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Gustatory Responses of Single Neurons in the Caudolateral Orbitofrontal Cortex of the Macaque Monkey

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SUMMARY AND CONCLUSIONS

1. In recordings made from 3,120 single neurons, a secondary cortical taste area was found in the caudolateral part of the orbitofrontal cortex of the cynomolgus macaque monkey, *Macaca fascicularis*. The area is part of the dysgranular field of the orbitofrontal cortex and is situated anterior to the primary cortical taste areas in the frontal opercular and adjoining insular cortices.

2. The responses of 49 single neurons with gustatory responses in the caudolateral orbitofrontal taste cortex were analyzed using the taste stimuli glucose, NaCl, HCl, quinine HCl, water, and blackcurrant juice.

3. A breadth-of-tuning coefficient was calculated for each neuron. This is a metric that can range from 0.0 for a neuron that responds specifically to only one of the four basic taste stimuli to 1.0 for one that responds equally to all four stimuli. The mean coefficient for 49 cells in the caudolateral orbitofrontal cortex was 0.39. This tuning is much sharper than that of neurons in the nucleus of the solitary tract of the monkey, and sharper than that of neurons in the primary frontal opercular and insular taste cortices.

4. A cluster analysis showed that at least seven different groups of neurons were present. For each of the taste stimuli glucose, blackcurrant juice, NaCl, and water, there was one group of neurons that responded much more to that tastant than to the other tastants. The other groups of neurons responded to two or more of these tastants, such as glucose and blackcurrant juice. In this particular region neurons were not found with large responses to HCl or quinine HCl, although such neurons could be present in other parts of the orbitofrontal cortex.

5. On the basis of this and other evidence it is concluded that in the caudolateral orbitofrontal cortex there is a secondary cortical taste area in which the tuning of neurons has become finer than in early areas of taste processing, in which foods, water, and NaCl are strongly represented and where motivation dependence first becomes manifest in the taste system.

INTRODUCTION

In primates there is a cortical representation of taste in the frontal operculum and anterior insula. This region of cortex was implicated in gustatory function by Bornstein (1940a,b), who observed ageusias in a dozen patients with bullet wounds in this area. Patton (1960), Ruch and Patton (1946), and Bagshaw and Pribram (1953) performed lesions in the same region in monkeys and noted a reliable, if temporary, elevation of taste thresholds. Benjamin and Emmers (1960) and Benjamin and Burton (1968) stimulated the peripheral taste nerves and recorded evoked potentials both on the lateral convexity of the postcentral gyrus and, with slightly longer latency, in the frontal operculum and insula. Burton and Benjamin (1971) interpreted this latter region as the pure taste area. Anatomic investigations with the autoradiographic anterograde fiber-tracing technique by Pritchard et al. (1986) have shown that there are projections from the thalamic taste area to the frontal opercular and insular cortices. These frontal opercular and insular regions of cortex have been shown to be cytoarchitectonically distinct by Jones and Burton (1976), Mesulam and Mufson (1982a,b), Roberts and Akert (1963), and Sanides (1968, 1970).

To investigate this region in the primate physiologically, Sudakov et al. (1971) recorded single-neuron activity in the frontal operculum and insula of the monkey in response to chemical stimulation of the tongue. Of 946 cells tested for gustatory sensitivity, only 33 (3.5%) gave responses—30 of them excitatory. Each neuron responded to more than one of the three stimuli (NaCl, sucrose, milk) employed. In a more extensive investigation, we have analyzed the responses of 165 neurons in the frontal operculum with gustatory responses to stimuli that included NaCl, glucose, HCl, quinine (QHCl), water, and a complex taste stimulus, blackcurrant juice (Scott et al. 1986b). The taste region was found to be located in the dorsal and anterior part of the frontal operculum; the neurons were found to be more specifically tuned to these stimuli than were neurons recorded in the same monkeys in the nucleus of the solitary tract (NTS) (Scott et al. 1986a), and it was found that satiety did not affect the magnitude of the responses of these opercular neurons to gustatory stimuli (Rolls et al. 1988). We have also analyzed the responses of 65 neurons in the insula with gustatory responses, with the use of the same stimuli (Yaxley et al. 1990). The taste region was found to be located in the dorsal and anterior part of the insula; the neurons were found to be more specifically tuned to these stimuli than were neurons recorded in the same monkeys in the NTS and in the frontal opercular taste cortex (Scott et al. 1986a,b), and it was found that satiety did not affect the magnitude of the responses of these insular neurons to gustatory stimuli (Yaxley et al. 1988).

Given that there are areas of taste cortex in the frontal operculum and insula, it becomes of interest to determine how this gustatory information is passed to the rest of the brain and whether, for example, there are secondary cortical taste areas. Given that there is no effect of hunger on taste processing in the NTS (Yaxley et al. 1985), the frontal opercular taste cortex (Rolls et al. 1988), and the insular taste cortex (Yaxley et al. 1988), it is likely that there are

further areas in the brain where taste is represented and where hunger does influence taste processing (Rolls 1986a). One further area in the brain in which there is some prior evidence for a gustatory representation is the orbitofrontal cortex, for here Thorpe et al. (1983) found that a small proportion of neurons (7.9%) had gustatory responses, which were in some cases very selective for particular gustatory stimuli. In contrast to the opercular and insular gustatory areas, in the orbitofrontal cortex taste neurons were intermingled with neurons with responses to stimuli in other modalities—for example, the visual modality (Thorpe et al. 1983). There is little evidence, however, on whether this multimodal area receives projections directly from the opercular and/or insular gustatory cortices or whether there is another gustatory area interposed. In this study we therefore searched for an area with gustatory neuronal responses, starting at the anterior boundary of the opercular and insular cortical taste areas and working forward toward the orbitofrontal area investigated previously (Thorpe et al. 1983). In this study, we discovered a taste area in the far-lateral and posterior (caudal) part of the orbitofrontal cortex. We describe the characteristics of the neuronal responses in this region to gustatory stimuli. To allow quantitative comparisons between the different parts of the gustatory system, not only were data on the tuning of the neurons expressed quantitatively, but also the present recordings were made in some of the same individual cynomolgus monkeys (*Macaca fascicularis*) in which the tuning of neurons in the NTS (Scott et al. 1986a; *monkeys BB* and *CC*), the frontal operculum (Scott et al. 1986b; *monkeys BB* and *CC*), and the insula (Yaxley et al. 1990; *monkeys CC* and *HH*), was investigated. (The recordings described here were made in *monkeys CC* and *HH*.) This approach was taken not only to allow direct comparisons of the results but also to conserve monkeys. The methods were thus the same as those used in the three previous studies (Scott et al. 1986a,b; Yaxley et al. 1990), and to facilitate comparisons, the results and analyses of the neuronal responses are presented in a similar format here as in our earlier papers. The overall aim of the current series of recordings is to advance understanding of the control of food intake and of its disorders (Rolls 1986a, 1989b).

METHODS

Subjects

The subjects were two male cynomolgus monkeys (*Macaca fascicularis*) weighing 3.8–4.0 kg during the course of data collection. They were prepared for recording by implanting a ring over the area from which recordings were to be made, as described previously (Rolls et al. 1979; Scott et al. 1986a,b). Full sterile precautions were observed throughout surgery. Each monkey was sedated with an intramuscular injection of ketamine (10 mg/kg im) and anesthetized with intravenous thiopentone sodium (50 mg/ml). The depth of anesthesia was monitored by frequently testing for the presence of a leg flexion reflex, and if this was present supplemental anesthesthetic was administered. Respiration rate was monitored throughout surgery. Atropine (0.1 ml/kg) was administered to prevent excessive salivation and glycerine applied to the eyes to prevent their drying. The monkey was placed in a Kopf stereotaxic instrument and his position confirmed by X-radiography. A section of skull over the orbitofrontal cortex was removed and replaced with a stainless steel ring to which an X-Y positioner and microdrive could be fitted during recording sessions. The implant also held electrodes that were placed stereotactically in the basal forebrain to provide constant referents relative to which the location of the recording electrode could be determined on each recording track by X-radiography. The implant was fixed in place with dental acrylic. Two stainless steel tubes (8 mm OD, 6 mm ID, 5-cm length) were cemented to the skull cap in front of and behind the ring, through which horizontal support bars could be inserted during data collection. Long- and short-acting antibiotics were administered over the next 2 wk, after which recordings began.

Recording

SESSIONS. Daily recording sessions lasted up to 6 h. Each monkey was transferred from his home cage to the primate chair where his head was supported by slipping bars through the tubes provided as part of the implant. He was otherwise free to move and normally adopted a relaxed sitting position. His comfort was continuously attended to, and he was offered food intermittently throughout the recording session.

ELECTRODES. Electrodes were glass-insulated tungsten, plated with gold and platinum black (Merrill and Ainsworth 1972) and had tip sizes of $\sim 2 \times 4$ μm.

The electrodes were systematically positioned from track to track by the use of a Kopf X-Y positioner attached to the implanted ring. The dura was anesthetized with 0.15 ml Xylocaine, and a sterile stainless steel guide tube (0.5 mm OD) was passed just through it. The sterile electrode was then lowered to a predetermined depth ($\sim$10 mm dorsal to the orbitofrontal cortex) and advanced with the use of a Trent-Wells hydraulic microdrive and chronic adaptor system.

ELECTRICAL SYSTEM. Neuronal activity passed through a high-input, impedance-field-effect transistor mounted on the microdrive. It was amplified by conventional band-pass-filtered amplifiers and displayed at high-speed time base (0.2 ms/cm) on the main oscilloscope. Action potentials of a single cell were identified by consistency of amplitude and waveform and by the requirement that two spikes never occur within a 2-ms interval. Accepted spikes were converted to TTL pulses for on-line analysis. They were also displayed on a second oscilloscope and audiomonitor, providing additional visual and auditory cues that permitted corrections if minor changes in recorded voltage occurred with electrode drift. Single-unit data, stimulus-onset trigger where applicable, and voice commentary were also stored on magnetic tape for off-line analyses.

Stimuli and stimulus delivery

Thirty-three sapid stimuli were employed. These included eight concentrations, in one-half log-mol steps, of each of the four prototypical stimuli (10^{-3}–3.0 M NaCl; 10^{-3}–3.0 M glucose; 10^{-5}–3×10^{-2} M HCl, and 10^{-6}–3×10^{-3} M quinine HCl), plus 20% blackcurrant juice concentrate (Beecham Products, Brentford, UK). Blackcurrant juice was included because it is both highly palatable to the monkey and complex in taste quality such that many neurons were responsive to it. This combination of attributes made it an effective probe stimulus for identifying gustatory cells.

Stimuli were delivered in quantities of 0.5 ml through a handheld syringe. Manual delivery was used in the alert monkey because it permitted repeated stimulation of a large and nearly constant receptive field through compensation for the different mouth and tongue positions adopted as the palatability of the solutions varied. The evidence that a large and nearly constant receptive field was stimulated was that different neurons with best

responses to all the different prototypical stimuli were found and that the responses of these neurons in repeated tests were consistent in our earlier studies (Scott et al. 1986a,b; Yaxley et al. 1990). If fixed delivery tubes were located in the mouth, the monkey learned to block or partially avoid the delivery of tastants through them.

Stimulus delivery was followed within 10 s by a 1.0- to 1.5-ml distilled-water rinse. At least 30 s of rest was permitted between stimuli, and if there were indications that either the behavioral (licking, facial expressions) or neuronal activity had not returned to prestimulus levels, this period was extended.

Fluid consumption

The monkeys were fed and offered water ad libitum at the end of each daily recording session so that they began the succeeding day ~18-h, food-and-water deprived. During a typical recording session a subject would consume ~200 ml of fluid and several pieces of fruit over a 5-h period. Over a 5-day wk of data collection, the monkeys took nearly one-half of their food and most of their fluid during recording sessions.

Analysis

A PDP11 computer measured the firing rate of the neuron in a 5-s period after stimulus application and performed basic statistics on-line. The neuronal spike collection was started by the experimenter during the experiment at the time when he applied the taste solution to the tongue. The accuracy of this method was confirmed by measuring the time of contact of the syringe with the tongue by the use of an impedance-measuring touch device. Our use of this touch device has been described previously (Scott et al. 1986a). A wire, shielded to its tip, was inserted into the lumen of the syringe from which the tastants were delivered. Stimulus contact completed a circuit through the animal, but one with sufficient impedance to maintain current levels two orders of magnitude below the threshold for electric taste (Bujas 1971; Chang and Scott 1984). The signal was amplified and used to trigger the computer data collection. Peristimulus time histograms of evoked neural activity measured in this way in the NTS have been presented previously (Scott et al. 1986a). Under the condition when the experimenter started the data collection at the same as he applied the tastant to the tongue with the other hand, the accuracy of the onset of data acquisition for hand started as compared with touch-contact started was within 50 ms. Because this accuracy was so good that it introduced little error into the 5,000 ms of collected data, and because no wire needed to be attached to the syringe, the experimenter often started the data collection in this way. Additionally, spike data collection was monitored continuously during stimulus application with the use of computer-generated and continuously displayed time courses of spontaneous and evoked neuronal activity (peristimulus time histograms) in 50-ms bins. Spike firing rates in the 5-s period after stimulus application provided material for derived analyses that included calculations of interneuronal and interstimulus correlation coefficients, multidimensional scaling routines, and cluster analyses as detailed in RESULTS. The statistical significance of the changes in firing rate was determined as described in RESULTS under *Spontaneous activity*, and the responses of all the taste neurons described in this paper were shown to be statistically significant with the use of this method and with the use of *t* tests to compare the measurements of spontaneous activity with the responses evoked on each presentation by a tastant.

Localization of recording sites

The position of each recording site was determined in two ways. First, following each track, X-rays were taken from frontal and lateral perspectives. The recording positions could then be reconstructed to within 250 μm relative to the deep electrodes permanently implanted in diencephalic and telencephalic structures. The positions of the deep electrodes were subsequently determined histologically. Second, in the final several sessions microlesions were made through the recording electrode (60 μA for 60 s, electrode negative). At the end of these experiments the subjects were tranquilized with ketamine and given a lethal intravenous injection of pentobarbital sodium. They were then perfused with 0.9% saline followed by formal saline. Their brains were stored in sucrose Formalin for at least 7 days after which 50-μm-serial frozen sections were cut and stained with cresyl violet.

RESULTS

Location and extent

Neurons responsive to chemical stimulation of the oral cavity were found in a far-lateral and posterior part of the orbitofrontal cortex, in the sites shown in Fig. 1. It was possible in the experiments described here to find and analyse the responses of 49 such neurons in the two monkeys. The area within which taste neurons were found is indicated quite precisely in Fig. 1, in that altogether in tracks made to define the limits of the area, the responses of ~3,120 neurons round this region were analysed. The cortex surrounding the area indicated in Fig. 1 was so extensively sampled that each individual neuron could not be indicated in Fig. 1. Many of the neurons in the surrounding areas, particularly laterally, had visual responses. Taste responses could be clearly distinguished from responses of neurons in other regions related to movements or somesthetic stimulation, in that the taste responses occurred after the tastant was applied to the tongue, had longer latencies than somatosensory responses, often developed with characteristic time courses (as illustrated for neurons in the NTS by Scott et al. 1986a, Fig. 4), were of different magnitude for a given taste neuron to the set of gustatory stimuli used, and the different neurons had different profiles of responsiveness to the different stimuli, as shown below.

Cytoarchitectonic and myeloarchitectonic analysis using the criteria for distinguishing each of the areas described by Mesulam and Mufson (1982a) showed that the gustatory neurons were in the dysgranular part of the orbitofrontal frontal cortex (OFdg) and were thus in an area distinct from the primary cortical taste areas in the frontal opercular taste cortex (Prco) and the adjacent part of the rostral insula (Idg).

Spontaneous activity

The mean spontaneous firing rate of taste cells in the caudolateral orbitofrontal cortex taste area of the awake monkey was 1.6 ± 0.7 (SD) spikes/s (range = 0.0–34.5). To define an evoked response we adopted a dual criterion of spontaneous rate ± 2.33 SD (i.e., $P < 0.01$) and a minimum discharge rate of 1.0 spike/s measured over a 5-s period after stimulus application. This is a strict criterion of a response in that it implies that with a single measurement (on a single trial) of firing rate to a stimulus, a significant response should be detected by the single neuron. In fact we made 4–8 measurements of firing rate (in random sequence) to each chemical and with the resulting small

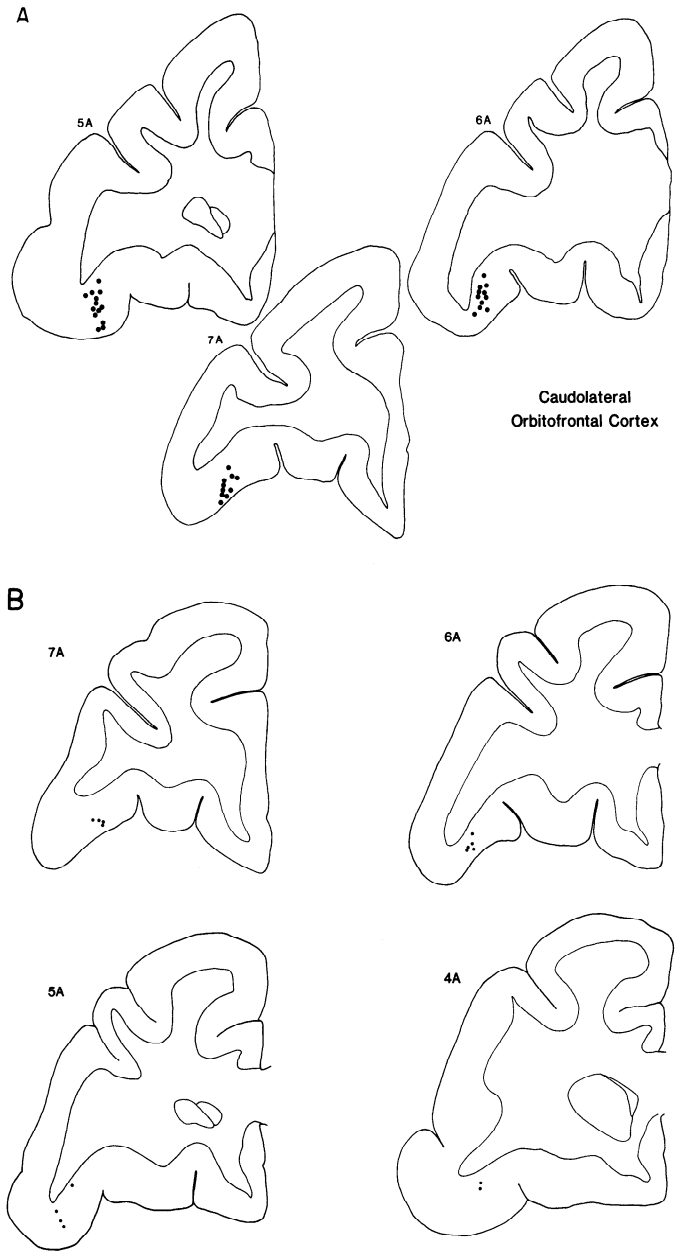

FIG. 1. *A* and *B*: coronal sections through the caudal orbitofrontal cortex showing sites at which neurons with gustatory responses were recorded. A–P coordinates are in millimeters anterior (A) to sphenoid.

standard error-of-the-mean response and the use of a *t* test could detect as significant and reliable much smaller changes than the ±2.33 SD criterion adopted. The criterion corresponds to detecting as significant a taste response based on one tasting of the chemical. The low-spontaneous activity precluded inhibition as a response option for 96% of the cells and required imposition of the 1.0-spike/s minimum on 57%.

Intensity-response functions

We tested two neurons for their responses to a 3.5-log-mol concentration range of the prototypical taste stimulus glucose. So few cells responded to the other gustatory stimuli that other intensity-response functions were not attempted. The intensity-response functions obtained to glucose are shown in Fig. 2. The dynamic range of sensitivity for these neurons to glucose was 0.01–1.0 M.

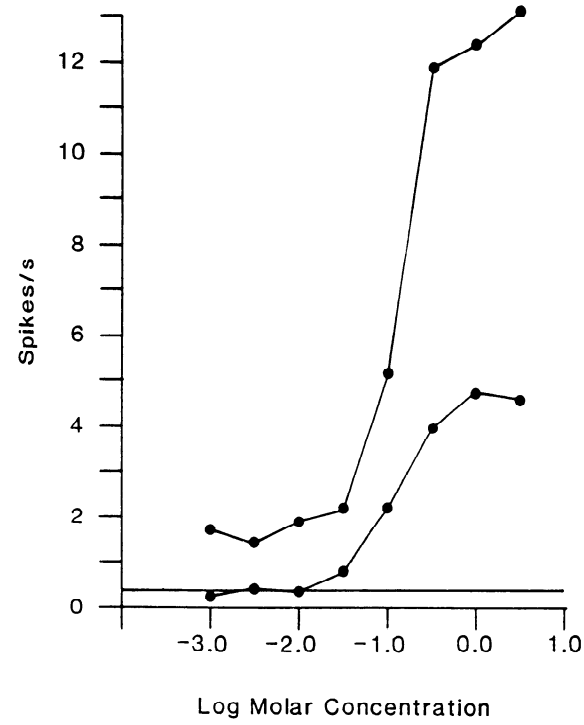

FIG. 2. Intensity-response functions of 2 individual neurons from the caudolateral orbitofrontal taste cortex of the monkey. Each cell was tested with a 3.5-log-mol concentration series of glucose.

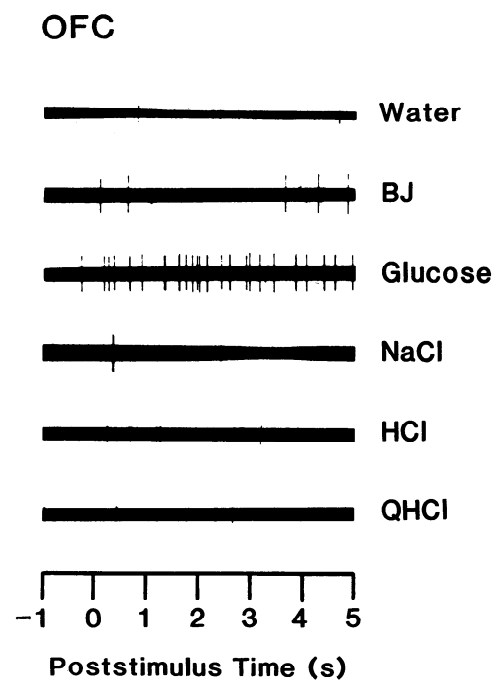

FIG. 3. Examples of responses recorded from 1 caudolateral orbitofrontal taste cortex neuron to 6 taste stimuli—water, 20% blackcurrant juice (BJ), 1 M glucose, 1 M NaCl, 0.01 M HCl, and 0.001 M quinine HCl (QHCl).

Standard concentrations for the remainder of the experiments were chosen on the basis of the intensity-response functions of neurons analysed previously in the NTS (Scott et al. 1986a), the opercular taste cortex (Scott et al. 1986b), and the insular taste cortex (Yaxley et al. 1990); the acceptance behavior of the monkeys; our need to effectively stimulate the taste system, and the benefits of using the same stimulus intensities as were employed to study taste in our earlier investigations (Scott et al. 1986a,b; Yaxley et al. 1990). The standard concentrations were (in M) 1.0 glucose, 1.0 NaCl, 0.01 HCl, and 0.001 QHCl. The remainder of this paper is based on activity evoked by these four stimuli plus 20% blackcurrant juice and deionized water. Examples of the responses evoked in one neuron in the caudolateral orbitofrontal cortex are shown in Fig. 3.

Mean evoked responses and chemotopic organization

The mean evoked responses in spikes per second measured over 5 s for each stimulus were deionized water, 2.5; 20% blackcurrant juice, 4.8; 1.0 M glucose, 7.2; 1.0 M NaCl, 2.1; 0.01 M HCl, 1.9; and 0.001 M QHCl, 1.7.

The responsiveness of each neuron as a function of its location in the orbitofrontal cortex was plotted to determine whether a chemotopic arrangement was apparent. No clear topography was apparent within the area shown in Fig. 1 in which neurons with gustatory responses were found. However, it was notable that the neurons recorded in this region had their best responses to glucose, NaCl, water, or blackcurrant juice, as described below, and that neurons with best responses to quinine HCl or HCl were not found in the area shown in Fig. 1. In this sense there is some chemotopic specialization of the region shown in Fig. 1 in which neurons were found.

Breadth of sensitivity

Of the 49 neurons tested with all solutions, two (4%) fulfilled our response criterion for responding to all four basic stimuli at these moderate-to-high concentrations. No neurons responded to three stimuli, six (12%) to two, 36 (74%) to one, and five (10%) did not exceed criterion to any basic taste solution (but, of course, they did in response to blackcurrant juice and/or deionized water) (see Table 1*B*). Conversely, the percentages of neurons that responded to each stimulus were 18% to water, 71% to blackcurrant juice, 82% to glucose, 12% to NaCl, 12% to HCl, and 8% to QHCl (see Table 1*A*). This is a very different pattern of sensitivity from that in the other taste areas, with neurons in the caudolateral orbitofrontal cortex taste area respond-

TABLE 1. *Three comparisons of the breadth of tuning of neurons*

	NTS	OPC	INS	OFC
A. Percentage of neurons fulfilling the response criterion for each prototypical stimulus				
1.0 M glucose	85	60	52	82
1.0 M NaCl	92	51	52	12
0.01 M HCl	63	51	48	12
0.001 M QHCl	86	56	42	8
Mean	82	54	49	29
B. Percentage of neurons responding to 4, 3, 2, 1, or none of the prototypical taste stimuli				
4/4	42	22	15	4
3/4	42	18	15	0
2/4	17	25	26	14
1/4	0	23	34	74
0/4	0	11	6	5
Mean	3.3/4	2.2/4	1.9/4	1.2/4
C. Mean breadth-of-tuning metric				
	0.87	0.67	0.56	0.39

NTS, nucleus of the solitary tract; OPC, frontal opercular taste cortex; INS, insular taste cortex; OFC, caudolateral orbitofrontal taste cortex.

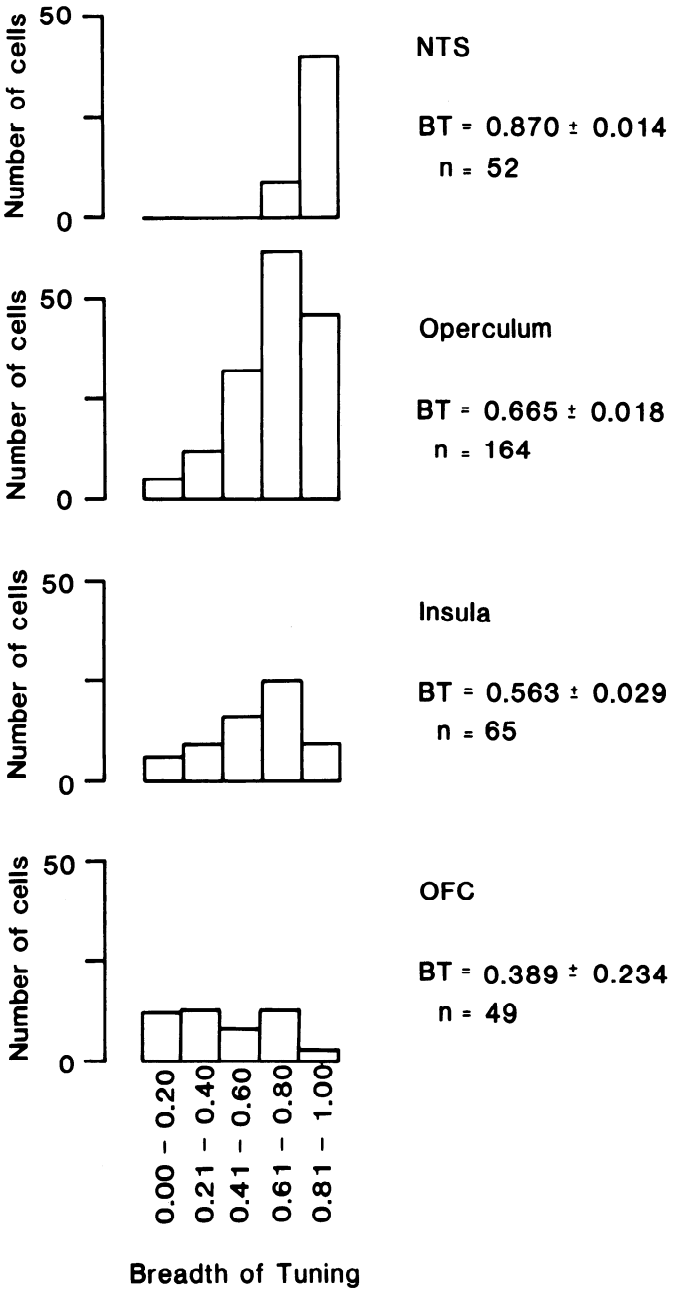

FIG. 4. Breadth-of-tuning index (see text) of 49 caudolateral orbitofrontal taste cortex (OFC) neurons analyzed (*bottom*). Breadths of tuning of neurons recorded in the nucleus of the solitary tract (NTS) and primary cortical taste areas in the frontal operculum and insula are shown also for comparison. Means (±SE) and the number of neurons in the sample for each area are shown.

ing mainly to sweet stimuli such as glucose and blackcurrant juice, a few neurons responding to water, and very few responding to NaCl, HCl, or QHCl (see Table 1*A*). Thus, ignoring water, 100 (34%) of the stimulus-neuron interactions resulted in responses that exceeded criterion—98 (33.3%) excitatory and two (0.7%) inhibitory. These percentages are lower than the corresponding values from NTS, frontal opercular taste cortex, and insular taste cortex (see Table 1*A*), implying that the mean breadth of tuning is narrower in the caudolateral orbitofrontal taste area.

To quantify this range of neuronal sensitivity, the breadth-of-tuning metric developed by Smith and Travers (1979) was applied. The proportion of a neuron's total response that is devoted to each of the four basic stimuli can be used to calculate its coefficient of entropy (H). The measure of entropy is derived from information theory and is calculated as

$$H = -k \sum_{i=1}^{n} p_i \log p_i \qquad (1)$$

where H = breadth of responsiveness, k = scaling constant (set so that $H = 1.0$ when the neuron responds equally well to all stimuli in the set of size n), p_i = the response to stimulus i expressed as a proportion of the total response to all the stimuli in the set. The coefficient ranges from 0.0, representing total specificity to one of the stimuli, to 1.0, which indicates an equal response to all of the stimuli. The values calculated from the responses to the four prototypical stimuli for the population of 49 caudolateral orbitofrontal cortex neurons analyzed are shown in Fig. 4. The mean coefficient was 0.39 (range = 0.00–0.91). This is lower than the mean value of 0.87 derived from NTS, lower than the mean value of $H = 0.67$ of neurons in the opercular taste cortex, and also lower than the mean value of $H = 0.56$ of neurons in the insular taste cortex (see Table 1*C*). Thus these caudolateral orbitofrontal cortex taste cells tended to be more specifically tuned across the standard range of taste qualities than do NTS, opercular, and insular taste cells. There was no evidence that the breadth of tuning varied systematically with neuronal location.

Neuron types

It is not yet resolved whether the taste system is composed of a small number of neuron types, each replicated to generate all cells of the system, or if each gustatory neuron is individualistic in its characteristics (Erickson 1985; Scott 1987; Smith et al. 1983; Woolston and Erickson 1979). One approach to the resolution of this issue is to determine whether there is a limited number of response profiles to which all taste neurons conform.

Shown in Fig. 5 are representative response profiles of caudolateral orbitofrontal cortex neurons categorized according to the chemicals to which each responded best: glucose (5*A*), blackcurrant juice (5*B*), deionized water (5*C*), and NaCl (5*D*). The shapes of the profiles are somewhat similar within each category, generating high mean product-moment correlations between the responses of the neurons within a category.

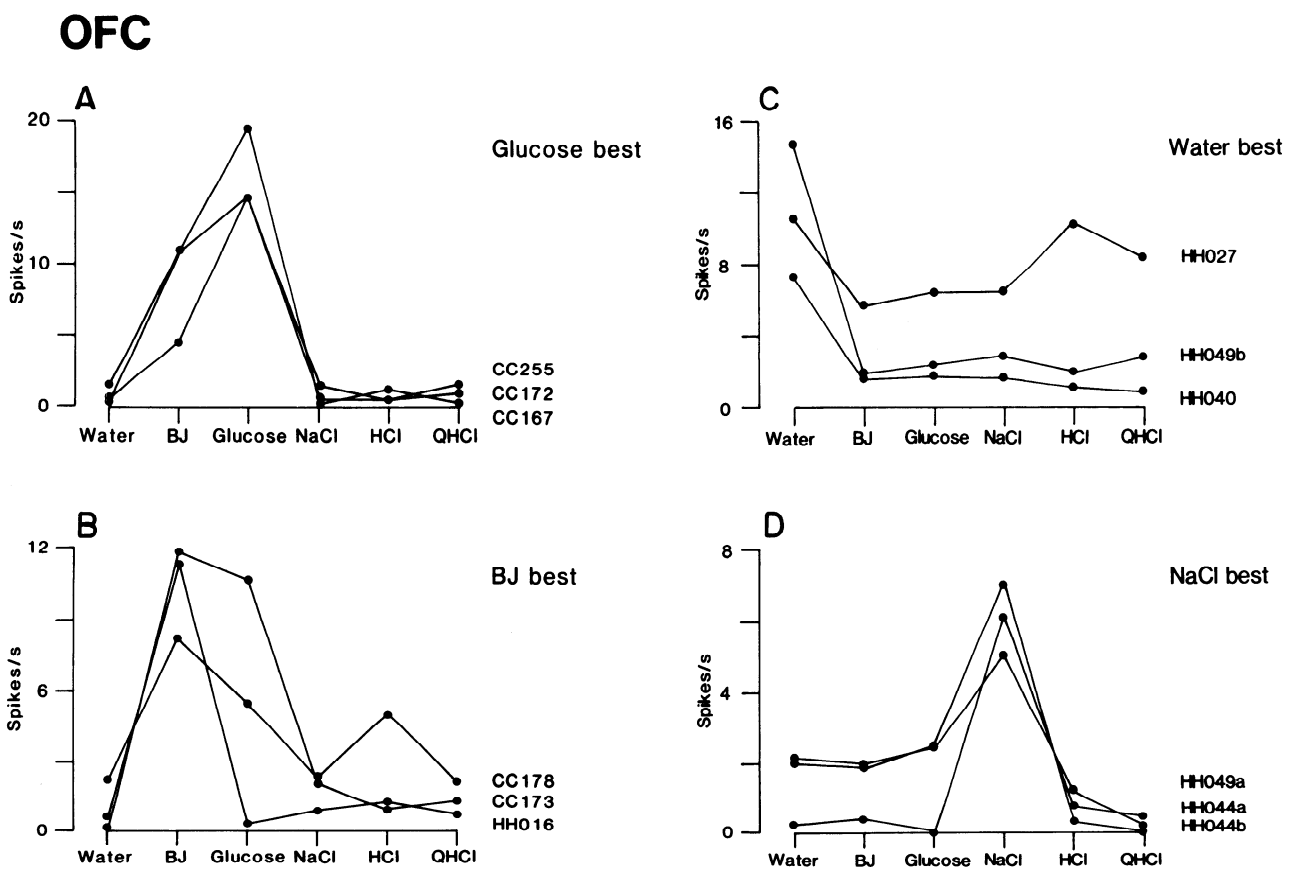

FIG. 5. Response profiles of 12 caudolateral orbitofrontal taste cortex neurons to different stimuli. Neurons are plotted according to the stimulus to which they responded best.

The general consistency within each category based on the stimulus to which a neuron responds best suggests a limited number of response profiles and so gustatory neuron types. However, it is possible that neurons that respond best to one stimulus may respond differently to other stimuli, so that there may be more types of neurons than indicated by the optimal stimulus categorization. Therefore a more comprehensive analysis that took account of the responses of every neuron to every stimulus was performed. To do this, we compared the profiles of the 49 neurons by the use of (Pearson product-moment) correlation of the responses shown by each neuron to that of all the other neurons and organized the resulting 1,176 correlations [$N(N-1)/2$] into a matrix that, in turn, was used to construct a multidimensional space with the use of multidimensional scaling (Bieber and Smith 1986; Cohen and Cohen 1975; Gurrman 1968) (Fig. 6). (For any 2 neurons the correlation between them was measured by calculating the Pearson product-moment correlation based on their responses to the 4 prototypical stimuli, to water, and to blackcurrant juice.) The goal of the multidimensional scaling was to produce a map (i.e., an arrangement of the neurons in space) in which the interneuron distances most closely match the associated proximities. The more similar two profiles are, the more closely the cells that generated them will be aligned in the space. Thus neuron types as defined by recurring sensitivity to the five stimuli plus water employed here would be indicated by groups of points, whereas the absence of groups would result in a homogeneous distribution throughout. The three dimensions in the space plotted in Fig. 6 accounted for 95.4% of the variance. (The first 2 dimensions accounted for 90.6% of the variance.) In Fig. 6 there is an interesting separation of neurons into different regions of the taste space. It is clear that the neurons are not scattered homogeneously throughout the space but are instead mostly situated in distinct regions of the space. This is an indication that what is being represented in the different dimensions is being represented quite sharply or unambiguously by the different neurons. Dimension 1 (which accounts for the largest part of the variance) appears to separate the sweet from the other stimuli. Dimension 2 separates neurons with best responses to glucose (*front*) from neurons with best responses to blackcurrant juice (*back*). Dimension 3 separates NaCl (*bottom*) from water (*top*).

To provide further evidence on the extent to which the putative groups of neurons apparent in Fig. 6 are internally consistent and independent of one another, a cluster analysis (Wishart 1978) was performed on the same correlation matrix as was used to generate the space shown in Fig. 6. This appears in Fig. 7 as a dendrogram. Neurons are numbered along the abscissa in the order in which they were isolated. Beneath each number is indicated the stimulus to which that cell gave its largest response, followed by any other stimulus that evoked at least 80% as much activity. The correlation between the two most similar pairs is represented by the *bottom horizontal* connecting line. Other similar pairs are joined until a connection is made at a height representing the mean correlation among the neurons involved. As more dissimilarity is permitted, larger groups are connected until all neurons are incorporated into the dendrogram. The more tightly a cluster is

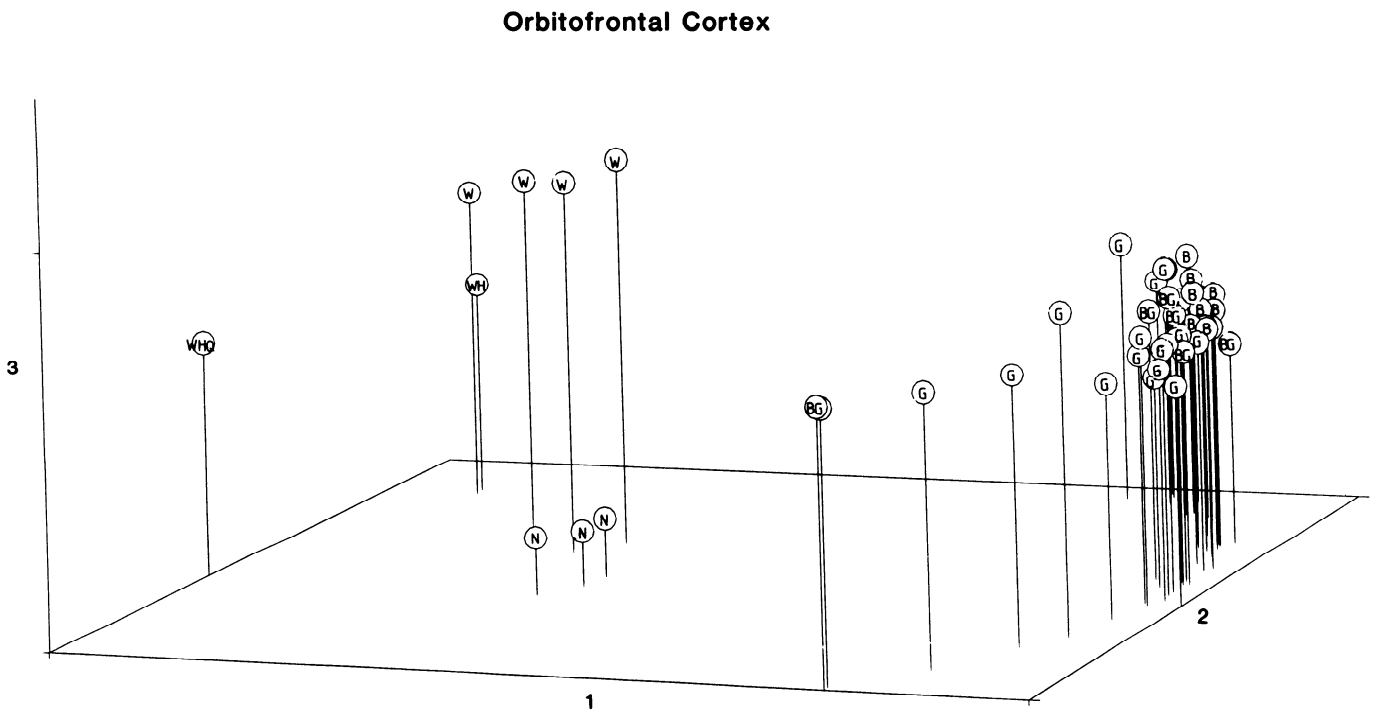

FIG. 6. Three-dimensional representation of relative similarity among neuronal response profiles. The more highly the response profiles of 2 neurons correlate, the closer they are positioned to one another in the space. This solution accounts for 95.4% of the data variance. Dimensions are numbered in the order of the amount of the variance for which they account. The stimulus or stimuli to which each neuron responded best is shown by the following symbols: N, NaCl; W, water; G, glucose; B, blackcurrant juice; H, HCl; Q, quinine HCl.

intercorrelated, the lower will be the horizontal line connecting its constituent cells. The more independent a cluster is from other neurons, the longer will be the vertical line leading to it. (A hierarchical cluster analysis with the average-linking method was used.) It is shown in Fig. 7 that the largest division is into neurons that respond best to glucose or blackcurrant juice, and those that respond to other stimuli best. The next division in the nonsweet cluster is between neurons that respond to water and those that respond to NaCl. The neurons in the sweet group show a number of subgroups. The cluster analysis thus corroborates the visual impression from the space that the response profiles of caudal orbitofrontal cortex taste neurons fall into a number of different categories.

To provide an indication of the profiles of responsiveness to the different stimuli of the clusters of neurons detected by the cluster analysis (see Fig. 7), the mean profile of the seven main clusters of neurons with high-interneuron (see below) correlations was calculated. These mean profiles (shown as a percentage of the maximal response of the neuron to any tastant) are shown in Fig. 8. For each of the taste stimuli glucose, NaCl, water, and blackcurrant juice, there was one group of neurons that responded much more to that tastant than to the other tastants. The other groups of neurons in some cases responded primarily to two of the tastants, such as glucose and blackcurrant juice. The cluster analysis is thus useful in helping to identify the characteristic response profiles of different groups of neurons (as detected by the cluster analysis) in the caudolateral orbitofrontal taste cortex.

Whether the groups or clusters shown in Fig. 7 are sufficiently coherent and different from other groups to warrant being designated neuron types is of interest (Erickson 1985; Scott 1987; Smith et al. 1983; Wishart 1978). One definition of neuron type derives from the suggestion of Woolston and Erickson (1979) that all cells of a putative neuron type should have identical response profiles to within the limit of experimental accuracy. Experimental accuracy was determined by repeating the application of a chemical during a session with one neuron and analyzing the responses by the same means as described above. The correlation between profiles generated by repeated applications should approach +1.00 as experimental error approaches zero. The mean correlation calculated by this method was +0.92. The lower limit of the 95% confidence interval for this distribution, as determined by the procedure described in Cohen and Cohen (1975) (see also Schiffman and Erickson 1971) is indicated by the dotted line in Fig. 7. Any neurons whose profiles do not intercorrelate at a level that meets or exceeds the lower limit of this distribution may be excluded from being functionally identical with a confidence of $P < 0.05$. Thus the groups of neurons apparent above the dotted line in Fig. 7 are more different from each other than would be expected by chance, with a probability

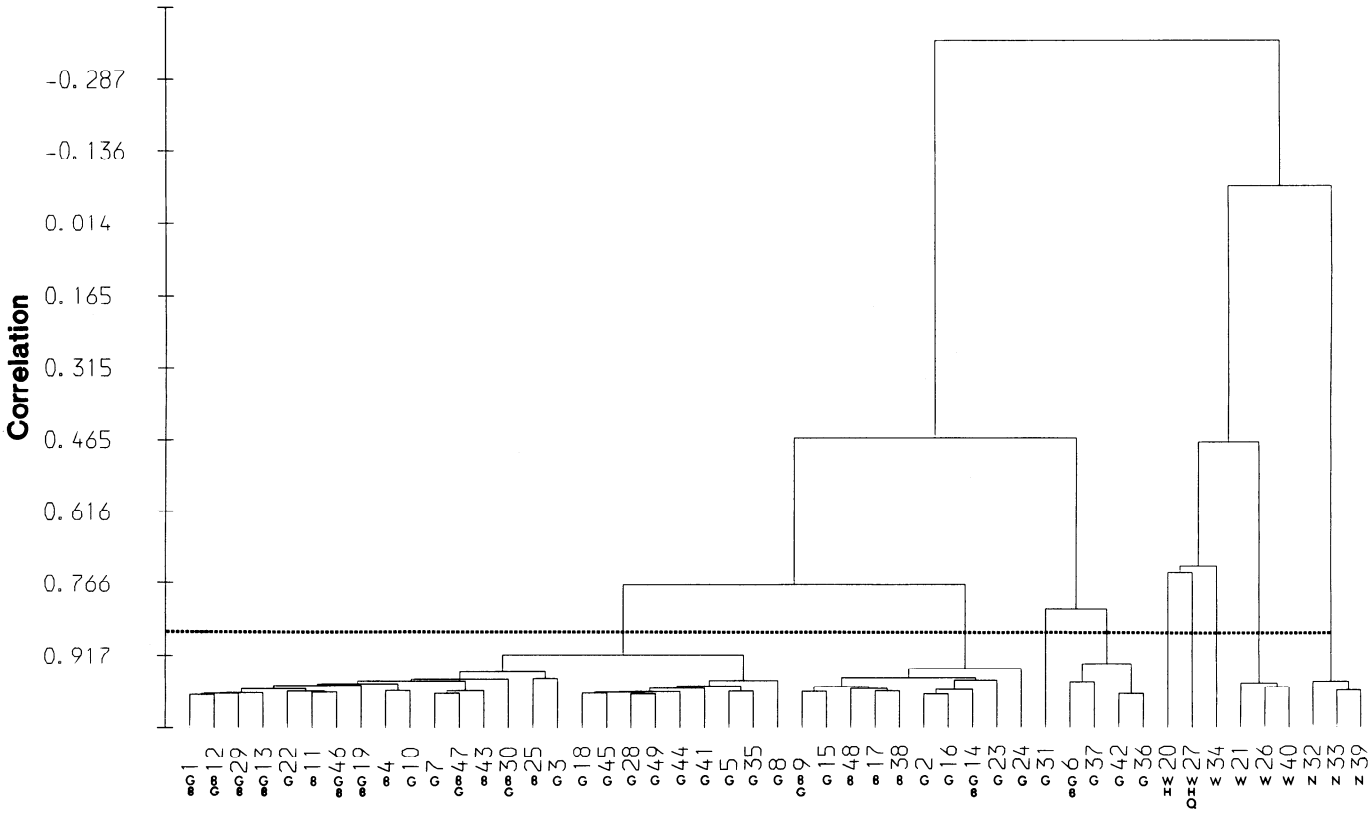

FIG. 7. Results of a cluster analysis performed on response profiles of 49 caudolateral orbitofrontal taste cortex taste neurons analyzed. Beneath the number of each cell is an abbreviation indicating the stimulus to which it gave its largest response followed by any other stimulus that evoked >80% of the best response. Any cluster that is not fully intercorrelated spatially below the dotted horizontal line can be excluded from being composed of neurons with identical response profiles at a $P < 0.05$ confidence level. Ordinate indicates the correlation level between profiles of neurons joined by a horizontal line at that level. N, NaCl; W, water; G, glucose; B, blackcurrant juice; H, HCl; Q, quinine HCl.

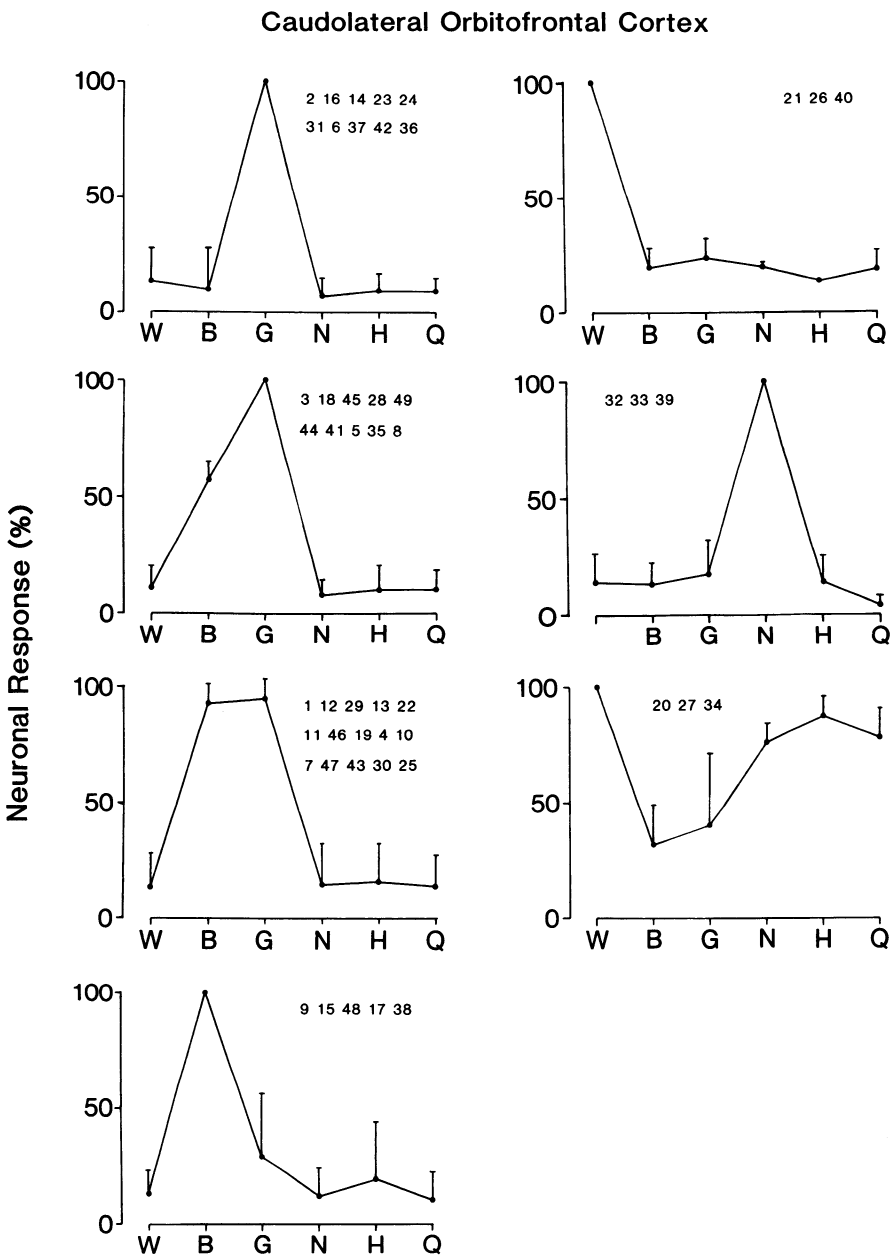

FIG. 8. Mean response profiles (±SD) of each of the main 7 clusters of neurons indicated in Fig. 7. Numbers of cells included in each cluster are annotated.

of error of 0.05. The mean profiles of each of the seven main such different groups of neurons are shown in Fig. 8.

Another way of assessing the number of clusters that are meaningful in a cluster analysis is to prepare a scree diagram in which the correlation between clusters is plotted as a function of the number of clusters (Bieber and Smith 1986). The use of this method on the data in Fig. 7 shows that there are at least five main groups of cells, with the *first two* from the *left* responding to blackcurrant juice and/or glucose, with the *third* cluster responding to most stimuli except glucose and blackcurrant juice, with the *fourth* group responding best to water, and with the *fifth* group responding to NaCl.

Stimulus quality

Just as the similarity among neuronal response profiles may be indexed by calculating correlation coefficients between each pair, so the similarity among stimuli may be measured by comparing the profiles of activity that each evokes across the 49-neuron sample. The correlations among these profiles have been shown in the rodent to

TABLE 2. *Correlation coefficients between profiles of activity generated by each stimulus*

	W	B	G	N	H	Q
W						
B	−0.01					
G	0.30	0.41				
N	0.87	0.04	0.27			
H	0.91	0.13	0.33	0.92		
Q	0.92	0.14	0.37	0.92	0.98	

W, water; B, blackcurrant juice; G, glucose; N, NaCl; H, HCl; Q, quinine HCl.

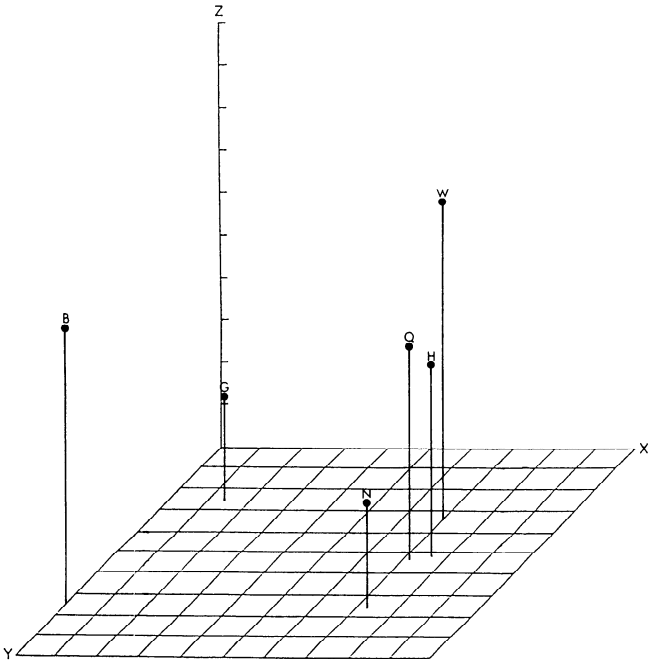

FIG. 9. Three-dimensional spatial representation of similarity among taste qualities as indicated by responses of caudolateral orbitofrontal taste cortex neurons. Three dimensions are undefined. Dimensions are numbered in the order of the amount of the variance for which they account. Symbols are as in previous figures.

offer accurate predictions of discriminative capacity. The 15 correlation coefficients between all pairs of profiles elicited by these six stimuli are shown in Table 2. In general the correlations between the different stimuli glucose, blackcurrant juice, and water/NaCl are relatively low, indicating that these neurons provide a representation of these stimuli in which they are well separated from each other. On the other hand HCl and QHCl, for which there were no very-responsive neurons, correlated highly with NaCl, indicating that the representation and discrimination of these stimuli was not a function for which these neurons in this part of the caudolateral orbitofrontal taste cortex were specialized.

As with the neurons, the correlation matrix may be used to generate a multidimensional space, this one containing the positions of stimuli relative to one another (Schiffman and Erickson 1971). A three-dimensional solution is shown in Fig. 9. In broad terms dimension 1 separates sweet from other qualities, and overall glucose, blackcurrant juice, water, and NaCl are well separated in the space, with quinine and HCl intermediate between NaCl and water.

DISCUSSION

In this study a gustatory area in the caudolateral orbitofrontal cortex has been found and analysed.

This region with gustatory neurons is in the caudal and far-lateral orbitofrontal cortex, as shown in Fig. 1. It is several millimeters anterior to the frontal opercular taste cortex (Scott et al. 1986b) and the insular taste cortex (Yaxley et al. 1990). In an anatomic investigation in which horseradish peroxidase was injected into this caudolateral orbitofrontal cortex taste area, we have shown that it receives projections from both the frontal opercular taste cortex and insular taste cortex but not from the thalamic taste area (VPMpc) (Wiggins et al. 1987). The frontal opercular taste cortex and the insular taste cortices, on the other hand, do receive from the taste thalamus. Thus the caudolateral orbitofrontal cortex taste area is a secondary cortical taste area. It receives its thalamic projections from the mediodorsal nucleus of the thalamus (pars magnocellularis) (Wiggins et al. 1987) and is therefore part of the prefrontal cortex (Thorpe et al. 1983).

The caudolateral orbitofrontal cortex taste area is different from the frontal opercular and insular primary taste cortices, in that there are neurons with responses in other modalities within or very close to it. For example, some neurons in this region had visual responses. Further medial is an olfactory area investigated by Takagi and his colleagues (Tanabe et al. 1975a,b). Whether there are any neurons with olfactory responses in the area with gustatory neurons we studied will be tested in a future investigation. It will also be of interest to determine whether any neurons in the caudolateral orbitofrontal cortex taste area have bimodal responses—responding, for example, to gustatory and visual stimuli or to gustatory and olfactory stimuli. Further medial, in the midmediolateral position of the caudal orbitofrontal cortex is the area investigated by Thorpe et al. (1983) in which are found many neurons with visual and some with gustatory responses. This latter region is implicated in a certain type of learning, namely, in extinction and in the reversal of visual discriminations, for which taste inputs are important in providing information about whether a reward has been obtained (Rolls 1986a,b, 1987, 1989a; Thorpe et al. 1983). It is possible that the caudolateral orbitofrontal taste area projects into this main part of the caudal orbitofrontal cortex to provide it with gustatory inputs. The further exploration of this region to determine the full extent of the gustatory area and whether there are a number of different subareas will be of great interest.

Taste cells in the caudolateral orbitofrontal cortex taste area are more sharply tuned (mean breadth-of-tuning index, $H = 0.39$) to the stimuli used than are cells in the NTS (mean $H = 0.87$) ($\chi^2 = 66$, df = 2, $P < 0.001$), and a little more sharply tuned than are cells in the frontal opercular taste cortex (mean $H = 0.67$) ($\chi^2 = 42$, df = 4, $P < 0.001$) and the insular taste cortex (mean $H = 0.57$) ($\chi^2 = 10$, df = 4, $P < 0.05$) (see Table 1*C*). Consistent with this, a relatively high proportion of caudolateral orbitofrontal cortex gustatory neurons responded to only one of the prototypical taste stimuli and a relatively low proportion to four or three of the prototypical taste stimuli (see Table 1*B*). A difference from the earlier taste areas studied (nucleus of the solitary tract, frontal opercular taste cortex, and insular taste cortex) was that a large proportion of neurons in the region analyzed responded primarily to sweet stimuli (glucose or blackcurrant juice), a few responded to water or NaCl, and any responses to HCl or QHCl were relatively minor. This is shown not only in Table 1*A* but also is apparent in Figs. 6 and 7. Consistent with this relative lack of representation of bitter and sour, the taste-stimulus space showed that caudolateral orbitofrontal cortex

neurons did not differentiate these well from NaCl (see Fig. 9). It will be of great interest to explore further within the orbitofrontal cortex, to determine whether there are regions where other tastants are represented. It will also be of interest to record in this region with a wider range of tastants and flavors, to determine whether there are some neurons that can be shown with the large set of stimuli to discriminate finely between the members of the set. When olfactory and taste inputs are combined, the possibility arises of producing some quite finely tuned neurons. [It can be noted that because neurons with best sensitivities to each of the taste stimuli were found in the primary taste cortex in the same monkeys (Yaxley et al. 1990), the relative paucity of neurons with best responses to quinine or HCl in the region of orbitofrontal cortex studied cannot be due to inadequate gustatory stimulation of the tongue. The possibility that there are further types of taste-responsive neurons in other parts of the orbitofrontal cortex is currently being explored.]

The cluster analysis helped to identify groups of neurons that had very high, within-group response profiles, to the different stimuli. The statistical analysis described above on which the dotted line shown in Fig. 7 was based provided an indication that when the experimental error is estimated, seven groups of neurons can be distinguished, the profiles of which are shown in Fig. 8. (The scree analysis suggested 5 main groups.) It is possible that with a larger stimulus array than the six used, and perhaps if these stimuli were used in combination, that even more groups of neurons would appear. It is clear from the profiles shown in Fig. 8 that some of these groups of neurons respond primarily to only one of the taste stimuli used, with very high, within-group correlations for a number of distinguishable groups in the caudolateral orbitofrontal cortex taste area compared with the considerably more-distributed representation found in the NTS (Scott et al. 1986a) and the somewhat more-distributed representation found in the primary taste cortices (Scott et al. 1986b; Yaxley et al. 1990). Some of the reasons for the finer tuning of neurons in the caudolateral orbitofrontal cortex taste area than in the NTS or the primary taste cortices are discussed elsewhere (Rolls et al. 1986a,b, 1987, 1989a,b).

The taste-space analysis (Fig. 9 and Table 2), neuronal-space analysis (Fig. 6), cluster analysis (Fig. 7), and the mean profiles (Fig. 8) show that neurons in the part of the caudolateral orbitofrontal cortex taste area studied clearly separate the representations of at least some of the tastants, particularly glucose, blackcurrant juice, water, and NaCl.

These findings thus show that this caudolateral orbitofrontal cortex taste area contains at least some neurons that are specifically tuned to respond to stimuli that include foods (glucose and blackcurrant juice), water, and NaCl. This suggests that this region may be specialized in some way for the control of responses to food and water. It is therefore very interesting that the gustatory neurons that respond to food only do so if the monkey is hungry, as shown during experiments in which the monkey is fed to satiety (Rolls et al. 1989). Similarly, the neurons that respond to water do so only if the monkey is thirsty (Rolls et al. 1989). This suggests that in this caudolateral orbitofrontal cortex taste area, the gustatory system is interfaced to motivation, resulting in motivation-dependent gustatory responses. These neurons could by virtue of this type of function be involved in appetite and the control of food intake, as described in more detail elsewhere (Rolls 1986a, 1987; Rolls et al. 1989). Further, the fine tuning of the neurons described here is probably part of the mechanism by which sensory-specific satiety is computed (Rolls 1986a, 1989a,b; Rolls et al. 1989), for these neurons, although ceasing to respond to the taste of foods with which the monkey has been satiated, nevertheless remain at least partly responsive to the taste of foods with which the monkey has not been satiated (Rolls et al. 1989).

In conclusion, this taste area in the caudolateral orbitofrontal cortex is a secondary taste cortical area that has at least some finely tuned neurons that are appropriate for differentiating between similar taste stimuli such as different foods and for the computation of sensory-specific satiety (Rolls et al. 1986a,b, 1987, 1989a,b; Rolls et al. 1989) and is the first stage of the primate taste system in which neuronal responses depend on hunger (Rolls 1986a, 1989b). It will be of interest in future studies to investigate whether multimodal representations are built here (between, for example, olfaction and taste), how learning affects the building of such multimodal neurons (cf. Rolls 1986a,b, 1989a, 1990; Thorpe et al. 1983), whether there are other subareas of the secondary taste cortex where other tastants are represented, and whether a tertiary cortical taste area can be located beyond the secondary taste cortex.

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