent studies have used PPIs to look at modulation of the gustatory cortex during attention to specific aspects of a taste, indicating that the amygdala and lateral prefrontal cortex play a role in judging the pleasantness of a taste for example (Bender et al. 2009; Grabenhorst and Rolls 2010). We recently observed interactions between the posterior parietal cortex and the gustatory cortex in a study of breaches of taste identity expectation. Connectivity analyses confirmed upregulation of response in the gustatory cortex by both the parietal cortex and ventral striatum (Veldhuizen et al. 2011). The modulation of sensory inputs by the posterior parietal cortex is consistent with the current observation. However, we do not observe activity in or interactions with the ventral striatum here, likely because in the current paradigm, there were no breaches of expectation. Since incorrect decisions to ingest something unexpected can pose a challenge to survival, it makes sense that reward areas such as the ventral striatum are involved in the encoding of an unexpected taste stimulus.

In summary, we demonstrate indirect modulation of the taste cortex by the attention network during selective attention to taste. Our results highlight the role of the anterior cingulate cortex in integrating taste and attention signals. These findings add to the growing body of literature that supports the existence of a multimodal attentional system (Kanwisher and Wojciulik 2000; Veldhuizen et al. 2007, 2011). They also accord with recent work showing that although the frontal eye fields and posterior parietal cortex were traditionally described as the visual–spatial attention network, it is in fact heteromodal and critical for attention in various modalities (Pugh et al. 1996; Kanwisher and Wojciulik 2000; Corbetta and Shulman 2002; Anderson et al. 2010).

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Fig. 1.

a, b Experimental design. Timeline of events within a trial. Events lasted 26 s and began with a 1-s auditory cue. In condition DETECT, the auditory cue was "liquid", after which a solution was presented, which could be sweet, sour, salty, or tasteless. Once delivery was complete, the subject indicated whether or not he or she had tasted something by pressing a button. After the 10-s response time, the sounding of a 3-s tone indicated the window during which subjects should swallow. This was followed by a 4-s rinse of the tasteless solution and then a second swallow tone during which subjects should swallow the rinse solution. In condition PASSIVE, the cue was "sweet", "salty", "sour", or "tasteless", and thus, the subject was accurately informed about the identity of the stimulus. In this condition, the subject was required to make a random button press

Fig. 2.

a Results from random effects analysis of DETECT_{tasteless}–PASSIVE_{tasteless} in insula and overlying operculum. Activations in the left anterior insula (AI), mid insula (MI), and parietal operculum (PO) are shown in the left axial section. Activations in the right anterior insula and frontal operculum are shown in the right axial section. The color bar represents the t values. **b** Results from random effects analysis of DETECT_{tasteless}–PASSIVE_{tasteless} in attention network. The color bar represents the t values. Axial and sagittal sections show activity in the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), left posterior parietal cortex (PPC), and right frontal eye fields (FEF)

Fig. 3.

Psychophysiological interaction results. The *top panels* show scatterplots of regression of activity in the anterior cingulate cortex on the activity in the seed regions parietal operculum, frontal eye fields, and posterior parietal cortex, and the *bottom panels* of activity in anterior insula and frontal operculum on the activity in the seed region anterior cingulate cortex during condition DETECT (dark red line and triangles) vs. PASSIVE (green line and squares). Each observation corresponds to the time-series interaction with that condition (averaged over subjects). For each condition, the correlation coefficient (Pearson's) between the activity in seed and target region is indicated. The section above each scatterplot shows the location of the seed region (circle size is not representative of sphere size of 15 mm), and the location of the region that shows neural response that was significantly associated with a stronger connectivity under DETECT vs. PASSIVE with the seed region. Color bar depicts *t* values

Fig. 4.

DCM models and model evidence. **a** Invariable configuration of all network models. Taste and tasteless events (collapsed across condition) were used as driving inputs into the anterior insula (anterior insula), and all models were specified to have full “steady-state” connectivity between the nodes in the network. **b** The three models that were tested in DCM differed in the connections between nodes that are modulated by DETECT vs. PASSIVE. Model A specified indirect modulation of the anterior insula by the attention network; the frontal eye fields, posterior parietal cortex, and parietal operculum modulate the anterior cingulate cortex; and the anterior cingulate cortex modulates the anterior insula. Model B specified direct modulation of the anterior insula by the attention network; the frontal eye fields, posterior parietal cortex, parietal operculum, and anterior cingulate cortex all modulate the anterior insula directly. Model C specified direct and indirect modulation of the anterior insula; the frontal eye fields, posterior parietal cortex, and parietal operculum modulate the anterior cingulate cortex and anterior insula; and the anterior cingulate cortex modulates the anterior insula (model C). **c** Exceedance probabilities of the three models. The exceedance probability is the probability that a model is more likely than any of the other models given the observed fMRI data. Exceedance probabilities showed strong evidence in favor of model A. **d** Estimates of parameters in model A. Next to each of the connections, the estimated modulation parameters are specified per condition (arbitrary units, averaged over subjects $\pm$ standard deviation). Significant differences between conditions DETECT and PASSIVE in modulatory strength are indicated with an *asterisk*. Next to the anterior

insula, the parameter estimate for the input strength is given for taste and tasteless events. Inputs significantly different from 0 are indicated with an *asterisk*

Table 1

Regions and their corresponding MNI coordinates

Region	MNI coordinates		
	x	y	z
Right anterior insula	33	18	9
Left anterior insula	-33	30	6
Left mid insula/frontal operculum	-39	9	3
	-39	0	6
Right frontal operculum	54	6	9
Left parietal operculum	-60	-15	9
Left posterior parietal cortex	-51	-36	51
Left middle frontal gyrus	-33	36	24
Right frontal eye fields	45	3	51
Anterior cingulate cortex	6	24	33
Posterior cingulate cortex	3	-27	30

Table 2

PPIs observed between the seed and target regions

Seed region	Target region	MNI coordinates			Cluster size in voxels	Z value	p_{FDR}^a
		x	y	z			
Left parietal operculum	Anterior cingulate cortex	6	36	39	15	3.38 ^b	0.059
	Right anterior insula and frontal operculum	39	18	-3	15	2.88 ^c	
Left posterior parietal cortex	Anterior cingulate cortex	3	27	36	4	3.23 ^b	0.029
	Right anterior insula	33	18	-6	11	2.86 ^c	
Anterior cingulate cortex	Right anterior insula	39	12	-3	18	3.77 ^b	0.032
	Right frontal operculum	48	0	6	18	3.38 ^b	0.047
Right frontal eye fields	Anterior cingulate cortex	12	18	24	7	3.46 ^b	0.034
	Right anterior insula	42	15	0	21	3.06 ^c	
	Right frontal operculum	48	15	0	16	2.97 ^c	

^a p value corrected by false discovery rate (FDR) for multiple comparisons across small volume^b T-map thresholded at $p_{uncorrected}=0.001$ ^c T-map thresholded at $p_{uncorrected}=0.005$