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# Hunger and Satiety Modify the Responses of Olfactory and Visual Neurons in the Primate Orbitofrontal Cortex

HUGO D. CRITCHLEY AND EDMUND T. ROLLS
*University of Oxford, Department of Experimental Psychology, Oxford OX1 3UD, United Kingdom*

## SUMMARY AND CONCLUSIONS

*1*. The primate orbitofrontal cortex is the site of convergence of information from primary taste and primary olfactory cortical regions. In addition, it receives projections from temporal lobe visual areas concerned with the representation of objects such as foods. Previous work has shown that the responses of gustatory neurons in the secondary taste area within the orbitofrontal cortex are modulated by hunger and satiety, in that they stop responding to the taste of a food on which an animal has been fed to behavioral satiation, yet may continue to respond to the taste of other foods.

*2*. This study demonstrates a similar modulation of the responses of olfactory and visual orbitofrontal cortex neurons after feeding to satiety. Seven of nine olfactory neurons that were responsive to the odors of foods, such as blackcurrant juice, were found to decrease their responses to the odor of the satiating food in a selective and statistically significant manner.

*3*. It also was found for eight of nine neurons that had selective responses to the sight of food, that they demonstrated a sensory-specific reduction in their visual responses to foods after satiation.

*4* The responses of orbitofrontal cortex neurons selective for foods in more than one modality also were analyzed before and after feeding to satiation. Satiety often affected the responses of these multimodal neurons across all modalities, but a sensory-specific effect was not always demonstrable for both modalities.

*5*. These findings show that the olfactory and visual representations of food, as well as the taste representation of food, in the primate orbitofrontal cortex are modulated by hunger. Usually a component related to sensory-specific satiety can be demonstrated. The findings link at least part of the processing of olfactory and visual information in this brain region to the control of feeding-related behavior.

## INTRODUCTION

The principal aim of these experiments is to advance understanding of the neural mechanisms involved in feeding, taste, and olfaction to shed light on processes whose failure may lead to eating disorders and disorders of body weight control (Rolls 1989, 1993, 1994, 1995; Rolls et al. 1994). More specifically, this study looks at the neuronal representation of food in the orbitofrontal cortex and the mechanisms by which satiety affects the responses of olfactory, visual and multimodal neurons that contribute to this representation.

The motivational changes that accompany feeding are of great importance in the control of food intake and the regulation of meal size. Both the sensory properties of food and a wide variety of internal signals that follow ingestion serve to modulate feeding behavior. In humans, perceptual changes occur during feeding, particularly when food is eaten to satiety. One such change is alliesthesia, which in the context of feeding refers to the modulation of the pleasantness of the sensory percepts of food by internal signals such as blood glucose level (or following the intake of protein and fat) (Cabanac 1971; Cabanac and Duclaux 1970). In a study of alliesthesia and olfaction in human subjects, Duclaux, Feisthauer, and Cabanac (1973) compared the rated pleasantness of food- and nonfood-related odors in fasted subjects before and after eating, with control subjects who remained fasted. The odors used were food-related odors of meat, cheese, fish, and honey, odors of "accompaniments to meals" of coffee, tobacco, and wine, and nonmeal-related odors of lavender, hypochlorite, and chinese ink. The subjects were allowed an ad libitum meal from a selection of normal foods. Ratings were compared before and after this meal, and it was found that food-related odors, which were generally rated as pleasant before the meal, were rated as less pleasant after the meal (when compared with the ratings of fasted controls). The difference in rating did not occur to nonfood odors.

In neurophysiological studies of the effect of satiety on the responses of neurons to food, it was shown that the responses of lateral hypothalamic neurons to the sight or taste of food decreased when the monkey was fed to satiety (Burton et al. 1976). During these experiments on satiety, it was observed that if a lateral hypothalamic neuron had ceased to respond to a food on which the monkey had been fed to satiety, then the neuron might still respond to a different food. This occurred for neurons with responses associated with the taste (Rolls 1981; Rolls et al. 1986) or sight (Rolls and Rolls 1982; Rolls et al. 1986) of food. Corresponding to this neuronal specificity of the effects of feeding to satiety, the monkey rejected the food on which he had been fed to satiety, but accepted other foods that he had not been fed. As a result of these neurophysiological and behavioral observations showing the specificity of satiety in the monkey, experiments were performed to determine whether satiety was specific to foods eaten in man. It was found that the pleasantness of the taste of food eaten to satiety decreased more than for foods that had not been eaten (Rolls et al. 1981a). This process was termed sensory-specific satiety. It was found that changing the flavor, color, shape, and texture of the same food would lead to increased food consumption (Rolls et al. 1981b), thereby implicating the sensory properties of the food in the satiety process rather than internal signals signifying nutritional intake.

In fact, the degree of satiety induced by a food can be increased by enhancing the visual, taste, and olfactory properties of the food, without changing the nutritional value of the food. The study of Rolls et al. (1981b), illustrated that

staple foods would be eaten in greater quantity if there was variation in the sensory properties of the food. The provision of the same foodstuff, but with differing flavors, textures, or visual appearance, delayed the satiating effect of the food. In a similar type of experiment, Warwick, Hall, Pappas, and Schiffman (1993) showed that the addition of taste and odor to bland high-carbohydrate and high-fat foods increased the ability of the food to induce satiety (measured by a decrease in hunger ratings). There was also shown to be some nonspecific decrease in the pleasantness of food-related flavors. Taken together these studies show that the sensory properties of food strongly influence behavioral satiety, including the termination of feeding, in advance of the nutritional and other postingestive qualities of the food.

In neurophysiological studies of earlier stages of taste processing than the lateral hypothalamus in the monkey, it was found that modulation by satiety did not occur in the nucleus of the solitary tract (Yaxley et al. 1985), which receives first-order gustatory afferents. Similarly, the gustatory responses of neurons in the primary taste cortical regions of the insula and frontal operculum were found to be unaffected by satiety (Rolls et al. 1988; Scott et al. 1985; Yaxley et al. 1988). Visual responses to food at the level of the inferotemporal cortex [a visual area known to project to orbitofrontal cortex (Barbas 1988; Morecraft et al. 1992)] were also not modulated by satiety (Rolls et al. 1977). Beyond the primary taste cortices, in the secondary taste cortex of the caudolateral orbitofrontal cortex (Baylis et al. 1994), the responses of taste neurons were found to be modulated by satiety, in a sensory-specific manner (Rolls et al. 1989). This thus appears to be the first site in the primate taste system at which hunger modulates taste processing (Rolls 1989, 1995).

The orbitofrontal cortex is also a site of convergence from a variety of sensory modalities (see Rolls 1989, 1993, 1995; Rolls and Baylis 1994). Takagi and colleagues have described two overlapping olfactory regions in the caudal and medial orbitofrontal cortex (Tanabe et al. 1975a,b; Yarita et al. 1980). Taste, olfactory, and visual information all reach the orbitofrontal region to converge on to the same regions and often the same neurons (Rolls and Baylis 1994). The olfactory input into the orbitofrontal region has been shown anatomically to project directly from the pyriform cortex into the caudal orbitofrontal region medial to the secondary taste cortex (Barbas 1993; Carmichael et al. 1994; Morecraft et al. 1992; Price et al. 1991a). Visual information about foods can reach the orbitofrontal cortex via projections from the inferotemporal cortical areas (Barbas 1988; Morecraft et al. 1992). The convergence of sensory information from many modalities, including taste, olfaction, and vision, provides a means by which a rich representation of food stimuli can be formed. In humans, the combination of taste and olfactory information to form flavors leads to discrete and relatively constant encoding of the chemosensory properties of individual foods. These "flavor constants" provide a plausible representation on which modulatory influences, such as satiety, can operate specifically on the neuronal and perceptual responses to individual foods.

The present study examines whether the responses of primate orbitofrontal cortex neurons that respond to olfactory and visual information about foods are influenced by hunger and whether there is a sensory-specific modulation of responsiveness. The responses of visual neurons in the orbitofrontal cortex are known to be influenced by the reward and taste association of the visual stimuli (Thorpe et al. 1983), yet the responses of orbitofrontal cells selective for food stimuli have not previously been shown to be influenced directly by satiation, as has been demonstrated for visual neurons in the hypothalamus (Rolls et al. 1986). Although some data (Pager 1974; Pager et al. 1972) have indicated that processing in the early stages of the rat olfactory pathway may be influenced by satiety (even at the level of the olfactory bulb), there have been no such studies for primates. The present study examines the olfactory responses to food in a region where there is convergence of olfactory, visual, and taste information about food and where the responses of taste neurons are known to be affected by satiety. The presence of multimodal neurons encoding food in the orbitofrontal cortex raises the interesting issue of how the responses of the neuron across modalities are influenced by feeding to satiety.

## METHODS

### *Recordings*

Recordings were made from single neurons in the orbitofrontal cortex, which included both the medial and lateral areas in which olfactory responses have been described previously. A few neurons also were recorded in the primary taste (insula) and primary olfactory (pyriform) cortical regions. The subjects were two male rhesus macaques (*Macaca mulatta*) and one male cynomolgus macaque (*Macaca fascicularis*) weighing 2.5–3.5 kg. Neurophysiological methods were the same as described previously (Rolls 1976; Rolls and Baylis 1994; Rolls et al. 1990; Scott et al. 1986; Yaxley et al. 1990). All procedures, including preparative and subsequent ones, were carried out in accordance with the *Guidelines for the Use of Animals in Neuroscience Research* of the Society for Neuroscience and were licensed under the U.K. Animals (Scientific Procedures) Act 1986. The monkey was fed during the experiments and on return to its home cage and was allowed ad lib access to water. Glass-coated tungsten microelectrodes were constructed in the manner of Merrill and Ainsworth (1972) without the platinum plating. A computer (IBM 486 DX) collected spike arrival times and displayed on-line summary statistics or a peristimulus time histogram and rastergram. To ensure that the recordings were made from single cells, the interspike interval was continuously monitored to make sure that intervals of $<2$ ms were not seen, and also the waveform of the recorded action potentials was monitored continuously using an analog delay line.

### *Localization of recordings*

X-radiography was used to determine the position of the microelectrode after each recording track relative to permanent reference electrodes and to the anterior sphenoidal process. This is a bony landmark whose position is relatively invariant with respect to deep brain structures (Aggleton and Passingham 1981). Microlesions made through the tip of the recording electrode during the final tracks were used to mark the location of typical units. These microlesions together with the associated X-radiographs allowed the position of all cells to be reconstructed in the 50-$\mu$m brain sections with the methods described in Feigenbaum and Rolls (1991).

### *Screening of neurons*

Orbitofrontal cortex cells were tested for their responsiveness to taste, olfactory and visual stimuli. Responses to odorants were

determined either clinically or using an olfactory discrimination task. The clinical criteria for olfactory responsiveness were a significant elevation of cellular firing above the spontaneous firing rate to an odorant (measured during a 5-s period of presentation in front of the monkey's nose of an cotton bud saturated in odor vapor), and no response to an odorless cotton bud used as a control. The olfactory discrimination task involved the randomised delivery of odorant saturated air via a computer-driven olfactometer (Critchley and Rolls 1996). A cue tone preceded the delivery, following which the monkey was required to sample each odor to identify odors as part of a Go/NoGo task. A lick response to a rewarded odorant was rewarded with the delivery of a sweet aspartame solution from the lick tube; a lick response on the NoGo trials was associated with the delivery of a mildly aversive saline solution. On-line rastergrams and statistics enabled the determination of olfactory responsiveness. An air extraction apparatus was located above the monkey's head to remove odor (see Critchley and Rolls 1996).

### *Olfactory satiety experiments*

Olfactory satiety experiments were performed on cells having effective and reliable responses to natural fruit odors when presented clinically as described above. Cell responses to a subset of pure chemical and natural food odors were measured before and after satiation. In most cases, a 20% blackcurrant juice solution was used to produce satiety, and the corresponding odorant was that of the blackcurrant juice concentrate. In some cases, a sweet solution (20% sucrose) with the odorant added to it was used (see RESULTS), and in one case, cream was used to produce satiety and as the odorant (see RESULTS). In some of the experiments, it was possible to record the responses of the cells to the odorants at intermediate stages of satiation. For each odorant, between 4 and 10 trials were performed to ensure statistical validity. Aliquots of 20–50 ml of the satiating solution were fed to the monkey during which the behavioral response to the solution was observed. The behavioral acceptance of this solution was rated according to the criteria used previously (e.g., Rolls et al. 1989). Scores on the scale of acceptance or rejection were based on the following behavioral criteria: +2.0, maximal acceptance: reaching for the solution with hands and mouth, avid licking; +1.0, clear acceptance: opening the mouth, licking and swallowing the solution; 0.0 ,neutrality: swallowing the solution when placed in the mouth, absence of avidness, no attempt made to obtain the solution; −1.0, clear rejection: pursing the lips to prevent administration of the solution, failure to swallow all of the solution placed in the mouth; and −2.0, maximum rejection: pursing the lips and closing the teeth, using the tongue to eject delivered solution, swallowing little, using the hands to push away the solution. If the behavior was intermediate between these types, then intermediate scores were given.

### *Visual satiety experiments*

Visual cells responsive to foods or food-related objects, such as a feeding syringe containing blackcurrant juice, were tested on repeated trials to the food stimuli, which were presented in front of the monkey using a shutter task (where the onset of the stimulus presentation is clearly defined by the opening of the shutter) or clinically. The responses were measured in the first 2.5 s after the appearance of the food, as it was brought from a distance of 1 m to a distance of 10 cm from the monkey's mouth. The procedure (see Rolls et al. 1983; Thorpe et al. 1983) allowed visual responses to the sight of food to be separated from anticipatory responses before the food was seen, or mouth-movement-related responses occurring as the food was brought very close to the monkey's mouth, both of which occurred in some other neurons. The clinical presentation of food stimuli enabled the screening of anticipatory responses and allowed the testing of neuronal responses related to the movement of food toward or away from the animal. The responses to the sight of a set of foods, on one of which the monkey was fed to satiety, were measured before and after feeding to satiety.

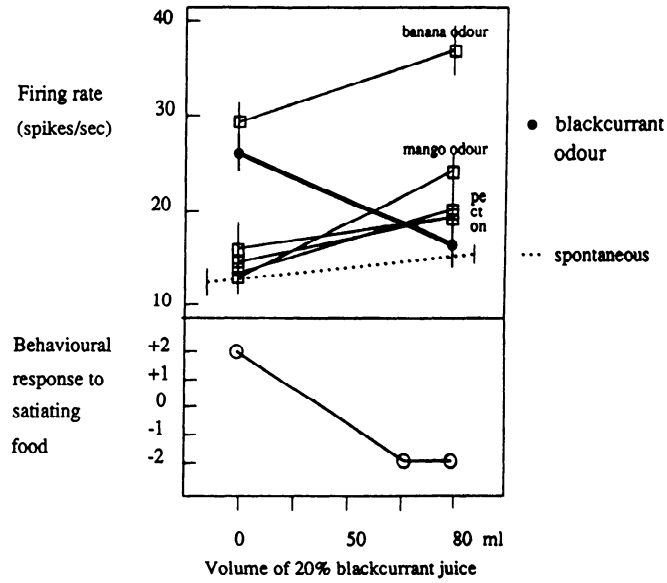


FIG. 1. Responses of a single olfactory neuron, au006, to odors of blackcurrant juice, banana, mango, phenyl ethanol (pe), citral (ct), and onion (on). The means and standard errors of neuronal responses are shown. Beneath these are plotted clinical measurements of behavioral acceptance of 20% blackcurrant juice, which was fed to the animal to induce satiety. These measurements range from +2 indicating maximal acceptance of food to −2 indicating maximal rejection, hence full satiation of the animal. There was a selective decrease in response of neuron to odor of blackcurrant juice after satiation.

## RESULTS

### *Olfactory experiments*

It was possible to perform nine separate satiety experiments on nine different odor-responsive cells from the orbitofrontal cortex. Three of these cells were also responsive to taste stimuli. In all the cells, there was a decrease in response after satiety to the odor of the satiating food. In eight of the nine cells, this decrease was sensory specific, in that it did not affect the responses to other food and nonfood odors to the same extent as the response to the odor of the satiating food. This was shown statistically as a significant interaction in a two-way analysis of variance (ANOVA) in which one treatment was the odor of the satiating food versus the other odors and the other treatment was before satiety versus after satiety. In most cases, the response to other odors remained the same or increased after satiety.

Figure 1 illustrates the responses of a unimodal olfactory neuron, au006, that responded to the odor of foods, in particular banana and blackcurrant juice. The cell did not respond well to other odorants, such as phenyl ethanol (pe), citral (ct), onion odor (on), or mango odor (ma). When the monkey was fed with 20% blackcurrant juice to satiety, the response of the cell to the odor of blackcurrant juice (bj) was decreased from 26.7 spikes/s to 17 spikes/s (the level of spontaneous activity). The response to the odor of banana

(ba) was increased from 29 spikes/s to 36 spikes/s, and the response to the other odorants showed a (nonsignificant) increase. This neuron therefore demonstrated a sensory-specific effect of satiety on the response to the odor of blackcurrant juice. In a two-way ANOVA, there was a significant interaction between blackcurrant odor and the other odorants, before and after satiety [$F(1,62) = 7.2$, $P < 0.01$].

Figure 2 shows the responses of the nine cells in the olfactory satiety experiments. The response to the odor of the satiating food is plotted by a continuous line and the mean response to the other odorants is plotted as a dashed line. Where possible, the responses to these other odorants are divided into the mean responses to food odorants and nonfood odorants and are plotted as dotted lines. The responses are plotted as a percentage of the presatiety response to the odor of the satiating food. In three of the cells (au060, aq028, and aq036), there was some generalization of the effect of satiation on the responses to other food odors. This is shown by a decrease in the response to the food odors relative to the response to the nonfood odors. Despite this, cells au060 and aq036 both show a sensory-specific satiety effect (with a significant interaction term in the two-way ANOVA) when the responses to all the odorants are taken together. In six of these experiments, satiation was attained using blackcurrant juice. Vanillin-flavored 20% sucrose solution was used in one experiment and limonene-scented 20% sucrose solution in another.

Cell au142 was a neuron that responded well to the odor of single cream, presented on a cotton bud for the animal to sniff. In this experiment, the monkey was fed to satiety using 50 ml of the single cream (Fig. 3). The neuron responded to the odors of cream, apple, and banana before satiety, but not to nonfood odorants such as caprylic acid. After satiety with cream, the neuron continued to respond well to the odors of apple and banana, yet stopped responding to the odor of cream. There was a significant interaction between cream and the other odorants before and after satiety [$F(1,46) = 3.6$, $P < 0.05$].

Two of the nine neurons did not show a statistically significant effect of satiety. These were cell au028 and cell au111. Cell au028 was a bimodal neuron, that responded to the taste of glucose, banana, and blackcurrant juice. Before satiety it had good responses to the odor of blackcurrant juice and not to the other odorants tested. After satiety, there was a decrease in the response of the cell to blackcurrant odor, and an increase in the mean response to the other odorants, but the interaction in the two-way ANOVA did not quite reach significance [$F(1,31) = 3.41$, $P = 0.07$]. Cell au111 was a unimodal olfactory neuron that responded well to a variety of food and nonfood odorants. When the animal was fed to satiety on 20% sucrose solution scented with limonene, the response of the cell did not alter significantly to any of the odorants.

Figure 4 summarizes the mean responses across the eight cells in which the response to the odor of the satiating food was reduced by satiety. This therefore excludes only cell au111. Across the cells, satiety was shown to decrease the response to the odor of the satiating food to 30% of its original value, while the responses to both other food and nonfood odorants remain unaffected by the satiety. In a two-way ANOVA, taking the mean neuronal responses for these cells (i.e., not normalized) as the dependent variable and the two conditions being before versus after satiety and odor of satiation versus other odors tested, there was a significant interaction term [$F(1,32) = 4.5$, $P < 0.05$].

*Visual experiments*

To investigate whether responses to the sight of food were affected by satiety, recordings were made from nine visually responsive neurons. All these neurons were selective to the sight of food or to food-containing objects such as a visually identifiable syringe from which the monkey was fed. Seven of the cells responded to the sight and the approach of foods, and two of these cells responded maximally when food was moved away from the monkey. Five of the nine visual neurons analyzed were also responsive to taste stimuli. In eight of the nine cells the response to the sight of the satiating food was decreased by feeding the animal to satiety. In these eight cells, there was a sensory-specific effect such that the visual responses to other foods were altered little by satiety, when compared with the response to the satiating food.

Figure 5 illustrates the responses of a unimodal visual cell, an144, to the sight of a syringe containing blackcurrant juice and to the sight of bite-sized pieces of apple, presented to the monkey using a pair of large forceps. The cell responded well to both these foods before satiety. After the monkey had been fed 125 ml of blackcurrant juice to the point of satiety, the neuron stopped responding to the sight of the blackcurrant syringe, yet continued to respond to the sight of the apple. There was thus a sensory-specific decrease in the response of the neuron to the sight of the satiating food, which was supported statistically by a significant interaction on a two-way ANOVA of the responses to the sight of blackcurrant versus apple, before and after satiety $F(1,32) = 55.2$, $P < 0.01$.

Figure 6 illustrates the responses of a neuron (au087) to satiety with 160 ml of blackcurrant juice. This neuron responded visually when food was removed from in front of the monkey. Before satiety, the cell responded well to the visual removal of apple, banana, and a syringe containing blackcurrant juice. As the monkey was fed blackcurrant juice (in aliquots of 40 ml) the response of the cell to the removal of the blackcurrant syringe was decreased. This decrease followed the behavioral signs of satiation. By 160 ml, the monkey was satiated fully and the cell no longer responded to the sight of the blackcurrant juice-containing feeding syringe, yet it continued to respond to the sight of apple and banana. In a two-way ANOVA there was a significant interaction [$F(1,29) = 5.4$, $P < 0.05$].

Figure 7 shows the effect of satiety on the responses of the nine visual cells in this part of the study. The responses for each cell are plotted as a proportion of the presatiety response evoked by the food used to feed the monkey to satiety. Two cells (an086 and au104) were satiated using banana, five neurons were satiated using blackcurrant juice, and two cells (aq016 and aq042) were satiated using monosodium glutamate solution, as part of a series of experiments investigating "umami" taste perception (Rolls et al. 1995b). Sensory-specific satiety, shown by a significant interaction term on a two-way ANOVA, was seen in eight of the nine neurons (all but neuron aq042).

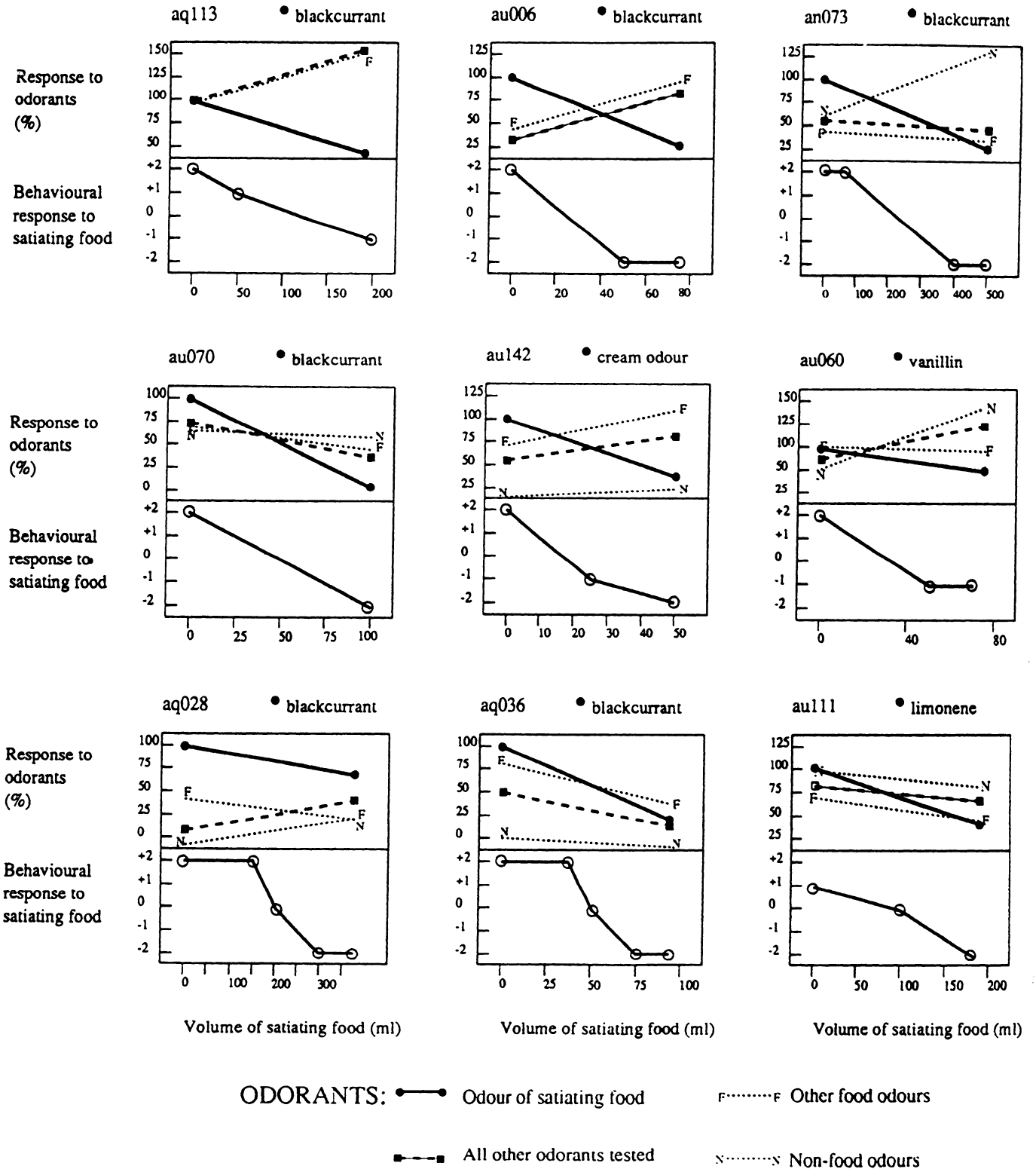


FIG. 2. Results of 9 experiments performed during recording the activity of individual orbitofrontal cortex olfactory neurons, responsive to odor of foods. For each experiment the neuronal responses to odorants are plotted as a percentage of the presatiety response evoked by odor of food of satiation. This odor is named above each graph. Change in acceptance of food by the animal is plotted below neuronal responses in the manner of Fig. 1.

Figure 8 summarizes these responses. In these eight cells (excluding aq042), there was a clear sensory-specific reduction by satiety of the responses of the cells to the sight of the satiating food, yet this did not generalize to other foods. The mean response to the food of satiation was decreased to 30% of the presatiety response. These data show that the responses of visual neurons in the orbitofrontal cortex of the monkey are modulated by the motivational state of the ani-

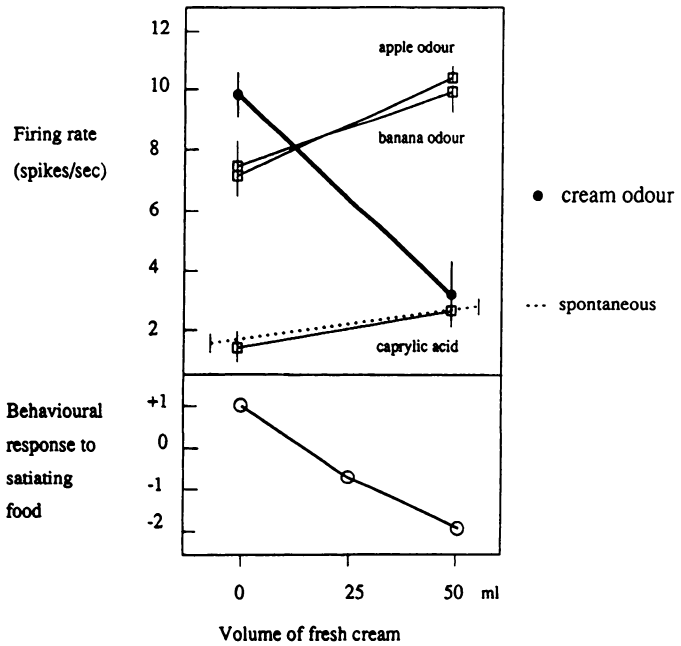


FIG. 3. Responses of a neuron to odors of dairy cream, apple, banana, and caprylic acid before and after feeding to satiety with 50 ml of cream. There was a specific reduction after satiation to odor of cream.

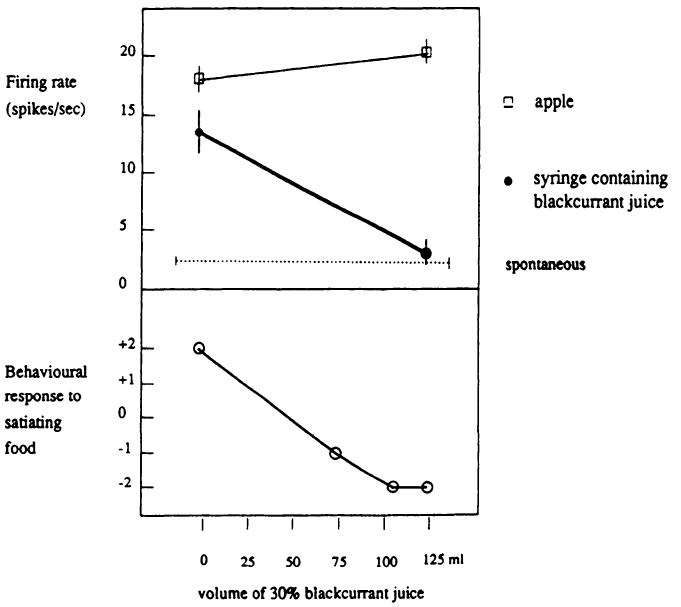


FIG. 5. Visual cell (an144) responding to sight of food. Response of neuron to sight of blackcurrant juice within a syringe was decreased to level of spontaneous activity after feeding animal to behavioral satiety with 125 ml of blackcurrant juice. Response of neuron to sight of apple was unaffected by satiation.

mal and show a sensory-specific reduction in responses after feeding to satiety.

### *Satiety effects on multimodal cells*

A number of satiety experiments were performed on cells that were responsive to food stimuli in more than one modality. Three bimodal neurons responsive to both the sight and taste of food, and one bimodal neuron responsive to the odor and taste of food, were tested for changes in responses in both modalities after satiation. In addition, one trimodal neuron, au036, was responsive to food stimuli in the three sensory modalities of olfaction, taste, and vision. These experiments examined the way in which satiety modulates the responses of multimodal cells. Of particular interest was whether the effect of satiation was the same across modalities or if there was evidence for the gustatory, olfactory, and visual representation of foods being controlled independently by motivational factors such as hunger and satiety. Each neuron will be described separately.

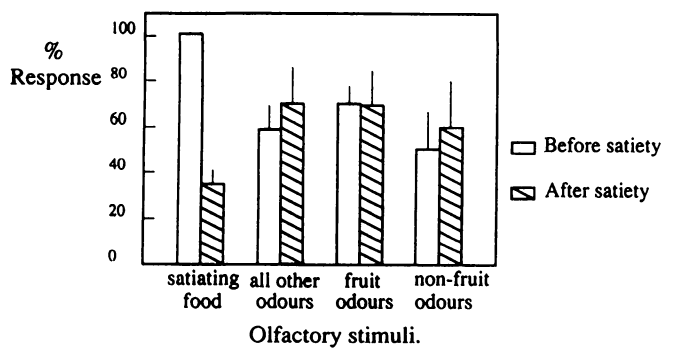


FIG. 4. A summary of responses of 8 cells whose responses to odor of satiating food was reduced by satiety. Responses before and after satiety are shown as a percentage of presatiety response of odor of satiating food.

### *Olfactory-taste responses*

Cell aq113 (Fig. 9) responded to olfactory and taste stimuli. It gave good responses to fruit odors, including that of blackcurrant juice, and to the taste of glucose and HCl. Blackcurrant juice evoked a presatiety response of 17.5 spikes/s when delivered into the monkey's mouth, and an almost identical response occurred when the monkey sniffed the odor of blackcurrant juice concentrate, presented on a cotton bud. Satiating the monkey with 200 ml of blackcurrant juice diminished the behavioral acceptance of the black-

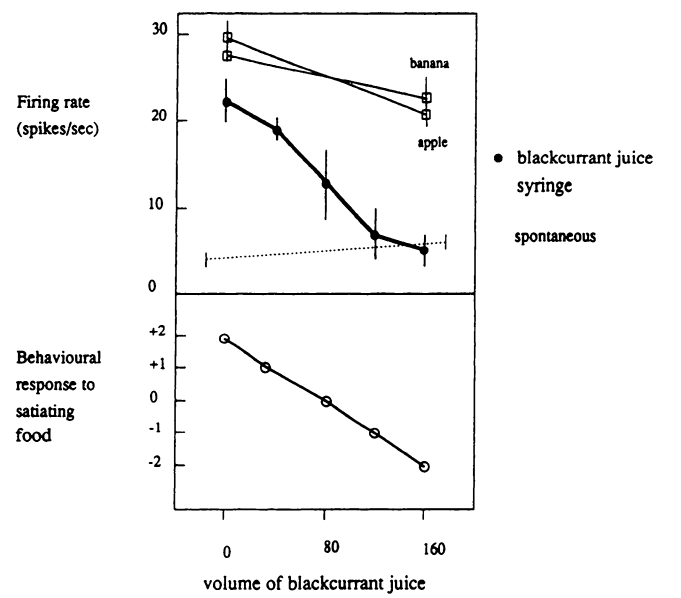


FIG. 6. Responses of neuron au087 to visual removal of foods. During satiation with 160 ml blackcurrant juice, response of neuron to sight of blackcurrant juice syringe was decreased, yet responses of cell to removal of banana and apple were only slightly affected.

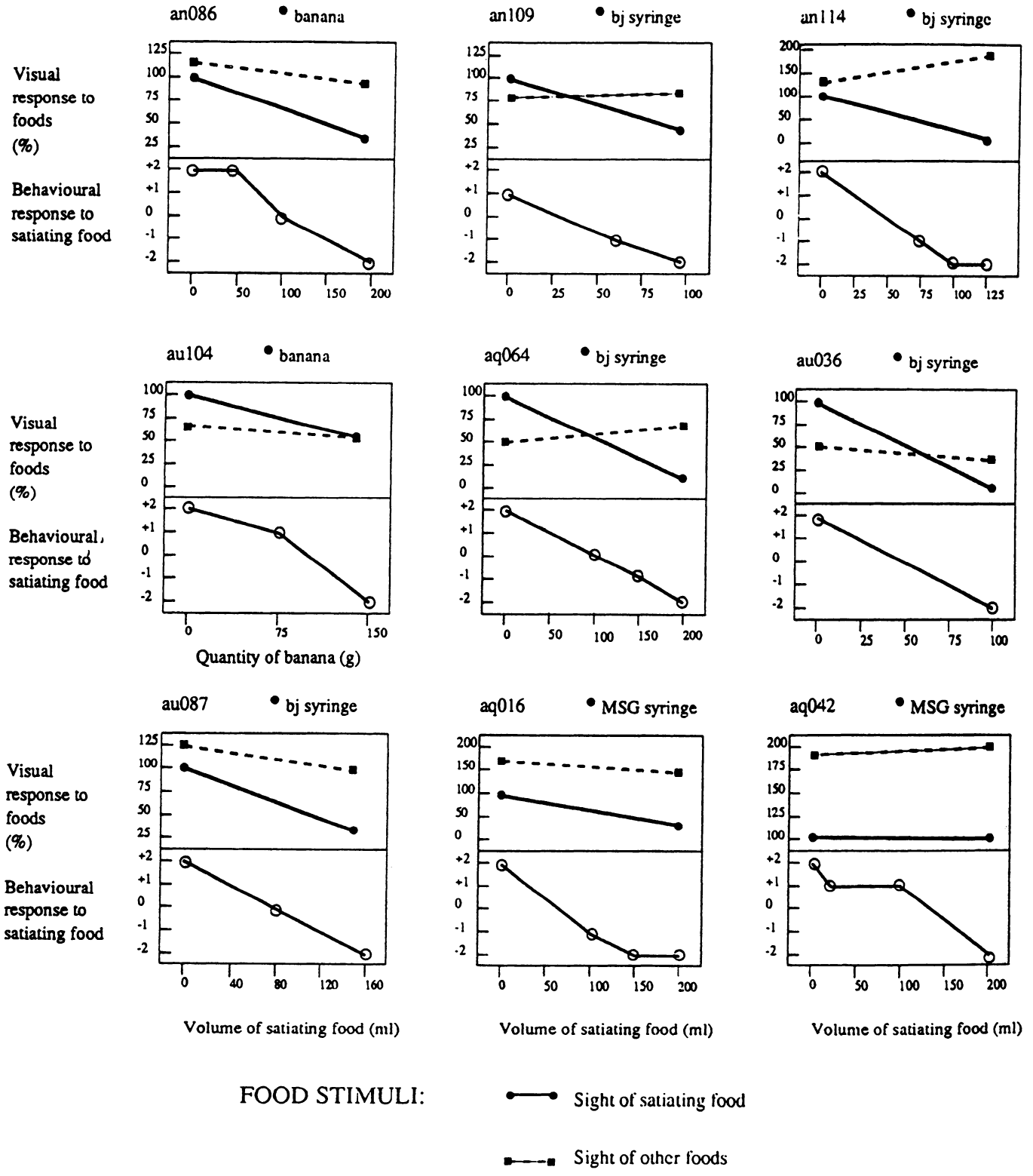


FIG. 7. Results of 9 experiments performed recording activity of individual orbitofrontal cortex visual neurons, selective for sight of foods. For each experiment, neuronal responses to foods are plotted as a percentage of presatiety response evoked by visual presentation of food of satiation. This food is named above each graph. Change in acceptance of food by animal is plotted below the neuronal responses in the manner of Fig. 2.

currant juice and resulted in a decrease of the neuronal response to both the smell and the taste of blackcurrant juice. In both cases, there was a sensory-specific effect of the satiation on the responses to the blackcurrant juice when compared with the other tastes or odorants. There was a significant interaction in the two-way ANOVA of these responses [$F(1,37) = 6.1$, $P < 0.05$ for olfactory responses, and $F(1,20) = 7.33$, $P < 0.05$ for the gustatory response].

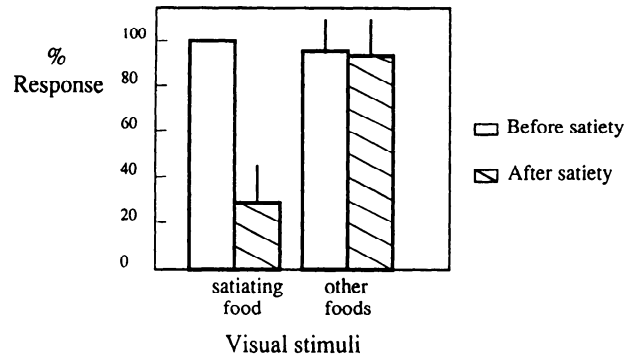


FIG. 8. Summary of responses of 8 visual cells for which there was an effect of satiety on responses of neuron to sight of food of satiation. Responses before and after satiety are shown as a percentage of presatiety responses to the odor of satiating food.

The decrease in the response to the taste of blackcurrant juice was not as marked as that to the odor of blackcurrant juice, and there was an indication that the olfactory satiety generalised to the odor of apple, which did not show the same increase in response after satiety as the odors of banana, mango, and citral. Despite this, the responses to the blackcurrant juice taste and odor were both decreased by feeding to satiety, indicating that the effect of satiety on the responses of this bimodal cell occurred for both modalities of input.

*Visual-taste responses*

Cell au064 (Fig. 10) was a bimodal neuron responsive to the sight and the taste of foods. The cell had a high spontaneous firing rate of 39.4 spikes/s. It responded much better to the taste of blackcurrant juice than to the prototypical tastants, but did not have any olfactory responses. Before satiety, this cell responded well to the sight and taste of both orange segments (bite-sized pieces, presented using feeding forceps) and blackcurrant juice (delivered in a feeding syringe). Full satiety was achieved after feeding 200 ml of blackcurrant juice to the monkey. The response to both the taste and sight of the blackcurrant juice was reduced after satiety to the level of spontaneous activity, yet the response to the sight of orange remained the same and the response to the taste of orange was increased significantly. In two-way ANOVAs, there was a significant interaction between the sight of the blackcurrant syringe versus the sight of the orange pieces and between the taste of the blackcurrant juice versus the taste of orange, before and after satiety [$F(1,26) = 13.9$, $P < 0.01$ for the visual experiment; $F(1,12) = 7.08$, $P < 0.01$ for the taste experiment].

Cell aq016 (Fig. 11) had robust responses to the sight of foods such as banana and blackcurrant juice. This neuron also responded well to the taste of blackcurrant juice, glucose, and monosodium glutamate. In the visual satiety experiment, responses were recorded to the visual presentations of banana, a syringe containing blackcurrant juice (labeled with red tape), and a syringe containing monosodium glutamate (MSG; labeled with black tape). Satiety was achieved after feeding the monkey with 200 ml of 0.1 M monosodium glutamate solution. During satiety, the response of the cell to the sight of the MSG-containing syringe was reduced from 56.5 spikes/s to 40.1 spikes/s (spontaneous activity went from 19.4 spikes/s to 23.4 spikes/s). The responses to the sight of the blackcurrant juice syringe and the sight of the banana pieces were not significantly changed by satiety. In a two-way ANOVA of the responses to the sight of

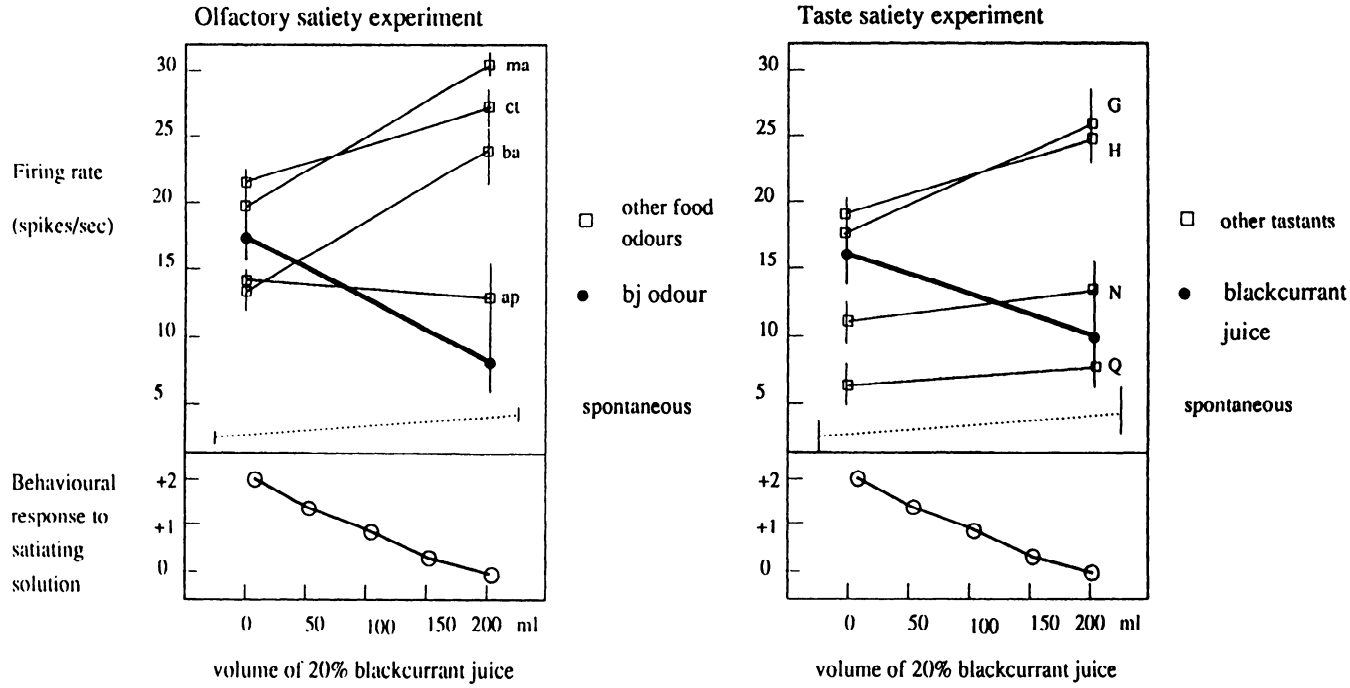


FIG. 9. Response of a bimodal taste/olfactory neuron, aq113, during satiation with blackcurrant juice. Responses of neuron to odors of banana (ba), citral (ct), apple (ap), and blackcurrant juice (bj) are shown (*left*). Responses of cell to 1.0 M glucose (G), 0.1 M NaCl (N), 0.001 M HCl (H), 0.0001 M quinine-HCl (Q), and blackcurrant juice (20%) are shown (*right*). Behavioral acceptance of satiating food is duplicated below both graphs.

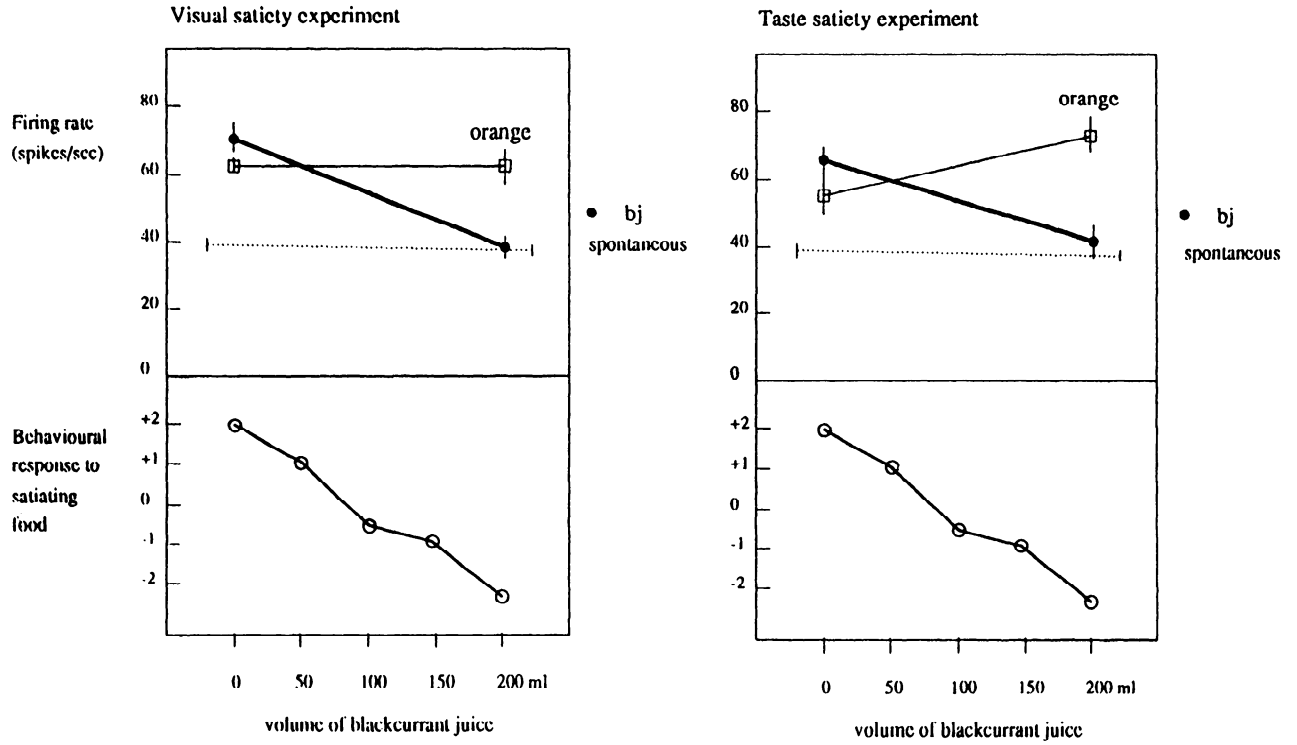


FIG. 10. Responses of a bimodal visual/taste neuron to satiety with blackcurrant juice (bj). Responses of cell to sight of blackcurrant juice (graph to *left*) and taste of blackcurrant juice (graph to *right*) were reduced to level of spontaneous activity after satiation. Responses of cell to sight and taste of orange pieces were not altered by satiation.

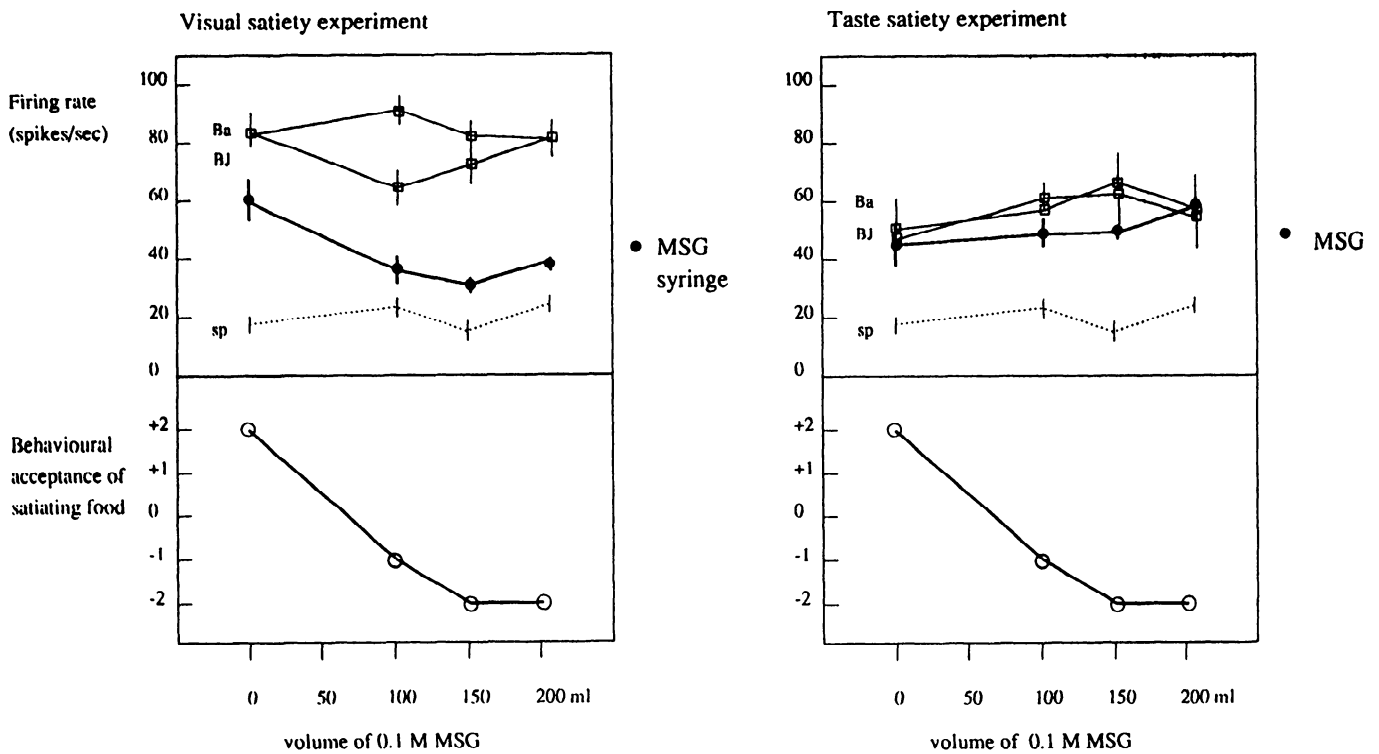


FIG. 11. Response of a bimodal visual/taste neuron, (aq016) during satiety with 0.1 M monosodium glutamate (MSG) Responses to sight of a labeled syringe containing MSG decreased by satiation almost to level of spontaneous activity of neuron, whereas responses to sight of banana pieces (Ba) and a syringe containing blackcurrant juice (BJ) remained the same. Responses to neuron to taste of MSG, banana, and blackcurrant juice remain same.

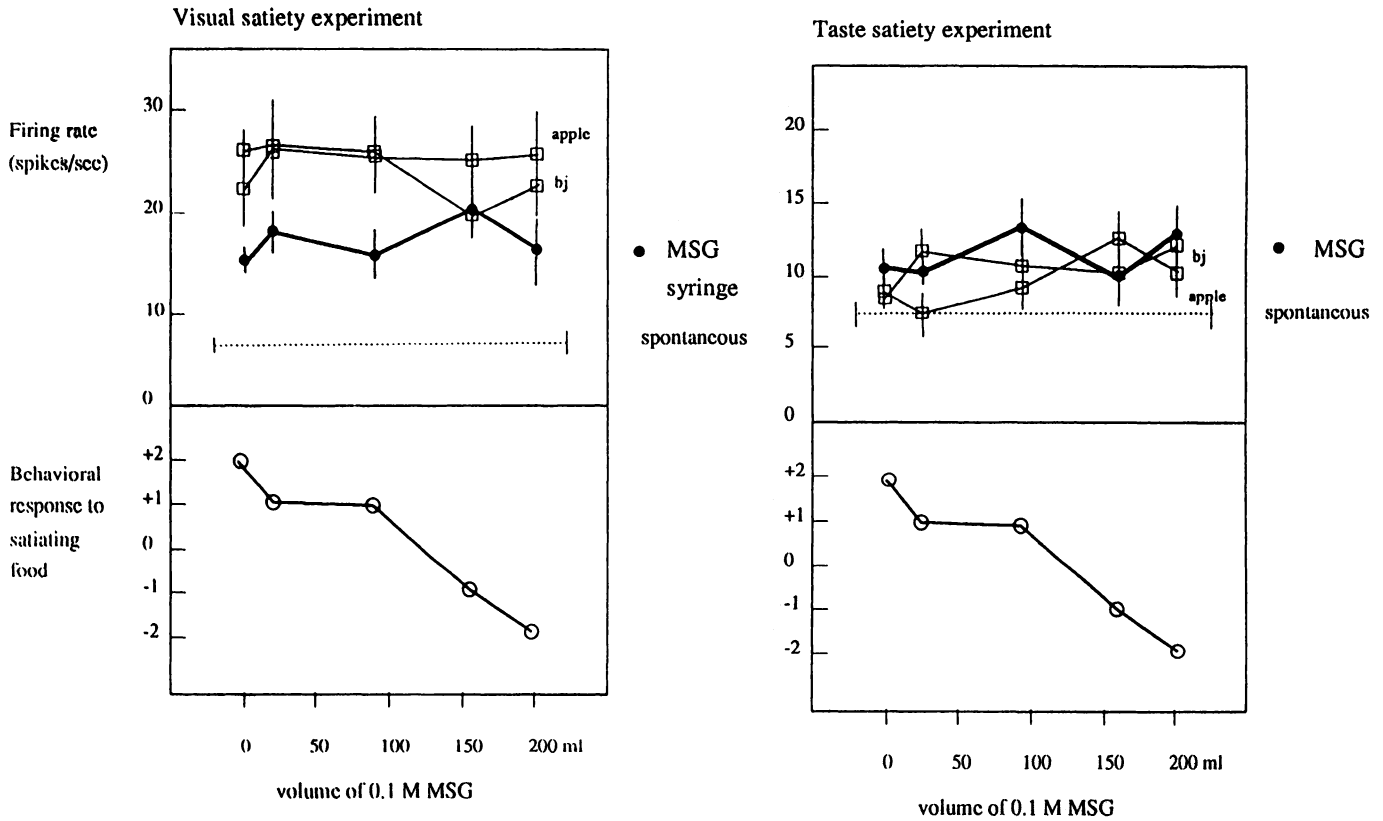


FIG. 12. Responses of a bimodal visual/taste neuron, aq042, tested during satiation with monosodium glutamate. Neither the responses of cell to sight of syringe containing MSG nor to the taste of MSG were affected by the satiation.

the MSG syringe versus the sight of other foods before and after satiety, the interaction term was not quite significant [$F(1,32) = 3.5$, $P < 0.07$]. In contrast to the visual responses, the responses of the neuron to the taste of monosodium glutamate were not changed by the satiation.

Cell aq042 (Fig. 12) also was tested during satiation with monosodium glutamate. The neuron responded to the taste of glucose and monosodium glutamate and also responded to the sight of foods and some novel objects. When the animal was fed to satiety, the cell did not change its responses to either the taste of monosodium glutamate or to the sight of the monosodium glutamate syringe. This cell therefore was not influenced by satiety.

### *Trimodal responses*

Cell au036 (Fig. 13) was responsive to the sight, smell, and taste of fruits and blackcurrant juice. Before satiety, the cell had good responses to the smell and taste of blackcurrant juice, banana, and apple. The response to the sight of the blackcurrant juice syringe was approximately twice that to the sight of apple and banana. The animal was fed to satiety with 100 ml of blackcurrant juice. In the visual, taste, and olfactory experiments, the neuronal responses to the blackcurrant juice were reduced and for the visual and taste experiments, this was predominantly sensory specific, with significant interaction terms in two-way ANOVAs of blackcurrant versus other stimuli × before and after satiety [ for taste, $F(1,60) = 3.6$, $P < 0.01$; for vision, $F(1,28) = 14.5$, $P < 0.01$]. In the case of the olfactory experiment, the response to the odors of apple and banana also was reduced by satiety. The response to citral was unchanged. This indicates that there was some generalization of the satiety effect to other food odors. In a two-way ANOVA, there was not a significant interaction [$F(1,59) = 2.3$, $P = 0.07$]. In the visual experiment, there was also a degree of generalization of the response to satiety; the response to banana also was decreased to the level of spontaneous activity. The response to the sight of the apple remained unchanged.

The effect of satiety with blackcurrant juice on this neuron's representation of banana was notable (see Fig. 13). Whereas satiety decreased the response of the cell to the sight and smell of banana, the response to the taste of banana was increased greatly by the satiation. The cell, though losing its responsiveness to the "external" attributes of the banana, became more responsive to the flavor of banana when delivered intraorally. The capacity of this cell to distinguish banana from the blackcurrant juice was maintained by the compensatory increase in the taste response to banana after satiety. Thus when all three modalities are considered together, the effect of satiety was specific to blackcurrant juice, though the expression of the satiety affected the responses in the visual, taste, and olfactory modalities independently.

### *Localization of recordings*

The reconstructed positions of the neurons in this study are shown on Fig. 14. Neurons responsive to olfactory stimuli are indicated by circles, and neurons responsive to visual

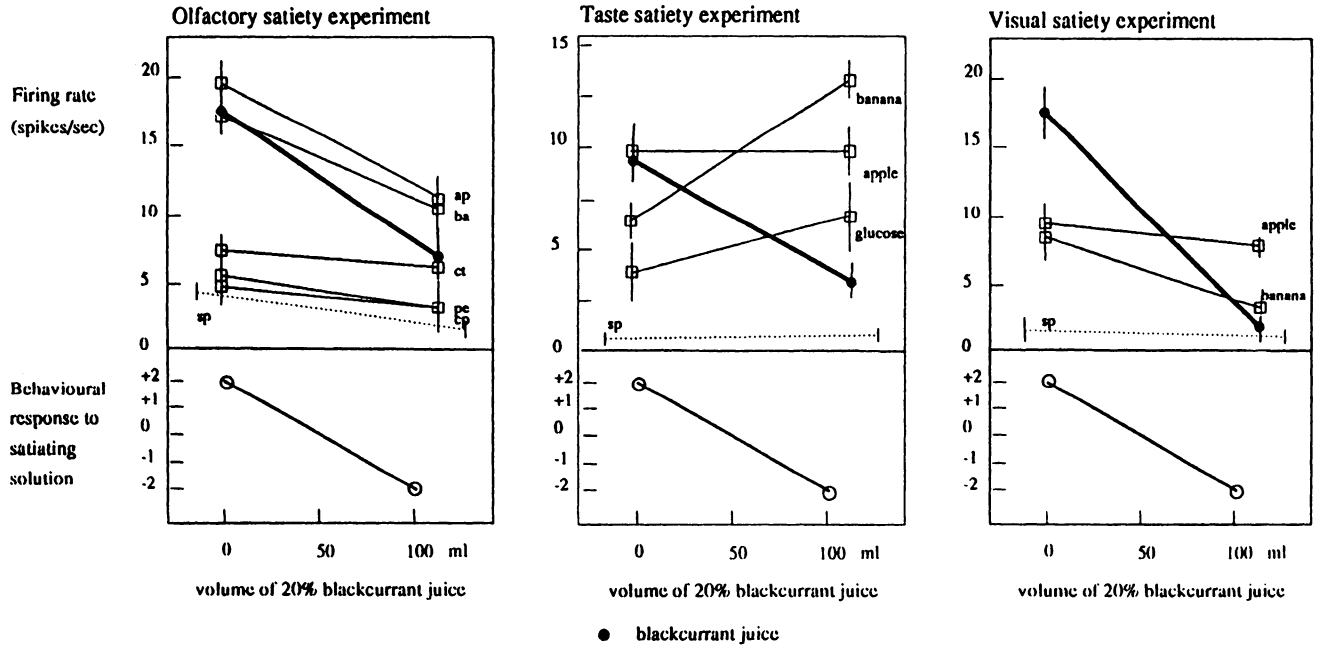


FIG. 13. Olfactory, taste, and visual satiety experiment performed on a trimodal neuron, au036. Cell was tested before and after satiation with blackcurrant juice. Odor stimuli were apple (ap), banana (ba), citral (ct), phenyl ethanol (pe), caprylic acid (cp), and blackcurrant odor. The neuron was also tested for responses to sight of a syringe containing blackcurrant juice and to apple and banana pieces. Taste responses were measured to the taste of blackcurrant juice, apple, banana, and glucose.

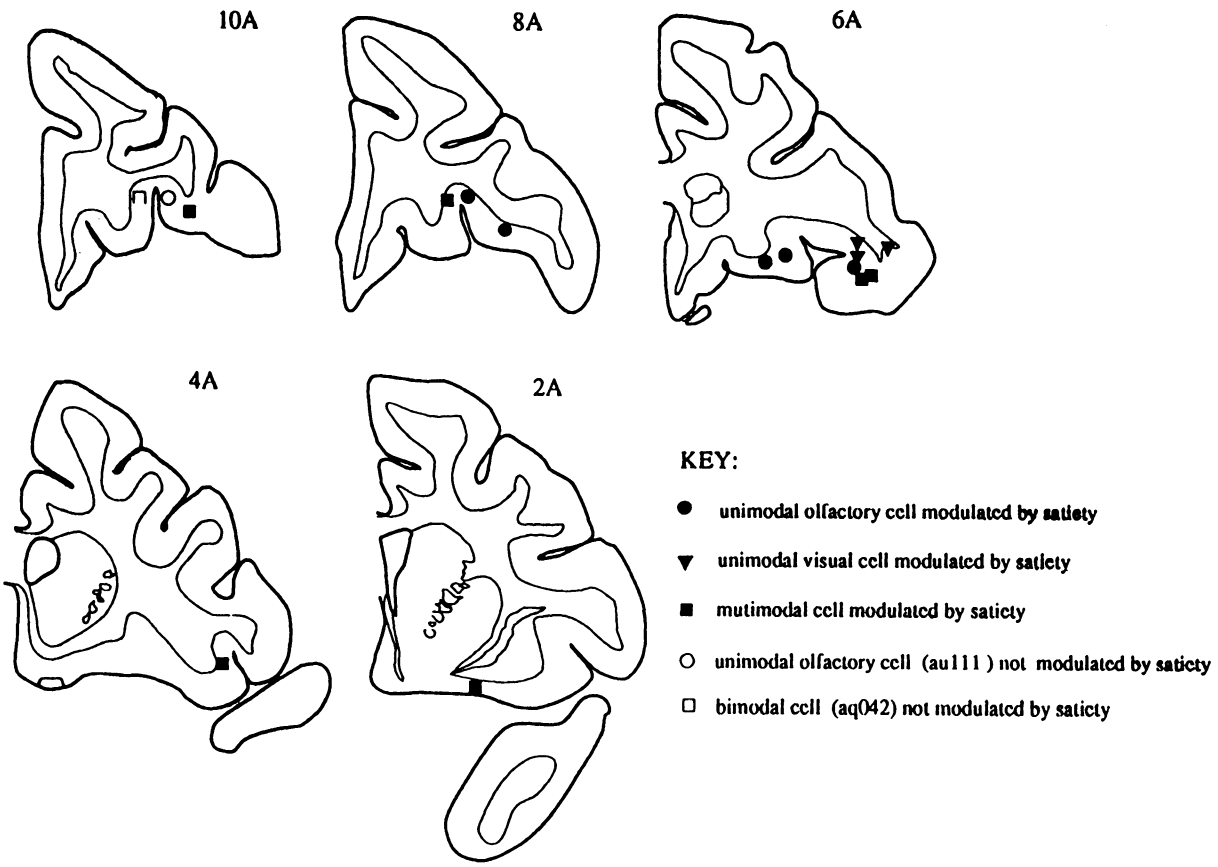


FIG. 14. Coronal sections through frontal region of a macaque brain, showing location of neurons in this study. Unimodal olfactory neurons (○ and ●), unimodal visual neurons (▼), and multimodal neurons (□ and ■) are illustrated. Filled symbols indicate a modulation of the neuronal responses by satiety.

stimuli by triangles. Multimodal neurons are shown as squares. Olfactory cell au111, and the bimodal cell aq042, whose responses were not affected by satiety, are marked with open symbols. The remaining neurons are marked with filled symbols, indicating that they were modulated by satiety. The majority of the neurons were located within the orbitofrontal cortical area, with one unimodal visual neuron located in a more lateral part of the inferior convexity. Visual neurons were located predominantly in the lateral orbitofrontal regions, as were bimodal cells responsive to taste and vision. There was also a tendency for cells responsive to olfactory stimuli to be located in centromedial orbitofrontal cortical areas. In the anteroposterior direction, neurons that were modulated by satiety were found at all anterior-posterior levels investigated (see Fig. 14). However, the two neurons that were not modulated by satiety were located at the anterior border of the area investigated here.

## DISCUSSION

The data presented above show that olfactory, visual, and multimodal representations of food stimuli in the orbitofrontal cortex are subject to modulation by satiety. This, added to the previously reported finding by Rolls et al. (1989) that the responses of taste neurons in the caudolateral orbitofrontal cortex also are influenced by satiety, supports the hypothesis that the orbitofrontal cortex is important in the regulation of feeding behaviour. Neurons that respond to the taste, smell, and/or visual properties of food only when hungry potentially could mediate the rewarding effects that foods have when the organism is hungry and also could contribute to autonomic effects to food that occur only while hungry. There is strong supporting evidence that neurons in this region are indeed involved in food reward, for monkeys will work for brain-stimulation reward of this orbitofrontal region (Mora et al. 1980), they will only do this if they are hungry (Mora et al. 1979), and neurons in this orbitofrontal region are activated from other feeding-related brain-stimulation reward sites (Rolls 1975; Rolls et al. 1980). In a complementary way, the findings described in this paper provide very strong support for the original hypothesis that brain-stimulation reward of the orbitofrontal cortex is related to inter alia the rewarding effects that the sight, smell, and taste of food have when hunger is present (Rolls 1975, 1976).

With respect to taste, there is evidence that the secondary taste cortex in the orbitofrontal cortex is the first stage in the primate taste pathway at which taste processing is modulated by hunger (Rolls 1989, 1995; Rolls et al. 1989). With respect to vision, it is known that the responses to visual stimuli of neurons in the inferior temporal cortex are not modulated by hunger (Rolls et al. 1977). As shown here, they are modulated by hunger in a cortical area one synapse on in the orbitofrontal cortex (Barbas 1988). It is not yet fully established whether the same modulation occurs in the primate amygdala (Rolls 1992; Sanghera et al. 1979), which provides an indirect route for information from the inferior temporal cortex to reach the orbitofrontal cortex (Rolls 1995). With respect to olfaction, it is not known whether in primates the orbitofrontal cortex is the first stage of olfactory processing at which neuronal responses are modulated by feeding. In rats, Pager et al. (1972) and Pager (1974) recorded the activity of neurons in the olfactory bulb and showed that responses to food odors were decreased after feeding the animal.

The modulation by satiety of the responses of orbitofrontal olfactory and visual neurons to the food on which the monkey has been satiated raises the question of whether this reflects a peripheral adaptation or habituation or is a more central mechanism to implement a control of hedonic (or at least hunger related) responses to a food. There is clear evidence that it is the latter, for at least visual and taste responses. In particular, given that the responses of inferior temporal visual cortex neurons are not modulated by hunger (Rolls et al. 1977), the modulation one synapse further on in the orbitofrontal cortex described here cannot be due to peripheral adaptation. Indeed, such a food-object specific modulation would be impossible to implement peripherally, for objects are not represented in the periphery of the visual system and there is no way in which the different image pixels that happen to convey the information that a food is present in different fractions of a second (every time the eyes moved) could be modulated by hunger (see Rolls 1994). Such control by satiety of responsiveness to a food object could only be implemented after object representations have been achieved in the visual system, that is in or after the inferior temporal visual cortex (Rolls 1994). It is for this reason that we propose that modulation by hunger of responses to visual stimuli is appropriate in general only after decoding has reached the object level (see Rolls 1989). Moreover, it is appropriate that the modulation should not be in the object representation itself, as a consequence might be that one would become blind to an object that one had just eaten. This would be maladaptive, for even when we are satiated, it may still be useful for us to learn where we have seen food, so that we can find it again when next hungry. The same arguments apply to taste processing, in which satiety does not modulate processing in or before the primary taste cortex, but does in the secondary taste cortex. Thus the modulation in neuronal responsiveness to the sight and taste of food observed in the orbitofrontal cortex cannot be due to peripheral sensory adaptation. Nevertheless, the mechanism if the sensory-specific satiety may involve a neuronal habituation mechanism, but implemented only after the inferior temporal cortex or primary taste cortex, in such a way that neurons that have been conveying such information into or within the orbitofrontal cortex for a few minutes (the time taken to eat a meal) do then show a decline in responsiveness (see Rolls 1989; Rolls et al. 1989). Consistent with this proposed mechanism, there is some reduction in the pleasantness of the taste of a food produced by rinsing that food in the mouth for several minutes, even when it is not swallowed. Consistent with this separation of visual object identity and taste from what may be described as the hedonic (or at least hunger dependent) representation of food, humans fed to satiety with a food report that its intensity changes very little, but that there is a great decrease in its pleasantness (Rolls et al. 1984). In the case of olfaction, we do not yet know in primates where the first stage of modulation by satiety occurs, and this remains for future investigation. However, it is not likely to be entirely due to peripheral adaptation, for we have observed in human subjects that the pleasantness of the smell of a food, but much

less its intensity, is decreased when that food is eaten to satiety (E. T. Rolls, M. Hinds, and H. D. Critchley, unpublished observations).

Sensory specific satiety in humans for visual stimuli has been described by Rolls et al. (1981b). The investigations described here suggest that it is implemented in the primate orbitofrontal cortex. As just stated, we also have found evidence for sensory-specific satiety for olfactory stimuli, and the investigation described here indicates that this is at least represented in the orbitofrontal cortex. The orbitofrontal cortex has been shown to be necessary for the discrimination of odors in humans (Jones-Gotman and Zatorre 1988) and in macaque monkeys (Tanabe et al. 1974, 1975a). In the study of Tanabe et al., the ability of monkeys to distinguish between food stimuli by olfactory cues was the basis of the discrimination task. In addition, an imaging study has reported increased blood flow in the human right orbitofrontal cortex to olfactory stimuli (Zatorre et al. 1992). The research described here provides an indication that the orbitofrontal area involved in olfaction is concerned at least partly with olfaction related to the control of feeding. Moreover, in recent studies, we have shown that some neurons in the orbitofrontal cortex reflect whether an odor is associated with a taste reward (Critchley and Rolls 1996), and that some orbitofrontal cortex neurons reverse the odor to which they respond when the association of the odor with a taste reward or punishment is reversed (Rolls et al. 1996). These two studies also support the evidence described here that odor hedonics is represented in the orbitofrontal cortex (though not to the exclusion of the identity of odors) (see Critchley and Rolls 1996). Consistent with this, food selection behavior is altered by orbitofrontal lesions in monkeys (Baylis and Gaffan 1991).

The presence of bimodal and multimodal neurons in the orbitofrontal cortex is a result of the sensory convergence into this brain region that allows the formation of a very rich representation of foods. Association learning in these neurons (Rolls et al. 1995a; Thorpe et al. 1983) can lead to the formation of strong odor-taste associations and hence the encoding of flavors (Rolls and Baylis 1994). The perception of flavors as discrete sensory events allows specific foods to be recognised and distinguished from others. This flavor constancy also enables very fine distinctions to be made between foods, while at the same time generalizes across the normal variations in sensory qualities of the same food. Such a mechanism is important for modulatory influences on feeding behavior to be directed at specific foods, while not affecting others. The demonstration that sensory-specific satiety affects the responses across modalities of multimodal neurons in the orbitofrontal cortex supports the idea that flavors or visual-taste associations contribute to the behavioral sequelae of satiation. The multimodal nature of the representation of these cells may enable satiety to exert a food-specific effect despite a generalized decrease in response in one or more modalities (see Fig. 13, cell au036).

The present study also shows that sensory-specific satiety is the general rule controlling the responses of orbitofrontal neurons to food. Alliesthesia, the decrease in the perceptual pleasantness of all foods as a consequence of postingestive signals, does not seem to have a correlate in the responses of orbitofrontal cortex neurons. If this were the case, satiety would decrease the responses of neurons to all foods. Recent human studies, such as that of Warwick et al. (1993) continue to emphasize the importance of sensory, rather than postingestive qualities of food in the process of satiation. The neurophysiological study described here demonstrates that the neuronal correlates of satiety, like the neuronal representation of food, are not restricted to one sensory modality. The contribution of many sensory influences provides not only a full and enriched representation of an extended variety of foods but more importantly a precise and finely tuned mechanism by which the intake of individual foods can be controlled, at least in the way made explicit in sensory-specific satiety.

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Address reprint requests to E. T. Rolls.

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