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Olfactory Neuronal Responses in the Primate Orbitofrontal Cortex: Analysis in an Olfactory Discrimination Task

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SUMMARY AND CONCLUSIONS

1. The primate orbitofrontal cortex receives inputs from the primary olfactory (pyriform) cortex and also from the primary taste cortex. To investigate how olfactory information is encoded in the orbitofrontal cortex, the responses of single neurons in the orbitofrontal cortex and surrounding areas were recorded during the performance of an olfactory discrimination task. In the task, the delivery of one of eight different odors indicated that the monkey could lick to obtain a taste of sucrose. If one of two other odors was delivered from the olfactometer, the monkey had to refrain from licking, otherwise he received a taste of saline.

2. Of the 1,580 neurons recorded in the orbitofrontal cortex, 3.1% (48) had olfactory responses and 34 (2.2%) responded differently to the different odors in the task. The neurons responded with a typical latency of 180 ms from the onset of odorant delivery.

3. Of the olfactory neurons with differential responses in the task, 35% responded solely on the basis of the taste reward association of the odorants. Such neurons responded either to all the rewarded stimuli, and none of the saline-associated stimuli, or vice versa.

4. The remaining 65% of these neurons showed differential selectivity for the stimuli based on the odor quality and not on the taste reward association of the odor.

5. The findings show that the olfactory representation within the orbitofrontal cortex reflects for some neurons (65%) which odor is present independently of its association with taste reward, and that for other neurons (35%), the olfactory response reflects (and encodes) the taste association of the odor. The additional finding that some of the odor-responsive neurons were also responsive to taste stimuli supports the hypothesis that odor-taste association learning at the level of single neurons in the orbitofrontal cortex enables such cells to show olfactory responses that reflect the taste association of the odor.

INTRODUCTION

The primate orbitofrontal cortex forms the ventral aspect of the frontal lobe and contains within it an area of secondary taste cortex (Baylis 1994; Rolls 1994a; Rolls et al. 1990). Taste-responsive neurons in this region are tuned more finely to tastants than lower down the taste system and are modulated by motivational factors such as hunger and satiety (Rolls et al. 1989, 1990). These findings strongly implicate the orbitofrontal cortex in mechanisms involved in the control of feeding (Rolls 1989, 1993, 1994). In primates, the primary olfactory (pyriform) cortex projects into area 13a in the caudal orbitofrontal cortex, from which there are onward projections to an extensive part of the orbitofrontal cortex (Barbas 1993; Morecraft et al. 1992; Price et al. 1991) (see Fig. 1).

In both human and nonhuman primates, the orbitofrontal cortex is involved in odor discrimination. In patients with damage to the right orbitofrontal cortex, the ability to identify odorants was found to be severely impaired, although the subjects were still able to detect the presence of odorants (Jones-Gotman and Zatorre 1988; Zatorre and Jones-Gotman 1991). Functional imaging of normal subjects using positron emission tomography (PET) shows that the right orbitofrontal cortex is activated by inhalation of odor stimuli and that there is bilateral activity in the region of the primary olfactory (pyriform) cortex (Zatorre et al. 1992). In nonhuman primates, bilateral lesions to the orbitofrontal cortex impair olfactory discrimination performed to obtain food (Tanabe et al. 1975a).

Recordings of the activity of single neurons in the orbitofrontal cortex have identified populations responsive to electrical stimulation of the olfactory bulb and to odorants (Tanabe et al. 1974, 1975a). In subsequent studies in which eight odorants were delivered intranasally, a central posterior area (corresponding to Walker's areas 13 and caudal 11) was found to contain broadly tuned olfactory neurons (with 50% of the neurons responding to >4 of the 8 odorants); and a caudolateral (lateral posterior) area that covered the orbital portion of area 12 and lateral area 13 was found to contained more finely tuned olfactory neurons (with no cells responding to >4 of the 8 odorants) (Yarita et al. 1980; see Takagi 1991). However, only 12 neurons were analyzed in the central posterior region, and further work is needed to determine whether the encoding of olfactory information is different in these two regions and if so, how it is different.

More recent recordings of the activity of single neurons in the orbitofrontal cortex have shown that some of the olfactory neurons (43%) could also be activated by taste stimuli (Rolls and Baylis 1994). At least some of these bimodal olfactory-gustatory neurons exhibited cross-modal correspondence of their responses, in that for example some neurons responding only to the odour of fruits responded to the sweet taste of glucose. This suggests that the olfactory representation for some of these neurons is influenced by the taste input that occurs at the same time as the odor. Further evidence for this was that in a two-odor olfactory discrimination task, neurons commonly responded differently to the odor associated with sweet taste and to the odor associated with the taste of saline (Rolls and Baylis 1994). In the olfactory discrimination task, when one odor was delivered in front of the nose by an airflow odorant delivery apparatus, the monkey could lick a tube to obtain glucose; and when the other odor was delivered, the monkey had to refrain from licking, otherwise saline was delivered from

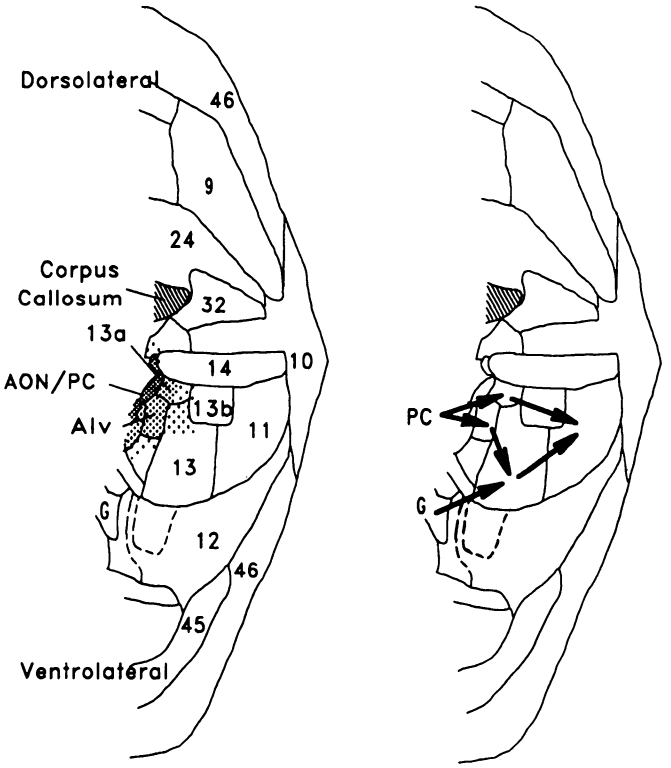


FIG. 1. Progression of olfactory inputs to the orbitofrontal cortex in monkey, drawn on unfolded maps of the frontal lobe. Cortex was unfolded by splitting it along principal sulcus, which is therefore located at *top* and *bottom* of each map. *Left*: inputs from primary olfactory (pyriform) cortex (PC) terminate in shaded region, that is in caudal medial part of area 13, i.e. 13a, and in ventral agranular insular cortex (Alv), which therefore could be termed secondary olfactory cortex. *Right*: secondary olfactory cortices then project into caudolateral orbitofrontal cortex, that is into secondary taste cortex in that it receives from primary taste cortex (G); and there are further projections into more anterior and medial parts of orbitofrontal cortex. (After Price et al. 1991, with permission).

the lick tube. The olfactory neurons that responded in this task had responses that were influenced by the odor delivered, in that the neurons did not respond in a visual discrimination task. The responses of the olfactory neurons were coupled tightly to the odor delivery, with response latencies as short as 150–200 ms (Rolls 1989; Rolls and Baylis 1984).

These neurophysiological findings provide evidence that the orbitofrontal cortex is involved in olfactory and taste information processing, that bimodal olfactory and taste neurons relevant to the representation of flavour are found here, and that hunger and satiety signals can influence responsiveness here (Rolls, 1989, 1993, 1994; Rolls et al. 1989, 1990, 1994). Further evidence consistent with this is that normal food selection is disrupted by bilateral lesions of the medial orbitofrontal cortex (Baylis and Gaffan 1991).

This series of investigations provides evidence that it is the reward value of taste, and not the identity of taste, which is represented in the orbitofrontal cortex. In particular, because these orbitofrontal cortex taste neurons only respond to the taste of food when the monkey is hungry, and not when he is satiated with a food, the neurons could not provide evidence about taste identity that is independent of hunger (Rolls et al. 1989). In contrast, neurons in the primary taste cortex do respond to taste independently of hunger (Rolls et al. 1988; Yaxley et al. 1988). Additional evidence that the reward value of food is represented in the orbitofrontal cortex is that monkeys work for electrical stimulation of this brain region if they are hungry, but not if they are satiated (Mora et al. 1979). Thus there is clear evidence that the reward value of taste is represented in the orbitofrontal cortex, and for this reason when referring in this paper to the aspect of taste in the orbitofrontal cortex with which olfactory neurons are associated, we refer to it as the reward value of the taste. In addition, we note that there is evidence that the responses of some olfactory neurons in the orbitofrontal cortex are related to reward, in that the responses of some orbitofrontal olfactory neurons decrease toward 0 for the odor with which the monkey is fed to satiety (Critchley and Rolls 1996b).

These studies leave open the question of how closely the olfactory responses in this region reflect the association of an odor with food. Is it the case that the responses of all orbitofrontal olfactory neurons reflect the association of an odor with taste, and thus that the encoding of olfactory information in this region is determined by taste associations? Do some neurons in this region represent olfactory information that is independent of the taste with which it is associated and thus potentially encode odor identity? When neurons do respond differently to odors associated with sweet taste versus saline taste, do they do this consistently across a wide range of olfactory stimuli associated with a taste? [In the previous study on this, only two odors were used in the olfactory discrimination task (Rolls and Baylis 1994)]. To address these issues fundamental to understanding the representation of olfactory information in the primate orbitofrontal cortex, we performed the investigation described here, in which a 10-odor olfactory discrimination task was performed by monkeys while recordings were made from orbitofrontal cortex neurons. Eight of the odors were associated in the Go-NoGo olfactory discrimination task with the delivery of sweet taste, and two with the delivery of aversive saline. With these 10 odors, we could determine whether olfactory neurons responded, for example, to all the odors associated with the sweet taste and to none of the odors associated with the saline taste (or vice versa). An alternative was that some neurons might have different responses between the eight odors all associated with sweet taste, in which case such neurons could convey information about the identity of the odor independently of its association with a taste reward.

We note that this study is part of a series of investigations in which the functions of the orbitofrontal cortex are being analyzed to provide evidence on feeding and its disorders (Rolls 1993, 1994b), on taste, olfaction and their disorders (Rolls 1994a), and on the causes of the emotional and motivational problems that can occur in patients with damage to this brain region (Hornak et al. 1996; Rolls et al. 1994). Indeed, the neurophysiological investigations on the learning mechanisms that are present in the orbitofrontal region have led to direct tests of whether such learning is impaired in patients with orbitofrontal cortex damage and, as a result of such clinical investigations, to new indications for the rehabilitation of these patients (Rolls et al. 1994). It is important that such neurophysiological studies directed toward

understanding the function of the orbitofrontal cortex in humans be performed on primates, for even the anatomic connections of the taste and olfactory systems are very different in primates from those in rodents (see Norgren 1984, 1990; Rolls 1994a), and in addition the orbitofrontal cortex is very little developed in rodents compared with its great development in primates.

METHODS

Recordings

Recordings were made from single neurons in the orbitofrontal cortex, which included both medial and lateral areas in which olfactory responses have previously been described. A few neurons also were recorded in primary taste (insula) and primary olfactory (pyriform) cortical regions. The subjects were two male rhesus macaques (*Macaca mulatta*) weighing 2.5–3.5 kg. Neurophysiological methods were the same as described previously (Rolls and Baylis 1994; Rolls et al. 1976, 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 on return to its home cage and was allowed access to water ad lib. 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 recordings were made from single cells, the interspike interval was monitored continuously to make sure that intervals of <2 ms were not seen and also the waveform of the recorded action potential 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 to 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-μm brain sections with the methods described in Feigenbaum and Rolls (1991).

Stimulus presentation

Odorants were delivered in a pseudorandom order using an olfactometer. The flow of pressurized air was controlled using a flow meter and pressure regulator and was diverted into a number of PVC tubes via a glass manifold. These tubes were linked to a series of solenoid valves operated by transistor-transistor logic (TTL) pulses generated by the computer. The opening of one of these valves caused the flow of air into a gas-wash bottle containing a solution of odorant. The resulting vapor containing the odorant passed from the gas-wash bottle via PTFE tubing to a stainless steel delivery nozzle that was designed to deliver odorants in the absence of spatial cues to the odorant identity. Dead space was minimized in the common nozzle to avoid mixing of residual odorants by bringing each stainless steel tube close to the common nozzle. A stream of odorless air (passed through propylene glycol solvent) was delivered in the intertrial interval between stimuli. This ensured the removal of the previous odorant before delivery of the next and provided the same degree of tactile somatosensory stimulation as the odor stimuli. At the time when an odor was being delivered, the clean air solenoid switched off, so that the pressure and flow were held constant throughout the experiment. The flow-rate of the air supply was kept constant in this way at 4.0 l/min. The nozzle was placed 2 cm from the monkey's nose. An air extractor was placed above the monkey's head to remove the odorant, such that there was laminar airflow upward around the monkey's head.

TABLE 1. *Odorants used in the olfactory discrimination task*

Odorant	Quality	Concentration of Solution	Abbreviation
Eugenol	Cloves	0.2 M*	eu
Hexylamine	Rotten fish	0.2 M*	hx
Phenylethanol	Floral	0.9 M*	pe
Butyric acid	Putrid	0.05 M	bu
Naphthalene	Moth balls	1.0 M*	na
Caprylic acid	Goaty/burnt plastic	100%	cp
Citral	Citrus/boiled sweets	0.1 M*	ct
Amyl acetate	Pear drops	100%	aa
Vanillin	Vanilla	1.0 M*	vn

* Diluted in propylene glycol.

A cue tone started 500 ms before delivery of an odorant and stopped when the odorant delivery started on each trial at *time 0*. The odorants were delivered in a computer-generated random sequence, in which the computer presented each odorant in the set once before it started a new random sequence. The odor duration was 1,000 ms. In the Go-Nogo olfactory discrimination task the monkey could lick a tube in front of his mouth when some odorants were delivered to obtain a rewarding sweet tasting solution (sucrose or aspartame) and had to refrain from licking the tube when other odorants were delivered to avoid obtaining a drop of aversive saline. Reward (or saline) were available throughout the 1,000-ms odor delivery, and for 500 ms after this in case the monkey already had initiated a lick. This period was sufficient for the monkey to obtain two to three licks of the sweet reward solution if his first lick was made quickly, and thus resulted in the monkey sniffing in at the termination of the tone, and sampling the odor immediately as its delivery started, so that the first lick could be made rapidly if it was a reward trial. This enabled accurate and reliable peristimulus time histograms of the responses of olfactory neurons relative to the time of onset of the odor to be produced. The intertrial interval was 9,000 ms to enable residual odor to clear and to minimize olfactory adaptation. The majority of odorants were associated with reward, but the presence of one or two saline-associated stimuli ensured that the monkey sampled each odorant presented to identify those from which a taste reward could be obtained.

A minimum of five presentations of each stimulus was required. The activity of neurons and the behavioral lick responses were recorded on-line by the computer and stored as rastergrams. Further analysis of the behavior and neuronal responses was performed after the experiment.

Stimuli

Suprathreshold concentrations of stimuli were determined such that each odorant could be identified easily and discriminated in conditions of delivery identical to those employed in related experiments (Critchley and Rolls 1996b; Rolls et al. 1996a,b), and were approximately equally intense. The odorants were selected as representative of differing putative odor classes (Amoore 1977) and were pure chemicals. They are listed in Table 1.

Reward associations

The monkeys were able to rapidly acquire the task and work for the reward with near 100% accuracy. Eugenol was associated with

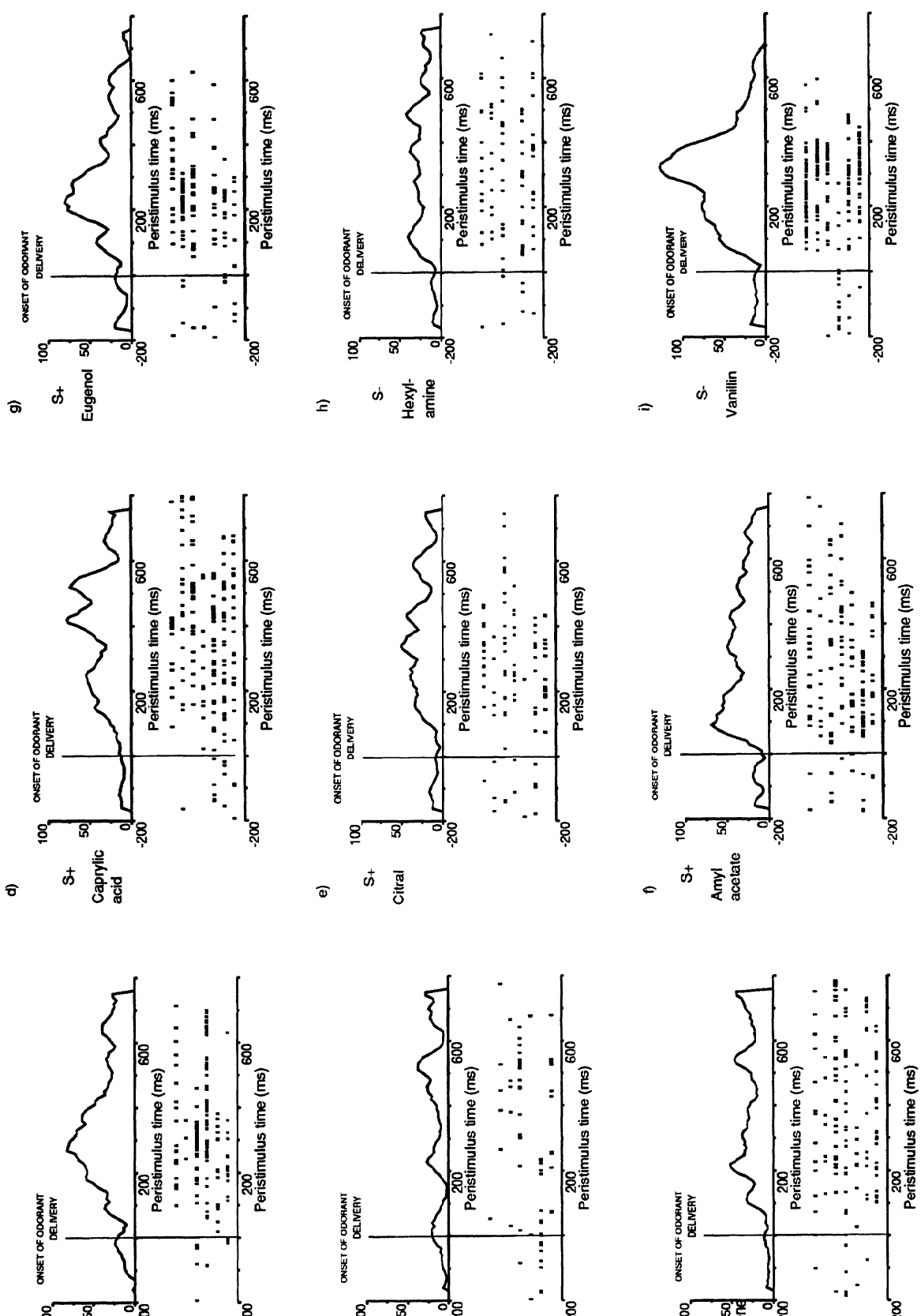


FIG. 2. *A–I*: Response of an orbitofrontal olfactory neuron during the performance of olfactory discrimination task. Peristimulus time histograms are plotted above firing of neuron on repeated trials of stimulus, shown as rasters below. Neuron responded well to majority of odorants, with exception of rewarded odorant butyric acid (*B*) and saline-associated odorant hexylamine (*H*). Odorants used are described in Table 1. S+, odorant associated with delivery of aspartame solution; S−, odorant associated with the delivery of saline solution.

the delivery of saline (and therefore was the S− odorant) for the first monkey. The rewarded odorants in these experiments were phenyl ethanol (pe), butyric acid (bu), naphthalene (na), caprylic acid (cp), citral (ct), and amyl acetate (aa). Ten cells (6 responding differentially) from this monkey are included in this study. Of these, three neurons responded differentially only between eugenol and the remaining odorants [one-way analysis of variance (ANOVA) with post hoc Newman-Keuls analysis]. To determine whether this was directly due to the reward association or due to some quality of eugenol as an odorant (such as trigeminal stimulation), the saline-associated odorant was changed to hexylamine in the task for the second monkey. Eugenol was a rewarded odor for the 38 cells collected from this monkey. At a later stage (for 24 cells in this monkey) a second odorant (vanillin) also was associated with saline, chosen because of its reported lack of trigeminal stimulation at discriminable concentrations.

Statistical analyses

ANOVAs were performed on the responses of each cell to the different odorants. Each firing rate was calculated from the mean neuronal responses in a 500-ms time-window beginning 100 ms after onset of the stimulus. This short time-period ensured that responses to the taste of the reward solution did not confound the analysis of the olfactory responses of cells responsive to both taste and olfactory stimuli. The monkey generally responded to the S+ stimuli by licking to obtain fruit juice 700 ms after onset of the odor stimulus.

The neuronal response was measured to 5–10 trials of each stimulus presented as described in a random sequence. A one-way ANOVA was performed to compare the responses with the different stimuli and with the spontaneous firing rate, to determine if there was a significant response to the olfactory stimuli. (In all but one neuron in this study, clearly defined neuronal response latencies were evident in the peristimulus time histograms). A subsequent one-way ANOVA was performed to determine whether there was a significant differential response to the olfactory stimuli (i.e. the spontaneous firing rate was not included as one of the conditions in this ANOVA). If this ANOVA was significant, subsequent post hoc Newman-Keuls' analysis was used to determine the significance of the difference between the responses to particular stimuli. The correlations, cluster analyses, and multidimensional scaling described here were performed using the SYSTAT and SPSS statistical packages. In these analyses, the response of the neuron is given, that is the evoked firing rate minus the mean spontaneous rate. The spontaneous firing rate was measured when olfactory stimuli were not being presented, and the monkey was sitting quietly without visual or taste stimuli being applied.

RESULTS

Overview

Orbitofrontal cortex neurons (34) were found to have significant differential responses to the odorants used in the olfactory discrimination task, representing 2.2% of the 1,580 orbitofrontal cortex neurons sampled during the experiments using this task. A further 14 orbitofrontal cells (0.9% of the total) responded to the olfactory stimuli used, but did not respond differentially to the different odorants as defined above. (In some cases, these 14 neurons responded differentially to other odorants presented on a cotton-bud or in the task if a different time-window was used to calculate the evoked responses to the stimuli). In the correlations, cluster analysis, and multidimensional scaling described below, the responses of only the 34 orbitofrontal cortex neurons with

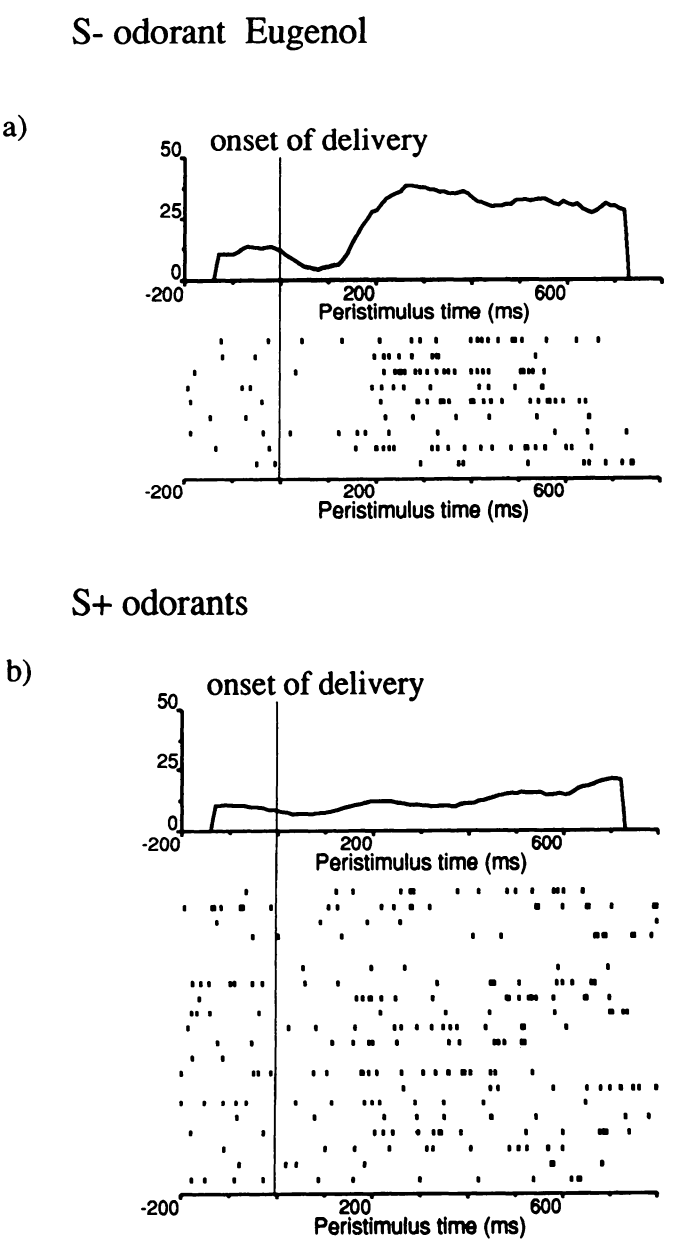
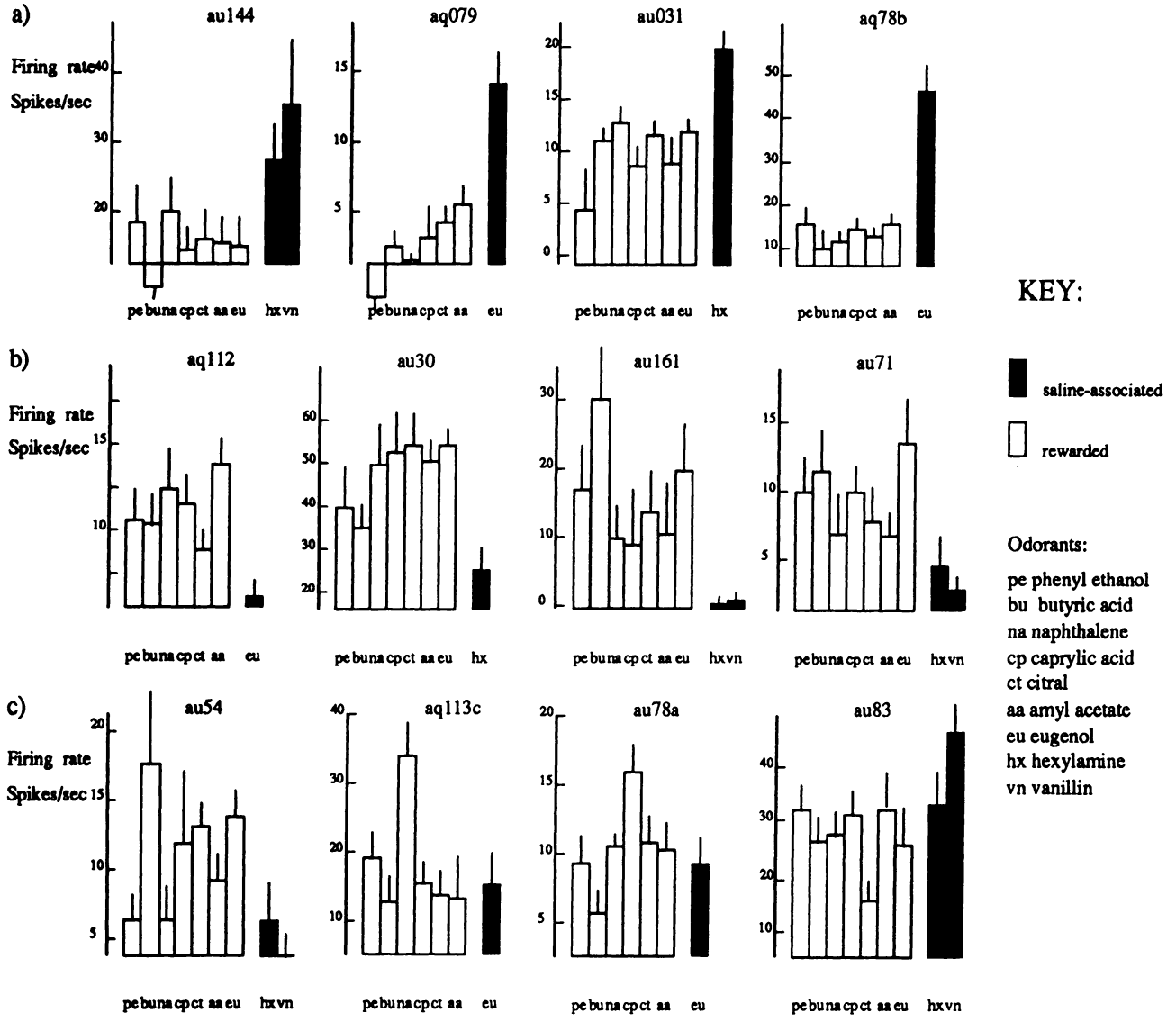


FIG. 3. Response of an orbitofrontal olfactory neuron during performance of olfactory discrimination task. Peristimulus time histograms (PSTHs) are plotted above firing of neuron on repeated trials of stimulus, shown as rasters below. Neuron responded robustly to saline-associated odorant, eugenol (*a*), but did not respond consistently to rewarded odorants, grouped together in PSTH and rastergram in *b*. Odorants used are described in Table 1.

differential responses to the different odours used in the task are considered. The mean spontaneous firing rate of these olfactory neurons was 9.6 ± 7.7 spikes/s (mean ± SD), whereas the mean maximum evoked firing rate, calculated from the 500-ms time window, was 29.5 ± 16.0 spikes/s.

Figure 2 illustrates the responses of a neuron (au122) with different responses to the different odorants during the olfactory discrimination task. The differential responses for this neuron were not based on the reward or saline association of the odorants. The neuron responded to many of the odorants by trains of spikes that began at ~150 ms after the onset of the stimuli and lasted for 200–300 ms. There was a



a: Examples of neurons responsive to the saline associated odorants
b: Examples of neurons responsive only to the rewarded odorants
c: Examples of neurons with differential responses to the rewarded odorants.

FIG. 4. *A–C*: Typical profiles of neuronal responses in task. Mean firing rate of neuron, calculated from 500-ms time window beginning 150 ms after onset of odorant delivery, is plotted for each odor stimulus to show differences from spontaneous firing rate. Error bars show standard error of responses over stimulus trials. Odorants are listed in Table 1. *A*: three examples of neurons that responded differentially only to saline-associated odorants; *B*: three examples of neurons that responded differentially equally to rewarded odorants but not to saline-associated odorants. *C*: examples of 3 cells that respond differentially to rewarded odorants and in some cases, also respond to saline-associated odorants. Examples of finely and broadly tuned responses are shown.

reliable response to the presentation of most of the rewarded odorants, especially phenyl ethanol, caprylic acid, amyl actetate, and eugenol. The neuron also responded robustly to the saline-associated odorant vanillin. The rewarded odorant butyric acid and the saline-associated odorant hexylamine elicited only weak responses from the neuron. For this neuron there were significant differential responses to the different odorants (calculated from the firing rate between 100 and 600 ms after stimulus onset) as shown by a one-way ANOVA [$F(8,59) = 3.4$, $P < 0.01$]. This neuron was located in the orbitofrontal cortex at the border between Walker's areas 13 and 11.

Figure 3 illustrates the responses of a second neuron (aq079) during the olfactory discrimination task. This neuron had no significant responses to the rewarded odorants, phenyl ethanol, butyric acid, naphthalene, caprylic acid, citral, or amyl acetate (Fig. 3*B*). The cell fired robustly to the saline-associated odorant, eugenol, with a latency of ~200

ms (Fig. 3*A*). Thus the only odor this neuron responded to was the odor associated with the S−. In a one-way ANOVA, there was a significant differential effect [$F(6,59) = 3.7$, $P < 0.01$].

Expression of the reward association of odorants

The responses of orbitofrontal olfactory neurons during the task revealed that some neurons, like the neuron shown in Fig. 3, had responses that reflected the reward association of the odorants. These neurons were divided into two groups: those that responded strongly to the saline associated odorant(s) and had much weaker responses to the rewarded odorants, and neurons that responded strongly to the rewarded odorants, and did not respond significantly to the saline-associated odorant(s). The remaining neurons had differential responses to the rewarded odorants and in some cases, also responded to the saline-associated odorants. Examples of these three neuronal types are illustrated in Fig. 4, *A–C*.

Figure 4*A* shows the response profiles of four neurons that had best responses to the saline-associated odorants. During the course of the experiments, either eugenol or hexylamine was reinforced negatively. At a later stage vanillin was associated with saline in addition to hexylamine. It can be seen from these profiles that in all cases the strong responses evoked by the saline-associated odorant(s) far exceeded those of the rewarded odorants. For neuron au031, the rewarded odorants also evoked responses, yet the mean response to the saline associated odorant hexylamine was 8 spikes/s greater than to the most effective of the rewarded odorants, naphthalene. Neuron au144 responded well to both of the negatively reinforced odorants, hexylamine and vanillin, showing that rather than reflecting the differences in the quality of these two odorants, the neuron reflected instead the situation that both these odorants were associated with saline. In these cells, there was a significant differential response of the cells on a one-way ANOVA, and post-hoc Newman-Keuls' analysis showed that the main significant differences were between the responses to the negatively reinforced odorants and to rewarded odorants.

Figure 4*B* shows four examples of neurons that responded to the rewarded odorants, yet had minimal responses to the saline-associated odorants. Cells au161 and au71 again illustrate the point that two very dissimilar odor qualities (hexylamine and vanillin) were treated similarly by the neuron on the basis of the reward association. In the cells in Fig. 4*B*, there was a significant differential response of the cells on a one-way ANOVA, and post-hoc Newman-Keuls' analysis showed that the main significant differences were between the responses to the rewarded odorants and to the negatively reinforced odorants. (For au071, the responses to both the saline-associated odorants were below the responses to each of the reward-associated odorants, and for the majority of all the individual comparisons for reward-associated odors to the pooled response to the two S− stimuli, the differences were statistically significant. Similarly, neuron au161 responded most strongly to the odorant butyric acid, and had quite large responses to all of the rewarded odorants. The major difference in the neuronal response was between the rewarded and saline-associated odorants.)

Figure 4*C* illustrates four neurons that did not respond to the stimuli solely on the basis of reward association. Cell au54 responded well to the odorants bu, cp, aa, and eugenol (eu). It did not respond well to the negatively reinforced odorants, hexylamine and vanillin, nor to the odorants pe and na. Cell aq113c was strongly tuned to the odorant naphthalene. The remaining odorants were as effective as each other, independently of whether they were reward- or saline-associated. Cell au78a responded well to the odorant cp and had very little response to bu. Cell au83 responded particularly well to the odorant vanillin, yet responded very little to the odorant citral. These neuronal profiles do not reflect the reward association of the stimuli in the olfactory discrimination task. Such neurons are therefore likely to contribute to the encoding of odor quality independently of reinforcement value. Within this cell population, the specificities of cells for individual odorants varied from the specific tuning such as shown by cell aq113c, to much broader tuning such as that shown in the response profile of cell au83. In these cells, there was a significant differential response of the cells to the different odors as shown by a one-way ANOVA.

TABLE 2. *The tuning of neurons to the reinforcement value of olfactory stimuli*

Expression of Reward Value by Orbitofrontal Olfactory Cells	Number of Cells	Percent of Cells
Negative reinforcement ≫ positive reinforcement	8	23.5
Positive reinforcement ≫ negative reinforcement	4	11.8
No differential response to reward association	22	64.5
Total	34	100

On the basis of the one-way ANOVA performed on each cell and the subsequent Newman-Keuls' analyses, it was possible to categorize each neuron as responding significantly more ($P < 0.05$) to the odor (or pooled odors) associated with saline than to any of the reward-associated odors; as responding more to all the taste reward-associated odors than to the saline-associated odor(s); or as having responses to the odors that were not consistently different to odors based on their taste association (see Table 2). It can be seen that 35.3% of the orbitofrontal olfactory neurons had responses that could be categorized as responding either on the basis of whether the odor was associated with the taste of saline (23.5%) or with a sweet taste (11.8%).

Because some orbitofrontal cortex neurons respond to both olfactory and taste stimuli (Rolls and Baylis 1994) and because a possible basis of the taste-dependent olfactory encoding is that olfactory inputs might make associative synapses directly onto taste neurons, we tested whether these olfactory neurons had responses to the prototypical tastes sweet (1.0 M glucose), salt (0.1 M NaCl), bitter (0.001 M quinine-HCl), and sour (0.01 M HCl). It is shown in Table 3 that of the 12 neurons that responded to the odorants on the basis of their reward association, 5 (42%) did have responses to the prototypical tastants. All three of the bimodal neurons that responded to the saline-associated odorants were tuned to the taste of NaCl, indicating that there was a close cross-modal correspondence of the responses to tastants and odorants that could have resulted from odor-taste association learning at the level of the

TABLE 3. *Biomodal responses of reward-related olfactory neurons*

Responses to Odorants According to the Reward Value of the Stimuli	Cell Number	Most Effective Tastant
Cells responding to rewarded odorants	aq112	glucose
	au30	NaCl/quinine
	au71	—
	au161	—
Cells responding to saline associated odorants	aq78b	NaCl
	au28	NaCl
	au37b	NaCl
	aq79	—
	au31	—
	au59	—
	au70	—
	au144	—

—, not taste responsive.

single neuron. Of the two cells that responded to the rewarded odorants and not to the saline-associated odorants and also were taste responsive, one (aq112) had a cross-modal correspondence between the taste and the olfactory responses, with the cell tuned to the sweet taste of glucose, and the other neuron (au30) responded to the aversive tastants NaCl and quinine. Thus four of the five bimodal neurons had corresponding sensitivities in the taste and olfactory modalities. The remaining seven cells shown in Table 3 did not have responses that could be elicited by the prototypical tastants presented alone. It is of course possible that such cells can be influenced by taste inputs only when they occur in conjunction with olfactory inputs, or that they respond only to taste mixtures, or that they respond to nonprototypical tastants such as monosodium glutamate (Baylis and Rolls 1991) or tannic acid (Critchley and Rolls 1996a).

Representation of individual odorants by the population of orbitofrontal olfactory cells

To analyze how the population of neurons represented the olfactory stimuli, a correlation matrix was made showing the correlations between every pair of stimuli. The correlation for any pair of odour stimuli was the Pearson product-moment correlation calculated from the firing rates of every cell to these two stimuli. A correlation of 1.00 between two odorants indicates that the population of cells responds similarly to these two odorants. A correlation score of 0.00 indicates that the responses of the population of cells are unrelated to these two stimuli. Table 4 shows the correlation matrix between the odorants for the whole population of 34 orbitofrontal neurons with olfactory responses [the matrix as a whole was significant as shown by Bartlett's χ^2 statistic ($\chi^2 = 130.7$, df = 21, $P < 0.001$)]. In most cases the rewarded odorants (pe, bu, na, cp, citral, aa, and eu S+) produced responses that were well correlated with each other, with correlation scores predominantly between 0.60 and 0.75. Butyric acid, however, was an exception to this trend, being less well correlated to the other rewarded odorants, and therefore appreciably different from them. Other dissimilarities exist: citral was not strongly correlated with either pe or eu. When eu was reinforced negatively, it was markedly dissimilar to the rewarded odorants. This was predominantly a result of three of the six cells (for which eu was associated with saline) being of the reward-related type described above. These three cells did not, because they responded primarily in relation to whether the odor stimulus was rewarded or not, show strong differential responses between the rewarded odorants. Hexylamine, which was always associated with saline, did not produce responses that correlated strongly with those to any of the rewarded odorants. In contrast, vanillin was correlated highly with all of the rewarded odorants except for bu and eu. The matrix therefore represents the way in which both odorant quality and reinforcement association contribute to the differentiation between odorants by this whole population of 34 orbitofrontal neurons.

One way in which the relationship between the stimuli in the representation provided by these orbitofrontal neurons can be visualized is by the use of hierarchical cluster analysis of the responses to the odorants. The Pearson correlation matrix was used to provide the distance measures between the stimuli. In the hierarchical cluster analysis procedure, the first link is made between the two most highly correlated stimuli, which are joined at the level of their Pearson correlation. An average linkage procedure joins clusters (and pairs) using the average correlation of the members of the cluster as the distance measure. The resulting dendrogram provides a measure of the similarity (as a Pearson correlation) between groups of stimuli and hence provides both a visual and mathematical indication of the way and how strongly the data are clustered.

The dendrogram of the olfactory stimuli, based on the

TABLE 4. *Correlation matrix of odorant responses*

	N	pe	bu	na	cp	ct	aa	euS+	euS−	hxS−	vnS−
Phenyl Ethanol		1.00									
Butyric Acid	34	0.28	1.00								
Naphthalene	34	0.70	0.38	1.00							
Caprylic Acid	34	0.72	0.30	0.69	1.00						
Citral	34	0.47	0.49	0.72	0.60	1.00					
Amyl Acetate	34	0.67	0.45	0.77	0.73	0.71	1.00				
Eugenol S+	28	0.70	0.42	0.60	0.71	0.46	0.64	1.00			
Eugenol S−	6	0.18	−0.06	−0.32	0.03	0.48	0.49	—	1.00		
Hexylamine S−	28	0.49	0.18	0.51	0.46	0.26	0.43	0.28	—	1.00	
Vanillin S−	20	0.81	0.18	0.87	0.73	0.75	0.78	0.48	—	0.68	1.00

See Table 1 for definitions.

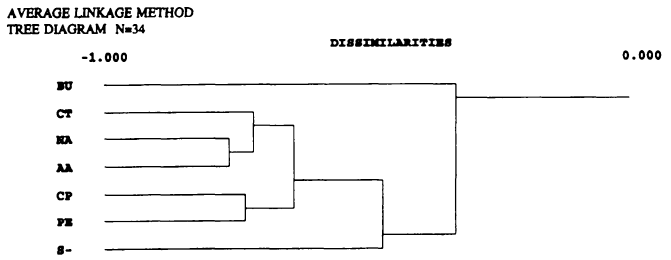


FIG. 5. A dendrogram based on cluster analysis of responses to odorants over population of 38 differentially responsive olfactory neurons. Junctions between groups are located at point of Pearson correlation coefficient between odorant groups and reflect degree of similarity between them. In this figure, saline-associated odorants are treated as a single stimulus. Abbreviations as in Table 2.

responses of the 34 differentially responsive neurons, is shown in Fig. 5. Because the saline-associated odorants were changed during the course of these experiments, they were entered as a single S− stimulus for the cluster analysis. The dendrogram shows that in the responses of this population, bu was separated most far from the other odorants, the correlation between bu and the remaining odorants being 0.35. The saline-associated stimulus also was represented away from the other odorants, being correlated with the nonbutyric odorant group at 0.45. The odor stimuli in the main group of rewarded odorants were approximately equally correlated with each other (correlation coefficients between 0.67 and 0.77), indicating that their representations by the whole population of olfactory neurons were similarly apart in the sensory space.

The relationship between the stimuli given by the responses of the population of neurons also can be examined using multidimensional scaling. The technique enables the individual stimuli to be plotted as points in a space with a specified number of (orthogonal) dimensions. The position of each point is determined by the interrelationship of the stimuli, such that they are placed to maximally represent the variance accounted for by the data. The dimensions of the space are ordered such that most of the variance of the data is plotted along dimension 1.

Figure 6 illustrates the two-dimensional scaling solution for the olfactory stimuli, measured from the responses across the 34 neurons. This two-dimensional solution accounts for 97% of the total variance in the data (a one-dimensional solution would have accounted for 94%). Figure 6 illustrates the important point that though both bu and the saline-associated odorants are poorly correlated with the remaining odorants, they are at opposite ends of the major dimension of the odorant space. This indicates first that the saline-associated odorants are distinctly represented from the rewarded odorants and second that bu is represented somewhat differently from the other rewarded odorants, but not similarly to the saline-associated odorants. The main group of rewarded odorants are grouped together, the differences between the odors in this group being revealed in both dimensions of the multidimensional space. For the analyses shown in Figs. 5 and 6, we combined the cases for the different S− stimuli, which were for different cells vanillin, hexylamine, and/or eu, so that the analyses could be based on all 34 neurons. We present the data (in Figs. 5 and 6) for the full 34 cells because such correlation-based measures operate better with

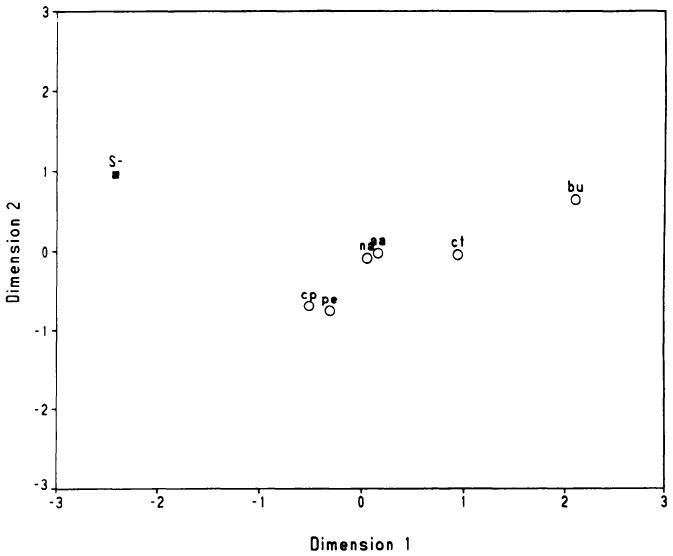


FIG. 6. Two-dimensional odorant space, created using multidimensional scaling, of responses of 38 differentially responsive neurons. In this figure, saline-associated odorants are treated as a single stimulus. Abbreviations as in Table 2.

as many cells as possible, but we were able to confirm in separate comparable analyses on the relevant subsets of neurons that whichever olfactory stimulus for the cells was an S−, it was placed away from the responses to the S+ odors. In particular, multidimensional scaling was performed based on the responses of the 20 orbitofrontal neurons for which both hexylamine and vanillin were associated with saline in the task. Figure 7 illustrates the 2-dimensional solution for the odorants, derived from multidimensional scaling of the responses of these 20 neurons (a 1-dimensional solution would account for 75% of the variance, whereas the 2-dimensional solution accounted for 96%). Figure 7 illustrates that the positions of both the saline-associated odorants, va-

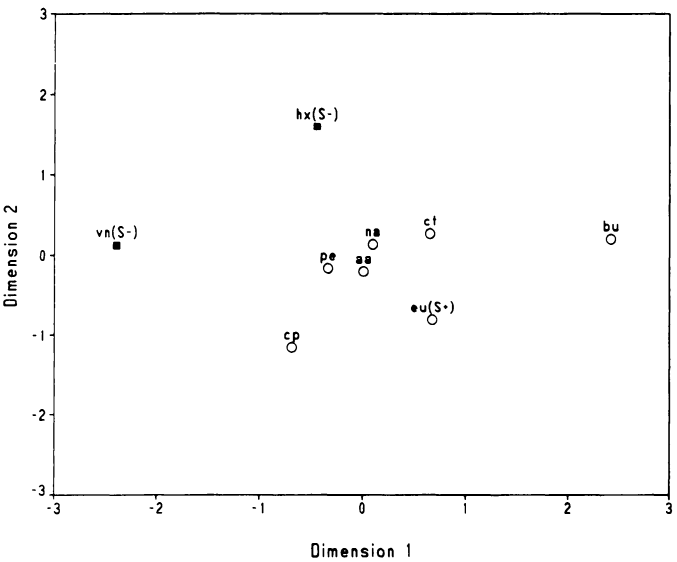


FIG. 7. Two-dimensional odorant space, created using multidimensional scaling on a subset of neurons used for Fig. 6. Figure illustrates separation of saline-associated odorants, hexylamine and vanillin, from the rewarded odorants.

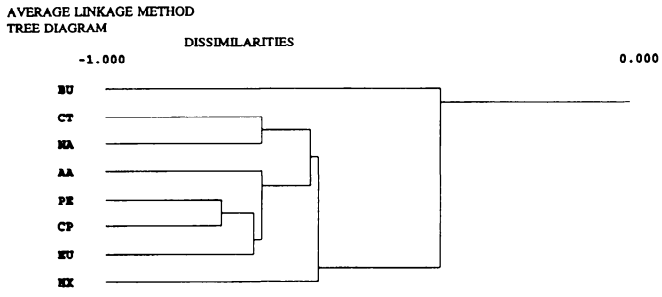


FIG. 8. A dendrogram based on cluster analysis of responses to odorants over a subset of 19 differentially responsive neurons that did not respond based on taste with which the odor was associated in olfactory discrimination task. Abbreviations as in Table 2.

nillin, and hexylamine, lie away from the major group of rewarded odorants. Butyric acid, as also shown in Fig. 6, is placed away from the rewarded odorants in the other direction.

The representation provided by these neurons analyzed in Table 4 and Figs. 5 and 6 was for the whole, unselected, population of 34 neurons with olfactory responses in the olfactory discrimination task. It has been shown above by the statistical analyses summarized in Table 2 that 12 of the 34 orbitofrontal neurons analyzed had responses in the task that reflected whether the odor was associated with a taste reward or with the taste of saline. To analyze the representation provided by the orbitofrontal olfactory neurons that did not categorize odors according to the taste with which they were associated, the types of analysis just described were performed on the remaining set of neurons that did not have responses that depended on the taste association of the olfactory stimuli. (Nineteen neurons were included in this set, which was the set of neurons with odor responses that were not related to reward for which the full set of 7 S+ stimuli had been tested.) The stimulus correlation matrix based on the responses of these 19 neurons is shown in Table 5. This correlation matrix was significant as shown by Bartlett's χ^2 statistic ($\chi^2 = 102.6$, df = 28, $P < 0.001$). It is clear that this set of neurons separated butyric particularly well from the other odorants, and that among the other odorants, there was no major grouping or confusion present between these different odors. These points are supported by the cluster analysis shown in Fig. 8 and the two-dimensional space based on multidimensional scaling shown in Fig. 9. The values for the interstimulus correlations (Table 5) show that the odors were at least as well separated by this subset of neurons as by the whole population (Table 2).

Latencies of neuronal responses

Figure 10 shows a histogram of the response latencies of the 48 odour-responsive orbitofrontal cells in this study. The average response latency was 187 ± 50 ms. The response latencies of those neurons that responded differentially to the stimuli (latency 180 ± 55 ms) were not significantly different from those that did not (latency 206 ± 38 ms).

Location of neurons

The locations of all the cells in this study are shown in Fig. 11. The open squares indicate the 14 cells that responded to the task with clear latencies, but did not significantly differentiate between the stimuli in their responses. The filled circles indicate the position of the neurons that responded to the odorants on the basis of the reward associations of the stimuli, and the open circles show the position of the remaining differentially responsive olfactory cells. The cells analyzed in this study came only from the orbitofrontal cortex. However, during the course of these experiments, a small number of other neurons were recorded from the neighboring regions of the insula, pyriform cortex, and ventral striatum. The responses of the neurons recorded in the other structures shown in Fig. 11 were similar to those of orbitofrontal neurons in the following respects. One differentially responsive neuron, tuned to the reward association of the stimuli, was located in the region of the primary taste cortex in the insula. Five neurons were located in the ventral striatum, of which two were differentially responsive to the odorants and tuned to the reward association. Four olfactory neurons were recorded from the primary olfactory cortical region, of which, only one was differentially responsive to the odorants. The spontaneous firing rates of the orbitofrontal and nonorbitofrontal neurons in the present sample were similar (9.6 and 8.8 spikes/s, respectively), as were their peak firing rates (29.5 vs. 29.7 spikes/s, respectively), whereas the average latency of the orbitofrontal differential neurons was 180 ± 55 ms, and of the nonorbitofrontal differential neurons was 130 ± 66 ms. Within the orbitofrontal cortex, neurons tuned to the reward association of the stimuli were located among both differentially responsive and nonselective olfactory neurons and therefore did not appear to be segregated separately.

DISCUSSION

The orbitofrontal cortex has been shown to be necessary for the discrimination of odorants and the normal selection of foods (Baylis and Gaffan 1991; Butter et al. 1969; Jones-Gotman and Zatorre 1988; Tanabe et al. 1974; Zatorre and Jones-Gotman 1991). The present study extends the knowledge about processing of olfactory information in this brain

TABLE 5. *Pearson correlations between 7 odorants*

	pe	bu	na	cp	ct	aa	eu
Phenyl Ethanol	1.00						
Butyric Acid	0.15	1.00					
Naphthalene	0.74	0.40	1.00				
Caprylic Acid	0.78	0.26	0.65	1.00			
Citral	0.53	0.62	0.70	0.66	1.00		
Amyl Acetate	0.75	0.55	0.70	0.69	0.58	1.00	
Eugenol	0.70	0.27	0.61	0.75	0.46	0.69	1.00

Results based on the responses of 19 olfactory cells that did not respond on the basis of the reward association of the stimuli.

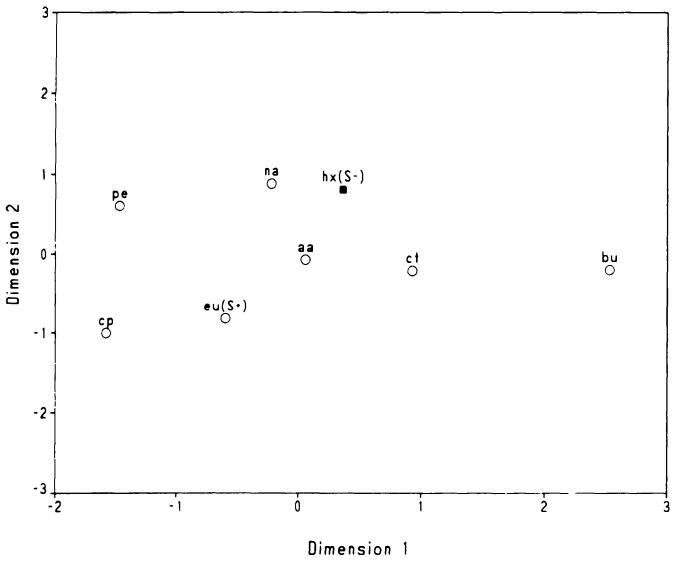


FIG. 9. Two-dimensional odorant space, created using multidimensional scaling, of responses of a subset of 19 differentially responsive olfactory neurons that did not respond based on taste with which odor was associated in olfactory discrimination task. Abbreviations as in Table 2.

region. The automated olfactory discrimination task required the monkey to show accurate behavioral discrimination between the odorants during normal physiological sampling of the odorants. The main advantage of this task was that it allowed the onset and duration of the odor stimuli to be accurately controlled, and this enabled the latency and time course of neuronal responses to be analyzed during normal olfactory behavior. The negatively reinforced odorants were placed in the task to ensure that the animal was attentive to and sniffed each of the odorants before either making a lick response or not. These saline associated odorants also led to the discovery that a significant proportion of the odor-responsive cells in this study were tuned to the reward association of the stimuli.

The 48 orbitofrontal neurons in this study exhibited varying degrees of tuning to the task odorants; 14 neurons did not discriminate the stimuli by their responses over repeated trials. ANOVAs for the responses of these cells to the odorants alone were not significant, despite clear latencies to the stimuli and significant ANOVAs when the spontaneous firing rate was included as a condition. This is consistent with earlier findings (Rolls and Baylis 1994; Tanabe et al. 1974, 1975; Yarita et al. 1980) that show the presence of predominantly broadly tuned responses to olfactory stimuli even at this higher stage of olfactory processing. (It was interesting to note that 3 of the 4 neurons recorded in the region of primary olfactory cortex showed this very broad tuning to the stimuli.) These broadly tuned cells were found over the whole of the orbital surface among more finely tuned olfactory cells. The location of all the neurons did not support the suggestion of Yarita et al. (1980) that there were two distinct olfactory regions on the orbital surface where neurons were more finely tuned to olfactory stimuli in the caudolateral region: we found finely tuned neuronal responses in even the most medial of the orbitofrontal cortical regions sampled. The proportion of olfactory neurons in the present study (3.1%) was relatively low and is consistent with earlier studies on this region (Rolls and Baylis 1994, found 2%). In partially overlapping subregions of the orbitofrontal cortex other neurons respond to gustatory and/or visual stimuli, but the proportion responding to any one modality is quite low (gustatory 5.4%; visual 3%) (Rolls and Baylis 1994). If recordings are concentrated in one of the subregions, the proportion of olfactory neurons may be higher (see Takagi 1991). However, even in the primary taste cortex, the proportion of neurons that are activated by taste stimuli is quite low, in the order of a few percent (Scott et al. 1986; Yaxley et al. 1990).

Of the orbitofrontal cortex neurons that differentiated between the odorants, 35% categorized odors according to the taste (sweet vs. saline) with which they were associated in the olfactory discrimination task. The finding that some of these cells were explicitly taste responsive indicates a way in which associations between odorants and stimuli in other modalities (here taste or reward value) may contribute toward finer or different representations of odorants than are necessary solely for accurate recognition and discrimination between odors. Indeed, the categorization found for this 35% of the neurons indicated that their activity reflected the taste association of the olfactory stimuli and might therefore be useful in mediating appropriate behavioral responses to such odors. These responses might include approach, working to obtain an odor to obtain food, and autonomic responses to odors that depend on the reinforcement association of the odor, e.g., salivation to the smell of a food when hungry. The categorization performed by this 35% of neurons could provide a representation of odor that simply reflects shaping of the representation by taste. Alternatively, the odor representation influenced by taste could represent the reward or reinforcement value of the odor, formed as a result of the association with tastes that are rewarding (e.g., glucose taste when hungry) or aversive (e.g., saline taste). Consistent with the hypothesis that this 35% of orbitofrontal cortex olfactory neurons are involved in hedonic re-

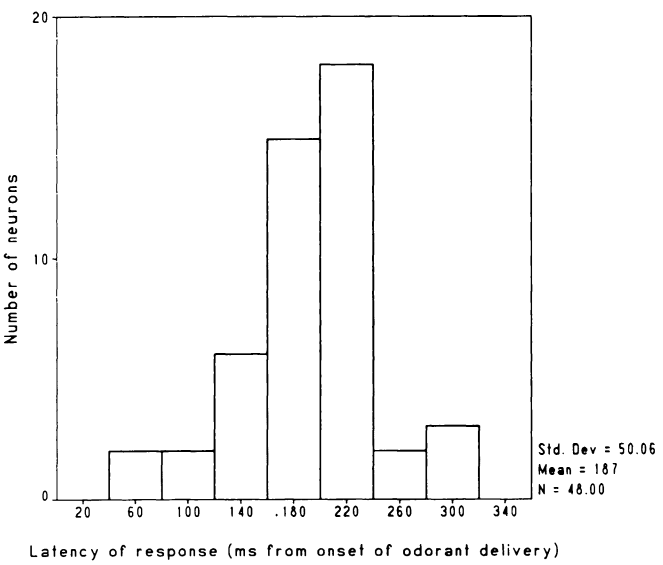


FIG. 10. Histogram of latencies of 48 olfactory neurons in this study.

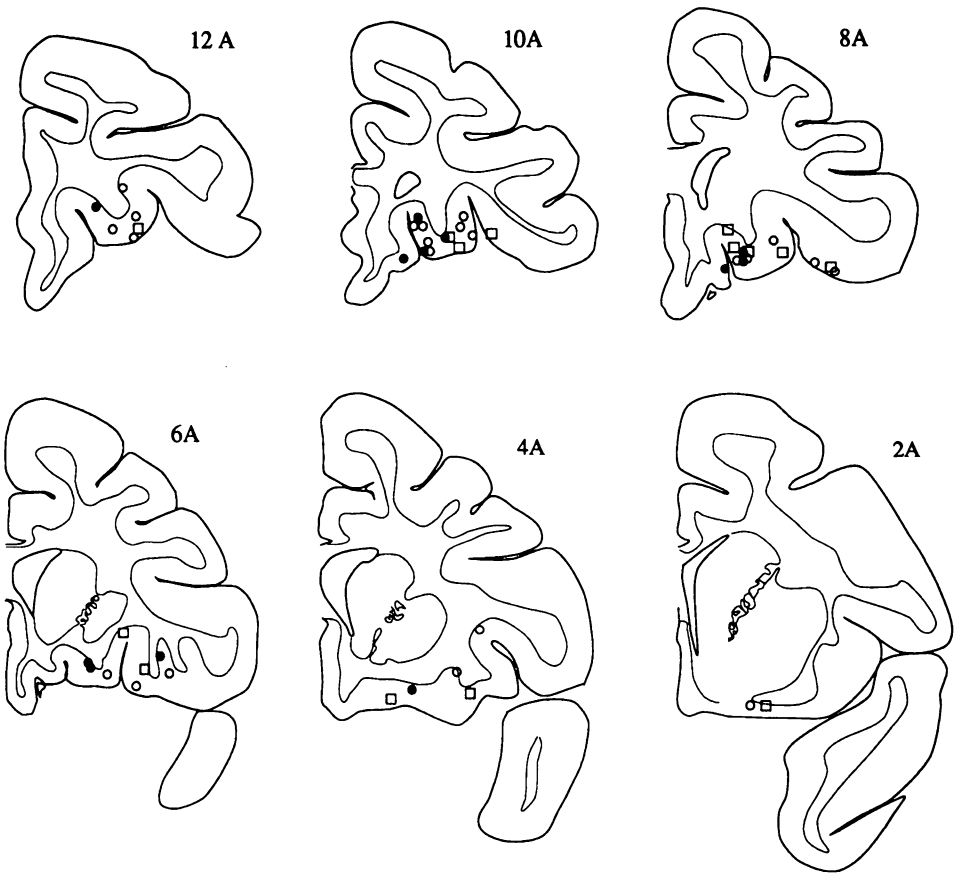


FIG. 11. Location of orbitofrontal neurons in this study. ●, neurons tuned to reward associations of odorants; ○, other differentially responsive neurons; □, sites of neurons that did not discriminate between odorants. Distances are given as millimeters anterior to anterior sphenoidal process.

sponses to odors is that the responses of taste neurons in this region reflect whether the food is rewarding, in that their taste responses are decreased by feeding the monkey to satiety (Rolls et al. 1989); and with the finding that the responses of many of the orbitofrontal cortex olfactory neurons also are decreased to the odor of the food with which the monkey is fed to satiety (Critchley and Rolls 1996b). Moreover, human psychophysical evidence indicates that there is a strong hedonic dimension to the perception of odors (e.g., Bergland et al. 1973; Schiffman 1979; Schiffman et al. 1977).

The orbitofrontal cortex is known to be involved in association learning that involves associations between, for example, visual stimuli and primary (unlearned) reinforcers such as the taste of food, and this has been demonstrated at the neuronal level (Rolls et al. 1994; Thorpe et al. 1983; see Rolls 1990, 1994). The finding described in this paper that the categorizations performed by 35% of orbitofrontal neurons with differential responses in the olfactory discrimination task reflect the taste reward/saline association of odors *suggests* that it is by olfactory to taste association learning that such categorizations occur. To test this hypothesis, we have measured whether the olfactory responses of orbitofrontal neurons reverse the odor to which they respond when the taste with which the odor is associated is reversed in the reversal of an olfactory discrimination task. We have found that this learning can influence the responses of at least some orbitofrontal olfactory neurons (Rolls et al. 1996a). This provides strong evidence, complementary to that described in this paper, that the responses of at least some orbitofrontal olfactory neurons are influenced by the taste with which the odor is associated. The most likely site for this learning is the orbitofrontal cortex, because both the primary gustatory and the primary olfactory cortices project into this region (see INTRODUCTION). However, further investigations will be required to determine whether the orbitofrontal cortex contains the first stage of olfactory processing at which neuronal responses are influenced by the taste association of the odor in primates.

A possible reason why in the previous studies of olfactory neurons in the orbitofrontal cortex (Takagi 1991; Tanabe et al. 1974, 1975b; Yarita et al. 1980) more specific neuronal responses to the olfactory stimuli have been reported in the caudolateral as opposed to the centromedial orbitofrontal cortex, may be related to the fact that the caudolateral region is adjacent to the secondary taste cortex. Odor-taste associations between the stimuli might enhance the proportion of neurons showing sharp categorization in this area, whereas in more medial areas there is less overlap in responses to olfactory and taste stimuli (Rolls and Baylis 1994).

Overall the data described here show that the responses of olfactory neurons in the region of the orbitofrontal cortex contribute to the encoding of olfactory information in two ways. The presence of a large proportion of broadly tuned neurons is consistent with ensemble encoding, which allows detailed and fine representations

of a large number of stimuli to be held, while at the same time conserving the number of neurons required (see Rolls and Tovee 1995). The much finer tuning or categorization of other olfactory neurons may be related to the need for an explicit representation of stimuli that reflects their taste or reward association, as is shown here and in the study by Rolls and Baylis (1994). This type of representation is necessary to avoid generalisation of modulatory influences (such as satiety in the taste system) onto other stimuli of the same class and thereby facilitates precise control of perceptual and behavioral responses to stimuli (see Critchley and Rolls 1996a; Rolls 1995; Rolls et al. 1989).

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