

The evaluation of brain activity in response to taste stimuli—a pilot study and method for central taste activation as assessed by event-related fMRI

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Abstract

Background: Brain pathways contribute to the regulation of appetite behaviors, and advancements in brain imaging offer new opportunities in determining whether disturbances of these pathways play a role in pathological feeding behaviors in humans. We developed a standardized method for the assessment of brain activation in response to taste stimuli. **Methods:** Five healthy control women were positioned in a 1.5 T GE magnet resonance (MR) scanner for functional MR imaging (fMRI). They received 1.0 cm³ samples of 1 M glucose solution or artificial saliva (25 mM KCl, 2 mM NaHCO₃). Fluid challenges were delivered by a programmable syringe pump (J-Kem Scientific, St. Louis, MO). E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA) coordinated taste stimulation with MR scanning. Data were analyzed using NeuroImaging software (NIS). **Results:** Healthy women showed increased orbitofrontal cortex activation when glucose was compared to artificial saliva. In addition, mesial and lateral temporal cortical regions contrasted glucose from artificial saliva. **Conclusions:** This study demonstrates a design for the systematic study of brain activation after taste stimulation using fMRI and computer controlled stimulus delivery. The results are consistent with previous studies, showing activation in higher order brain centers that are involved in emotional coding of taste experience. © 2003 Elsevier B.V. All rights reserved.

Keywords: Functional magnet resonance imaging (fMRI); Taste; Activation; Orbitofrontal cortex; Amygdala; Temporal cortex

1. Introduction

The modulation of food intake involves peripheral and central mechanisms. The brain is thought to contribute taste memory, reinforcement and reward, as well as habituation (Bray, 2000). In addition, food intake is closely associated with emotional responses such as a hedonic sensation or “liking” or “food avoidance” (Berridge, 1996; Saper et al., 2002). This concept of pleasure and hedonic experiencing is based on internal sensations in response to stimuli that are experienced as useful (Cabanac, 1971). Dopaminergic pathways in turn may be implicated in the transmission of those sensations and following behavioral activation (Kelley et al., 2002; Koob, 1996). In fact, dopaminergic brain areas

involved in the taste reward circuit may include the ventral tegmental area (Shimura et al., 2002) and the ventral striatum containing the nucleus accumbens (Schultz et al., 2000). Normal gustatory responses include preference for sweet taste such as chocolate, and dislike for highly salty taste (Zald et al., 1998), and such signals may be involved in the regulation of normal meal size (Poothullil, 1995). Disturbances of central regulatory mechanisms may be associated with disordered eating patterns (Blundell and King, 1996; Cooke et al., 1997; Wurtman and Wurtman, 1995). The frontal operculum and dorsal insula are considered to be primary areas of taste representation in the brain (Ogawa, 1994). Moreover, single neuron activation studies in primates indicate that the orbitofrontal cortex acts as a secondary or higher order taste center that is involved in the emotional coding of taste stimuli (Rolls, 1989). It is believed that the representation of emotional values of stimuli is located in the amygdala (LeDoux, 1995; Rolls, 1995), and that

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the orbitofrontal cortex reevaluates those valences including their rewarding properties based on current experiences (Rolls et al., 1999).

Most in vivo brain-imaging techniques in humans found that food stimuli activate specific brain regions, in particular the insula (Small et al., 1999). In addition, increased activity to taste stimuli has been shown in the perisylvian region, anterior cingulate gyrus and centromedial thalamus in a paradigm that used sodium chloride, aspartame, quinine hydrochloride, D-threonine, glycyrrhizic acid and 5'-guanosine monophosphate as taste stimuli (Cerf et al., 1998; Faurion et al., 1998, 1999). The imagination of sweet and salty taste produced activation in orbitofrontal, frontal, insular, and temporal cortex as well as in the amygdala (Levy et al., 1999). The orbitofrontal cortex has often been associated with emotional coding of taste stimuli (Francis et al., 1999) and recently, another taste stimulation paradigm that compared glucose to a salty solution showed increased activity in the opercular/insular cortex, orbitofrontal cortex and amygdala (O'Doherty et al., 2001). In addition, taste reward *anticipation* activated midbrain, posterior dorsal amygdala, striatum, and orbitofrontal cortex, whereas in that study actual reward receipt activated orbitofrontal cortex only (O'Doherty et al., 2002). A study focusing on the time course of taste activation also showed orbitofrontal cortex and cingulate activation as well as hypothalamus, somatosensory and cerebellar activation (Liu et al., 2000).

Our group has been interested in investigating central mechanisms related to disordered eating in people with anorexia and bulimia nervosa. Relatively, little is known about the regulation of appetite in these disorders. Altered responses to food tastes could be related to anxiety or obsessions due to a fear of eating, or might be an abnormal physiologic response to food. In order to systematically investigate the central mechanisms that are possibly related to normal or disturbed eating behaviors in humans in vivo, our laboratory developed a method of blind administration of liquid solutions of food substances and brain activation responses. In order to test this methodology, we studied healthy women. Based on the studies described earlier, we hypothesized that we would find altered orbitofrontal activity in response to a sweet—and presumably pleasant—stimulus compared to a rather neutral stimulus. Moreover, we also expected cingulate cortex, and the mesial temporal cortex to be involved in the response to taste stimuli.

2. Methods

2.1. Subject selection

Five healthy volunteer women were recruited. These women had to be between the ages of 18 and 45 years and at a weight between 90 and 125% of average body weight since puberty. Healthy volunteers had laboratory tests, medical and psychiatric histories, and physical and neurological

examinations that indicated no evidence of present or past psychiatric, medical or neurologic illness. Healthy volunteers had no signs suggestive of an eating disorder. Healthy volunteer women that were pregnant or nursing were excluded. All volunteer women of childbearing potential had a pregnancy test within 24 h prior to each functional magnet resonance imaging (fMRI) scanning session and were excluded if pregnant.

After signing a written informed consent, all subjects underwent several structured interviews (SCID-I, SCID-II; First et al., 1996), and had a medical evaluation (physical examination, electrocardiogram, vital signs, hemoglobin, hematocrit, total leukocyte with differential, plasma electrolytes, liver and thyroid function (T3, T4 and TSH levels), urinalysis and toxicology and pregnancy tests. Test results were reviewed prior to study entry. The Edinburgh Inventory for analysis of handedness assessed the dominant hand. Subjects were compensated with US\$ 100 for travel, time and lost income.

2.2. Taste stimuli application (Fig. 1)

Subjects received 1.0 cm³ samples of artificial saliva (25 mM KCl, 2 mM NaHCO₃) or 1 M glucose solution that was similar in design to studies of another laboratory (Francis et al., 1999). These fluid samples were administered through two food grade Teflon tubes (0.32 cm. i.d., 0.48 cm. o.d., FDA/USDA approved, Cole-Parmer, Vernon Hill, IL) which subjects had placed in their mouth. Because subjects had to lie in an fMRI scanner, they were trained to hold the plastic tubes in their mouth while in a supine position. Subjects were trained to simply hold the tubes in their mouth and not to withdraw fluid from the tubes into their mouth by sucking, or to manipulate the tubes with their lips, teeth or tongue. The tubes were attached to the MR scanner's head holder to reduce motion. In addition, subjects were trained to perform one tongue motion (swishing the tongue across the gum) after each application of taste stimulant, in order to wash the taste stimuli around the mouth and stimulate taste buds. Subjects that were not capable of carrying out these required procedures were excluded from the study.

Fluid challenges were delivered to the subject by a semi-automatic programmable customized syringe pump (J-Kem Scientific, St. Louis, MO; Fig. 1). The syringe pump delivered samples from either of two reservoirs through FDA approved food grade Teflon tubes (Cole-Parmer) into the subject's mouth. The reservoir tube and the tube to the subject were connected via a Teflon valve, enabling the syringe pump to draw solution from the desired reservoir into the two glass syringes that are part of the syringe pump mechanism. The valve at the syringe pump switches direction depending on if the pump fills the syringes or pumps solution to the subject. For solution delivery, the taste stimulus was then pressed from the syringe through the Teflon tubes that were directed toward the subject. The delivering tubes were approximately 10 m in length and

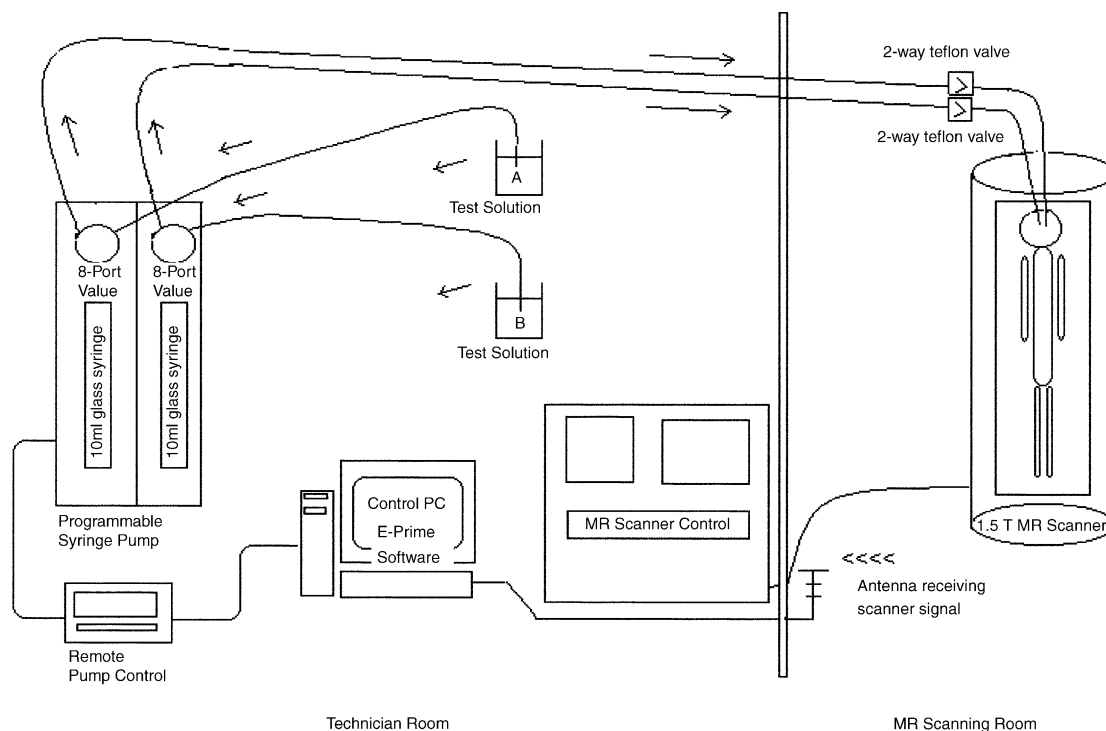


Fig. 1. Experiment set-up for the taste stimulation paradigm. The programmable syringe pump withdraws taste stimuli from the reservoirs A and B into two syringes. Following the fMRI scanning signal via antenna and cable connection, the E-Prime software is triggered that then triggers the delivery of taste stimulus A or B to the subject.

were pre-filled with sample solutions so that 1.0 cm^3 of solution could be administered to the subject in less than 1 s. There were 12 s between samples during which fMRI scanning was performed. The syringe pump was located in the MRI technician room, and the tubing to the subject ran from the pump to the subject in the MRI scanner room through a filter port in the wall of the MRI scanning room.

The syringe pump's hardware was connected to a PC (Compaq 650, Compaq, USA) in the technician room. E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA) controlled the rate of administration of the solution as well as solution choice and was also the interface between syringe pump and the MRI scanner panel. The PC was connected to an antenna in the scanner room that received a signal from the fMRI scan. Instantaneously, with the start of the scanning procedure, E-Prime software then triggered the programmable syringe pump delivering the taste stimulus (trial). Over the next 12 s, E-Prime was in a non-responsive state, not accepting trigger signals from fMRI scanning. After that period, it was available for another taste stimulus, stimulating another trial of taste stimulus application. During this 12 s interval, each individual trial was followed by four fMRI scans of 3 s duration each.

We applied test solutions in blocks of 20 trials. The same solution (e.g. glucose) was given over one block, i.e. 20 times in a row (one block), followed by artificial saliva in

the following block (again 20 trials in a row). Four blocks of taste stimulations and scanning were applied. The subjects were randomized regarding stimulus application (ABAB or BABA) in alternating order.

2.3. fMRI data methods and analysis

All studies were conducted using the research dedicated 1.5 T GE MRI scanner with a standard head coil at the MR Research Center, University of Pittsburgh. Structural images were obtained using a standard T1-weighted pulse sequence (36 slices, TR 12 ms, TE 500 ms, flip angle 90° , FOV 24 cm).

Functional scans were obtained using a two-shot T2*-weighted spiral-scan pulse sequence (TR 1500 ms, TE 35 ms, flip angle 60° , FOV 24 cm). A total of 20 slices of functional scans starting with the frontal cortex through the posterior temporal cortex were acquired. Scans were acquired coronally with a voxel size of 3.75 mm^3 . Scanning was synchronized to stimulus presentation as described earlier, and multiple images were obtained during the course of an experimental trial, permitting us to examine the temporal dynamics of regional brain activity associated with taste-task functions of interest.

Reconstructed images were corrected for small head movements using a six-parameter automated image registration (AIR) algorithm (Woods et al., 1992) and registered to the first image in the series. Images for all subjects were

co-registered to a reference structural MRI scan using a 12-parameter automated algorithm (Woods et al., 1992, 1993). They were then smoothed using an 8 mm FWHM three-dimensional Gaussian filter, to accommodate individual differences in anatomy. Finally, data were pooled across subjects to increase signal to noise.

2.4. Statistical analysis

For the assessment of fMRI data we used the NeuroImaging software (NIS, <http://www.nimh.nih.gov/neuroinformatics/cohenj.cfm>). In brief, the NIS package is a collection of UNIX-based programs and shell scripts used for conducting each of the primary steps involved in preprocessing and analyzing neuroimaging datasets, as well as statistical analysis using ANOVA. Most of the programs are provided with an optional graphical user interface (written in Java). The NIS package uses the ANALYZE format (16-bit integer) for all image data. Data were analyzed using a contrast that used subject as random factor and condition (A (artificial saliva) versus B (glucose)) by scan (image within a trial) as independent factors. Data were analyzed using a design file that linked the individual taste stimulus information to the corresponding image sequence (trial and scan). Data were thresholded for exclusion of non-brain areas, and significant areas of activation had to be at a voxel contiguity of eight to control for multiple comparisons. A significance level of $P = 0.005$ was applied. In addition, two-sided independent t -tests compared results by condition for each time point (scan within trial) using the individual time activity data. Subject 1's structural image was selected as reference image and significant areas of activa-

tion were overlaid on this image for assessment of regional activation.

3. Results

The healthy control women had a mean age of 25.6 years (standard deviation (S.D.) = 3.4 years), and a body mass index (BMI) of 22.8 (S.D. = 0.8). All subjects were right-handed. Head movement was minimal across subjects with less than 1.5 voxels in each subject. Comparing the two conditions, at a significance level of $P < 0.005$, five areas of significantly different activation across conditions were identified.

Activation in the right orbitofrontal cortex (Fig. 2, ROI-1) was greater after glucose stimulation compared to artificial saliva. Significant differences were observed at scan times 2 ($t = -2.31$, $P = 0.02$) and 3 ($t = -3.17$, $P = 0.002$). Both right (Fig. 3, ROI-2; scan 2, $t = -2.36$, $P = 0.02$) and left (Fig. 3, ROI-3; scan 2, $t = -3.04$, $P = 0.003$) lateral temporal cortex (middle temporal gyri) activation showed early negative activation for both taste stimuli, being more negative after artificial saliva compared to glucose. The right mesial temporal cortex (Fig. 3, ROI-4) showed a pattern of initial decrease and subsequently increase of brain activity for both taste stimuli, with faster rise of activation for artificial saliva at scan 3 ($t = 2.23$, $P = 0.03$). The left mesial temporal cortex (Fig. 3, ROI-5) showed a similar pattern with initial decrease followed by increase in activation for both conditions that was delayed for the glucose condition compared to artificial saliva. Here, the conditions differed significantly at scan 3 ($t = 3.512$, $P = 0.001$).

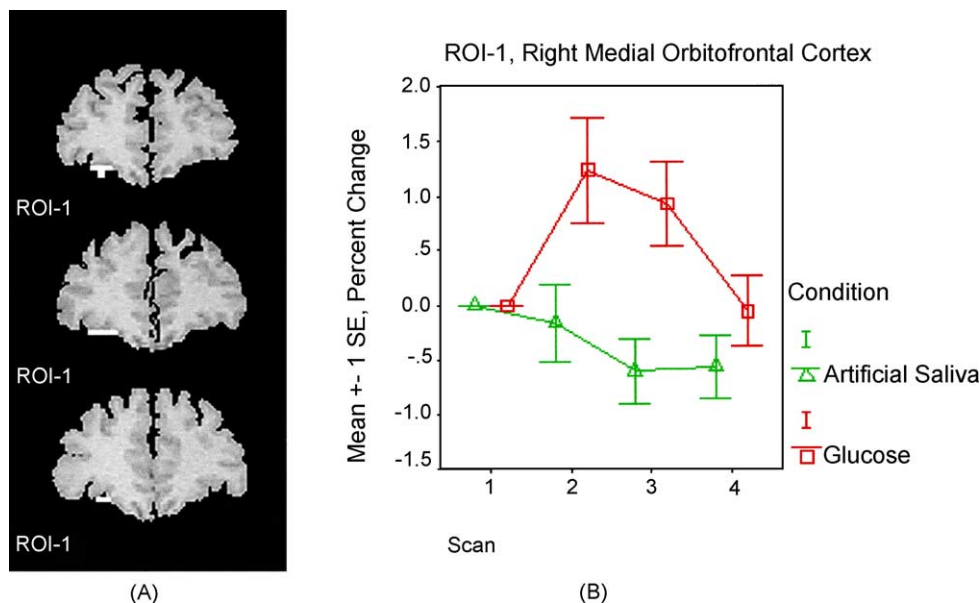


Fig. 2. Increased orbitofrontal cortex activation after glucose compared to artificial saliva at $P = 0.005$. (A) Orbitofrontal activation over three brain slices. (B) Time-activity curves (percent change from baseline) with increased activation after glucose activation compared to artificial saliva (ROI: region of interest; SE: standard error).

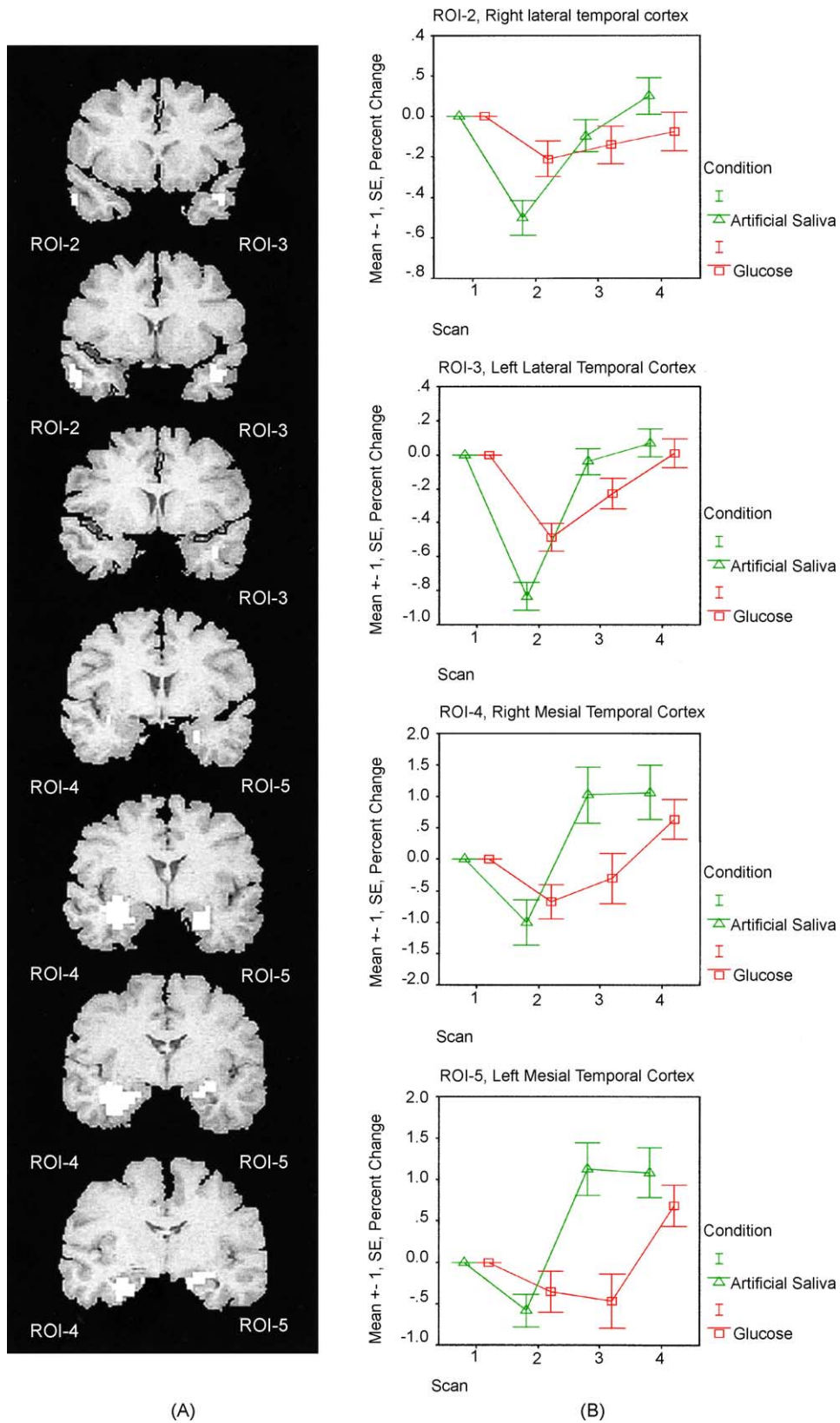


Fig. 3. Regional activation overlaid on reference brain at a $P = 0.005$. (A) Regions of interest 2–5 with significantly different activity across conditions. (B) Time–activity curves (percent change from baseline) for the corresponding region of interest (ROI: region of interest; SE: standard error).

4. Discussion

This study describes a method for the systematic investigation of brain activation in response to blind administration of taste stimuli. In the past, some methods for taste activation and brain imaging have been described (Berns et al., 2001; Cerf-Ducastel et al., 2001; Faurion et al., 1999). However, to our knowledge, no similarly automated methodology for event-related fMRI has been described.

We found different activation for orbitofrontal, mesial temporal and lateral temporal cortical areas when glucose was compared to artificial saline in this group of healthy women. Relative few studies have investigated taste in humans or non-human primates, *in vivo*, using brain-imaging methodologies. Taste paradigms included sweet, salty, bitter, neutral, and other stimulants. In addition, the forms of stimulus application were different, variable time frames for image acquisition after stimulation were used across studies, and there was inconsistent information regarding the relationship between the taste stimulus and the start of the imaging procedure. The use of different brain-imaging modalities such as positron emission tomography (PET) or fMRI makes the comparison of studies even more complicated.

We found, for the orbitofrontal cortex, that glucose produced significantly higher activation than did artificial saliva. Our findings are consistent with previous studies using glucose as taste stimulant together with fMRI (Francis et al., 1999; O'Doherty et al., 2001). This may indicate a higher hedonic value for the sweet taste compared to the artificial saliva stimulus that is represented in the orbitofrontal cortex. In this study, left and right mesial temporal cortex regions (amygdala and hippocampus) were activated after both glucose and artificial saliva with an initial decrease in activity with subsequent increase. However, after the initial decrease of activation, increase of activation after artificial saliva occurred faster for than for glucose. Earlier studies have reported activation in the amygdala as well (Bray, 2000; O'Doherty et al., 2001).

Previous studies have tended to use block designs that summed the response compared across groups. However, time-course patterns have been less frequently described. One study (Liu et al., 2000) showed that central activation post taste stimulus might occur over several minutes. This does not follow the classic hemodynamic response seen over 6–10 s as commonly seen in event-related fMRI using psychological tasks (Posner and Raichle, 1998). O'Doherty et al. (2002) showed the temporal pattern of brain activation during taste stimulation for one subject. The hemodynamic response to taste stimuli went beyond 10 s after stimulus presentation and did not occur within the 9.5 s time frame that was applied otherwise in that study. It is therefore possible that we missed later activation, e.g. in the mesial temporal cortex that further contrasted stimuli.

This study found differences across conditions for the lateral temporal cortex. We are not aware of other studies finding such activation. However, since the primary taste cortex has close connectivity with the mesial temporal cortex, which projects to lateral temporal cortical areas (Nieuwenhuys et al., 1988) an involvement of those areas is possible. We did not focus on activation of primary taste cortical areas such as insula and operculum. Since all taste stimuli per definition should be represented in that region (Barry et al., 2001; Cerf et al., 1998; Kobayakawa et al., 1999; Small et al., 1999) and other areas are activated secondarily to that region, we did not expect a difference of activation across conditions for that area. However, in a supplemental analysis, contrasting by scan only, we found prominent bilateral insular activation in addition to striatal and thalamic activation across time (data not shown).

The main shortcoming of this study is the temporal restraint of scans that were limited to 12 s post taste stimulus. Whereas the response in the orbitofrontal cortex appears to occur within the estimated time frame, the mesial temporal response may be ongoing. This will need to be addressed in future studies that allow a longer time frame for scanning such as a window of 1 min with multiple scans or even up to 12 min as suggested by Liu's study (Liu et al., 2000). Another limitation is the number of brain slices that were acquired during each scan. Thus, it is possible that areas of activation were missed in more dorsal areas such as the ventral tegmental area that might be a part of the central regulation of food reward (Shimura et al., 2002). A limitation may be that we studied female subjects only. However, since gender may have an impact on the result of central activation (Cailhol and Mormede, 2002), we decided to study one gender for the development of the methods for this taste activation paradigm.

In summary, this study describes a method for delivering individual taste stimuli in a timely manner in relation to the fMRI procedure using a computer controlled delivery system. Consistent with other studies, it contrasted different stimuli in orbitofrontal and mesial temporal cortex, possibly distinguishing their hedonic value. More studies are needed for the systematic application of various taste stimuli and assessment of brain response. This study design will help to further understand human food-related brain activity and biologic mechanisms that contribute to normal as well as pathologic eating behavior.

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