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Orbitofrontal Cortex Neurons: Role in Olfactory and Visual Association Learning

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SUMMARY AND CONCLUSIONS

1. The orbitofrontal cortex is implicated in the rapid learning of new associations between visual stimuli and primary reinforcers such as taste. It is also the site of convergence of information from olfactory, gustatory, and visual modalities. To investigate the neuronal mechanisms underlying the formation of odor-taste associations, we made recordings from olfactory neurons in the orbitofrontal cortex during the performance of an olfactory discrimination task and its reversal in macaques.

2. It was found that 68% of odor-responsive neurons modified their responses after the changes in the taste reward associations of the odorants. Full reversal of the neuronal responses was seen in 25% of these neurons. Extinction of the differential neuronal responses after task reversal was seen in 43% of these neurons.

3. For comparison, visually responsive orbitofrontal neurons were tested during reversal of a visual discrimination task. Seventy-one percent of these visual cells showed rapid full reversal of the visual stimulus to which they responded, when the association of the visual stimulus with taste was reversed in the reversal task.

4. These findings demonstrate that the responses of many orbitofrontal cortex olfactory neurons are modified by and depend on the taste with which the odor is associated.

5. This modification is likely to be important for setting the motivational value of olfactory stimuli for feeding and other rewarded behavior. However, it is less complete, and much slower, than the modifications found for orbitofrontal visual neurons during visual-taste reversal. This relative inflexibility of olfactory responses is consistent with the need for some stability in odor-taste associations to facilitate the formation and perception of flavors.

INTRODUCTION

Feeding, emotional, and social behavior are disrupted by lesions of the orbitofrontal cortex in primates including monkeys and humans (Baylis and Gaffan 1991; Butter and Snyder 1972; Butter et al. 1970; Hornak et al. 1996; Rolls et al. 1994). In analyses of the basis for these deficits, it has been shown that lesions to the orbitofrontal cortex in monkeys disrupt performance in a variety of tasks. These include extinction tasks, in which the no-longer-rewarded visual stimuli are still chosen (Butter 1969); visual discrimination reversals, in which the no-longer-rewarded visual stimuli are still chosen (Jones and Mishkin 1972); go/no go visual discrimination tasks, in which the objects are chosen even on no go trials, when they should not be selected (Iversen and Mishkin 1970); and object alternations (Mishkin and Manning 1970). In all these tasks, the orbitofrontal monkeys select stimuli that should no longer be selected. Moreover, the orbitofrontal cortex is a site at which potent brain stimulation reward occurs (Rolls 1975). Therefore the hypothesis has been developed that the orbitofrontal cortex is involved in processing information about rewards, and in particular is involved in detecting when nonreward has occurred and in correcting behavior to make it appropriate for current reinforcement contingencies (Jones and Mishkin 1972; Rolls 1975, 1986, 1990, 1994a). According to this hypothesis, the social impairments follow orbitofrontal damage because social behavior cannot be modified rapidly and appropriately to meet the continuously changing reinforcement contingencies typical of social behavior, and therefore inappropriate social responses, which do not reflect reinforcement contingencies, are made. The emotional changes are held to follow orbitofrontal damage because emotions, which can be analyzed in terms of states elicited by rewarding and punishing stimuli, are impaired if they are no longer elicited appropriately by changes in reinforcement contingencies (Rolls 1986, 1990, 1994a). For example, insensitivity to the nonoccurrence of expected rewards is associated with flatness of affect, and a failure to care about the consequences of one's actions and to correct behavior appropriately (Rolls 1990; Rolls et al. 1994). The altered feeding after orbitofrontal damage, in which nonfoods as well as foods are selected and eaten, may also be understood as a failure to interpret correctly the reinforcement associations of visual and other food-related stimuli (Rolls 1990, 1994a; Thorpe et al. 1983).

These approaches to understanding the functions of the primate orbitofrontal cortex have been complemented recently by fundamental discoveries about the functions of the orbitofrontal cortex in taste, olfactory, and visual information processing. It has been discovered that the lateral part of the orbitofrontal cortex contains the secondary taste cortex (Baylis et al. 1994; Rolls 1989; Rolls et al. 1990). It has been shown that in the secondary taste cortex, but not in the primary taste cortex, the neuronal responses reflect the reward (or "motivational") value of the taste, in that the neurons respond to the taste of a food only if hunger is present (Rolls et al. 1989; Yaxley et al. 1988). (In this respect, what is sometimes called "hedonics" in the taste system is represented in the orbitofrontal cortex.) It also has been shown that the temporal visual cortical areas, which are concerned with representing objects including faces (Rolls 1994b), project into the orbitofrontal cortex (Barbas 1988; Barbas and Pandya 1989; Morecraft et al. 1992), that neurons in the orbitofrontal cortex respond to visual stimuli such as the sight of food (Thorpe et al. 1983), and that such visual neuronal responses reverse when the taste (sweet vs. salt) associated with choosing a visual stimulus reverses from sweet (rewarding) to salt (aversive) in the reversal or

extinction of a visual discrimination task (Thorpe et al. 1983). The responses of orbitofrontal neurons to visual stimuli thus reflect the reward associations of visual stimuli, and reverse those responses by association learning in typically one trial only (Thorpe et al. 1983).

When visual-to-taste or olfactory-to-taste association learning is described here, the taste representation is sometimes referred to as representing reward or reinforcement value. This follows from the points made above, that the taste neurons in the orbitofrontal cortex (but not earlier in taste processing in primates) are modulated by hunger, and so could not reflect taste identity, but instead reflect the reward value of the taste. 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 we refer 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 zero for the odor with which the monkey is fed to satiety (Critchley and Rolls 1996b).

It also has been shown that the primary olfactory cortex projects into the orbitofrontal cortex (Price et al. 1991), that there are neurons in parts of the orbitofrontal cortex that respond to olfactory stimuli (Rolls 1989; Rolls and Baylis 1994; Takagi 1991; Tanabe et al. 1975), and that in humans orbitofrontal activation produced by olfactory stimuli can be imaged with positron emission tomography (Zatorre et al. 1992). The orbitofrontal olfactory neurons often respond differently to olfactory stimuli associated with taste reward and with (aversive) saline (Rolls 1989). It has recently been shown that the olfactory and taste inputs converge onto some single neurons in the orbitofrontal cortex (Rolls and Baylis 1994), thus providing a potential neural substrate for association learning between odor and taste. This would occur with modification of synapses from active olfactory neurons conveying the to-be-associated stimulus onto active neurons responding unconditionally to taste. Consistent with this, there is frequently some correspondence between the odor (e.g., of fruit) and the taste (e.g., sweet) that activates an orbitofrontal neuron (Rolls 1989; Rolls and Baylis 1994). In another investigation in which an olfactory discrimination task was used in which six odors were paired with reward taste, and one or two with the taste of saline, 35% of selective olfactory neurons in the orbitofrontal cortex categorized the odors depending on the taste with which they were associated (Critchley and Rolls 1996a). All of these findings provide an indication that the olfactory stimuli to which at least some orbitofrontal cortex olfactory neurons respond is influenced by the taste with which they are associated by pairing. This would be appropriate for two rather different functions. The first is to enable behavior to be directed appropriately (approach or withdraw, work to obtain or avoid) toward an odor on the basis of the taste previously associated with it. This might well extend beyond odor-taste association learning to associations between odors and other primary reinforcers important in emotion. This process might be quite rapid, and indeed is for visual-to-taste association learning (Thorpe et al. 1983). A second function of odor-taste association learning might be to build representations of flavors, by combining evidence from odor and taste, and this type of association might be expected to be more stable, that is slow to be learned and slow to be forgotten, because flavors need some stability even if the consequences of those flavors alter.

Therefore the aim of the research described here is to investigate directly whether the learning of odor-taste associations does affect the responses of orbitofrontal cortex neurons, by teaching the monkey one odor-taste association in an olfactory discrimination task and then investigating during recording from orbitofrontal cortex neurons whether the odor to which the neuron responds alters or reverses when the pairing between the odor and the taste is reversed in the reversal of an olfactory discrimination task. This will show directly whether the odor to which an orbitofrontal cortex neuron responds is affected by the taste with which it is paired. If so, it is likely that this learned association takes place in the orbitofrontal cortex, for this is where in primates the olfactory and taste pathways show major convergence (Rolls 1995b; Rolls and Baylis 1994), although modification at an earlier stage of olfactory processing, perhaps by back-projections from the orbitofrontal cortex, would still be a possibility to be investigated. An important part of the design of the experiments was to train the monkeys on both olfactory-taste and visual-taste discrimination tasks, so that it would be possible to test whether olfactory-taste associations in primates reverse as completely and rapidly as do visual-taste associations, which can occur on one trial. In rats, odor-taste (or at least, odor-food) association reversal learning may not be very flexible, in that it is not fast, and may not reflect the acquisition of a reversal learning set (Reid and Morris 1993).

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, 1994), on taste and olfaction and their disorders (Rolls 1995b), on emotion (Rolls 1990, 1995a), and on the causes of the emotional, social, 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, 1988; Rolls 1995b), 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 cortical region that includes the secondary taste cortex, and in the

primary taste cortex in the frontal operculum and rostral insula, of three behaving cynomolgus macaques (*Macaca fascicularis*) weighing 3.2–4.0 kg. The 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 approved by the Society for Neuroscience, and were licensed under the UK Animals (Scientific Procedures) Act 1986. The monkey was fed on return to its home cage and was allowed access to water ad libitum. Glass-coated tungsten microelectrodes were constructed in the manner of Merrill and Ainsworth (1972) without the platinum plating. A computer (DEC Microvax II) ran fully automatically the olfactory and visual discrimination reversal tasks, and collected spike arrival times and displayed and saved peristimulus time histograms, rastergrams, and summary statistics. We ensured that recordings were from only a single cell by continuously monitoring the interspike interval to make sure that intervals of <2 ms were not seen, and by continuously monitoring the complete waveform of the recorded action potentials with the use of an analog delay line.

Localization of recording sites

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

Visual and olfactory discrimination tasks

Monkeys were trained in olfactory and visual discrimination tasks and their reversal. The olfactory discrimination task was as follows. 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 polyvinyl chloride tubes via a glass manifold. These tubes were linked to a series of solenoid valves operated by transistor-transistor logic pulses generated by the computer. The opening of one of these sound-muffled 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 polytetrafluoroethylene 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.

A cue tone started 500 ms before delivery of an odorant, and stopped when the odorant delivery started on each trial at time zero. The odorants were delivered in a computer-generated random sequence, subject to the constraint that not more than three trials of the same type could occur in succession. The odor duration was 1,000 ms. In the go/no go olfactory discrimination task the monkey could lick a tube in front of its mouth when one odorant (the S+) was delivered to obtain a rewarding sweet-tasting solution (10% sucrose or aspartame, both odorless), and had to refrain from licking the tube when the other odorant (the S−) was delivered to avoid obtaining a drop of aversive saline. The odorants used for the two-odor discrimination reversal task were amyl acetate and cineole, chosen because of their perceptual distinctiveness. Reward (or saline) was available throughout the 1,000-ms odor delivery, and for 500 ms after this in case the monkey had already initiated a lick. This period was sufficient for the monkey to obtain two to three licks of the sweet reward solution if the first lick was made quickly, and thus resulted in the monkey sniffing in at the termination of the tone, to sample 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 activity of the isolated cell and the monkey's lick responses were saved as peristimulus rastergrams in series of 20 trials. The mean response of the cell to each stimulus was displayed on-line at the end of each series. If a cell discriminated between the olfactory stimuli in its responses, and adequate ($>85\%$ correct) behavioral discrimination was achieved by the monkey over a number of series, then the task was reversed. The reversal of the task occurred by changing one parameter in the computer driven task, which switched the taste reward associations of the olfactory stimuli. No cues were given before or at the time of the reversal. After reversal of the task, the activity of the neuron and the behavioral responses of the monkey were recorded in the same manner.

The visual discrimination task operated similarly except as follows. Two visual stimuli were used, a triangle and a square presented on a video monitor placed directly in front of the monkey. The stimuli were equiluminant, had the same area, and there was no change of overall luminance when a discriminative stimulus appeared. The stimuli were presented in a pseudorandom sequence as above.

Statistical analyses

The mean firing rate of the cell's response to each trial was calculated from the number of spikes falling in a time window occurring after the stimulus onset. In the olfactory discrimination a 1,000-ms time window was used, beginning 200 ms after the onset of the odorant delivery. This enabled the capture of most of the olfactory response, which was typically of longer latency and duration than visual responses in the task. A 500-ms time window, beginning 100 ms after the onset of the stimulus presentation, was used for calculating the responses of visual cells during the visual discrimination task. The mean response to the stimuli over series of 20 trials ($\sim$10 trials of each stimulus) is plotted in spikes/s in the figures below. The neurophysiological data are compared with the behavioral performance of the monkey to the task, calculated from the number of correct responses and the number of errors of omission and commission during each series of 20 trials.

Analysis of the neuron's response to the stimuli before and after reversal was used to determine whether there was a significant change in activity after reversal of the task. This was shown by a significant interaction in a two-way analysis of variance (ANOVA) in which the two stimuli were one condition, and before and after reversal was the other.

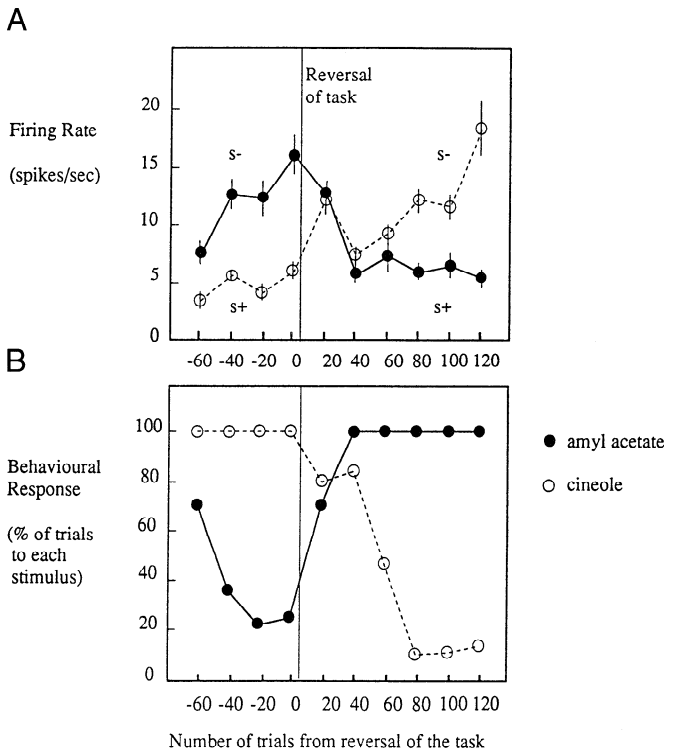

FIG. 1. *A*: activity of a single orbitofrontal olfactory neuron during the performance of a 2-odor olfactory discrimination task and its reversal. Each point represents the mean poststimulus activity of the neuron to ~10 trials of the different odorants. The standard errors of these responses are shown. The odorants were amyl acetate (initially S−) and cineole (initially S+). After 80 trials of the task the reward associations of the stimuli were reversed. This neuron reversed its responses to the odorants after the task reversal. *B*: behavioral responses of the monkey during the performance of the olfactory discrimination task shown in *A*. The number of lick responses to each odorant is plotted as a percentage of the number of trials to that odorant in a block of 20 trials of the task.

RESULTS

Overview

It was possible to replicate the experiment of olfactory discrimination reversal while analyzing the activity of a single orbitofrontal olfactory neuron 28 times on 28 different neurons. Of these 28 neurons, 19 changed their responses in relation to the reversal of the olfactory discrimination task. In the comparison study it was found that 16 of 17 visual neurons changed their responses during the visual discrimination reversal task, and that neuronal reversal that occurred rapidly was typical of the visual responses. The neurons were located in both medial and lateral regions of the orbitofrontal cortex.

Reversal responses to the olfactory discrimination task

Figure 1*A* illustrates the activity of an orbitofrontal olfactory neuron during performance of the olfactory discrimination reversal task. Each point represents the mean neuronal activity over ~10 trials to each stimulus, together with its standard error. The neuron responded differentially to the two odorants, firing before reversal at ~12 spikes/s to the negatively reinforced odorant amyl acetate, yet not responding well (5 spikes/s) to the odorant cineole, which was rewarded. (The mean spontaneous firing rate of the neuron was 2.3 spikes/s.) The behavioral responses of the monkey to the odorants are illustrated in Fig. 1*B*. After 80 trials, the reward association of the odorants was reversed so that the amyl acetate now became rewarded and the cineole negatively reinforced. The monkey behaviorally reversed its responses to the stimuli over the following 60 trials, with few errors of omission (no response to the new S+) 40 trials after the reversal and few errors of commission (a lick response to the new S−) 80 trials after the reversal. The neuron initially extinguished its differential responses to the olfactory stimuli, with this change in neuronal response evident during postreversal trials 1–20 (for the new S−). By the fourth postreversal block of trials (i.e., postreversal trials 60–80) the neuron showed significant reversal in its neuronal response, with the neuron now again responding more to the S− (which was the opposite odor from the prereversal S−) than to the new S+. This difference continued to develop. This neuron therefore showed full neuronal reversal during the olfactory discrimination reversal task. A significant interaction effect was obtained on a two-way ANOVA [$F(1,157) = 118$, $P \ll 0.01$].

Figure 2 illustrates in peristimulus time histogram and rastergram form the responses of one of these reversing cells. The responses of the cell to individual trials of the odorants are shown as rasters beneath the peristimulus time histogram of the response. The neuron responded with a typical latency of between 100 and 200 ms from the onset of stimulus delivery. Before reversal (Fig. 2, *A* and *B*), the neuron responded to the odorant amyl acetate, which was associated with the sweet solution (S+), but had only moderate responses to the odorant cineole, associated with saline (S−). After reversal of the taste associations of the odors (Fig. 2, *C* and *D*), the responses to the odorant amyl acetate (now associated with saline) decreased relative to the prereversal responses, and the neuron responded strongly to the odorant cineole, which was now associated with the sweet solution (S+).

Full neuronal reversal to the olfactory discrimination task was seen in 7 of the 28 neurons tested during behavioral reversal to the olfactory task.

Extinction responses in the reversal of the olfactory discrimination task

Twelve neurons altered their activity when the reinforcement contingencies changed in the olfactory reversal task, but instead of fully reversing their responses, these neurons stopped responding differentially to the discriminative olfactory stimuli. These neurons may be described as having conditional differential responses in the task, in that they responded differentially to the discriminative stimuli conditional on one of the physical stimuli being S+ and the other S−.

Figure 3 illustrates the response of one such neuron in the reversal of the olfactory discrimination task. The neuron responded well before the reversal to the rewarded odorant, cineole, but not to the negatively reinforced odorant, amyl acetate. After reversal the monkey reversed its behavior rapidly (to the former S− within 20 trials, and to the former S+ within 40 trials). The neuronal response to the new rewarded odorant, amyl acetate, was increased, but the response to the cineole odorant remained unchanged from the

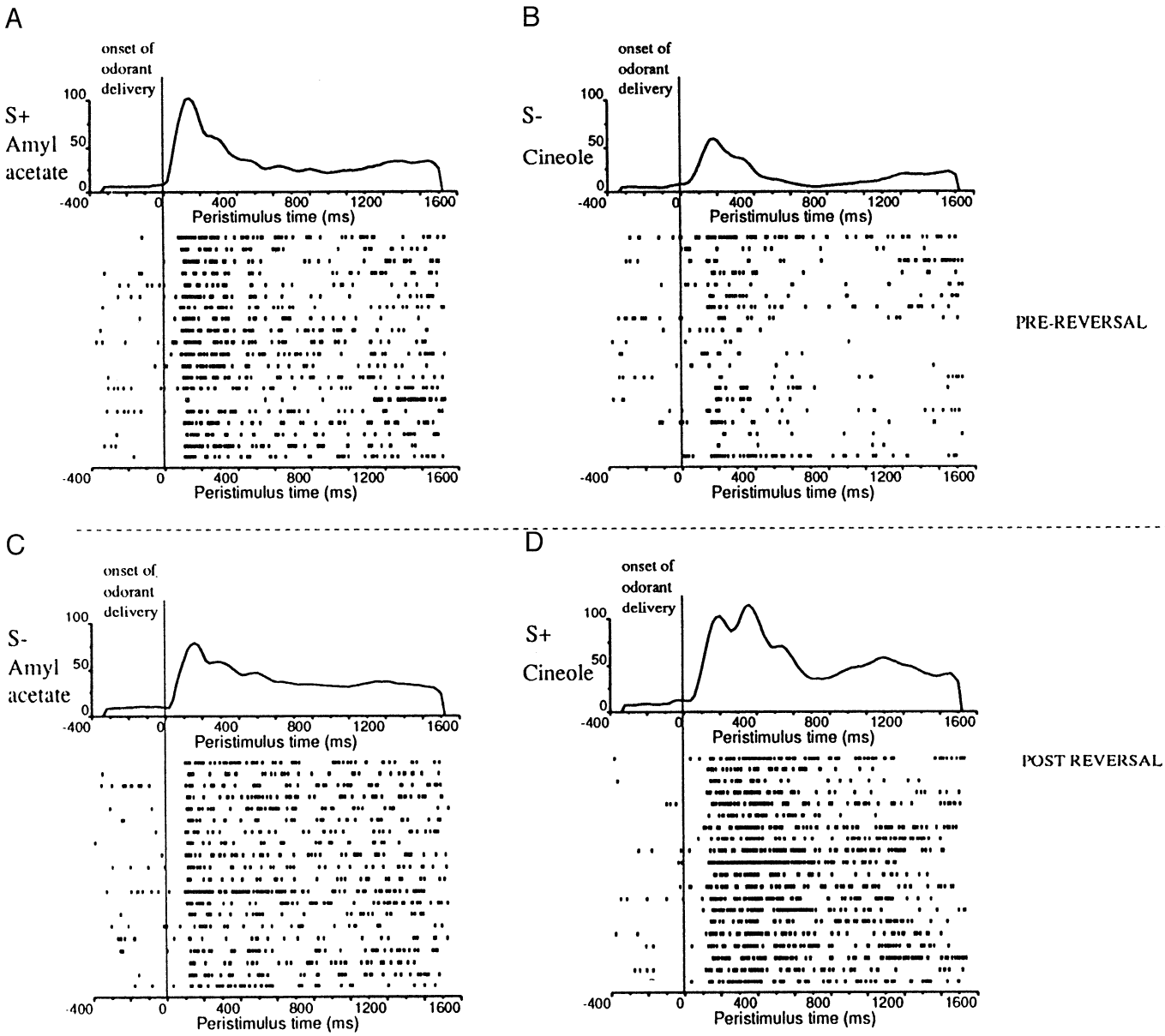

FIG. 2. *A–D*: rastergrams and peristimulus time histograms of the activity of a single orbitofrontal olfactory neuron to the odorants amyl acetate and cineole before (*A* and *B*) the reversal of the task and after (*C* and *D*) the behavioral learning of the reversed stimulus associations. S+ denotes that the odorant was associated with the sweet tasting solution. S− denotes that the odorant was associated with saline solution.

prereversal level. As a result the neuron responded to the odorants after reversal, but did not differentiate between the stimuli after reversal. In this sense, there was an extinction of the differential response of the neuron after the reversal. There was a significant interaction effect shown on a two-way ANOVA for before and after reversal, by odorant [$F(1,176) = 31.75$, $P \ll 0.01$].

Of the 28 olfactory neurons in this study, 12 showed this conditional differential effect. These neurons were divided into two groups, depending on whether the extinction of the differential response was due to an increase or decrease in the response to one of the odorants. In 5 of 12 cases the response to one odorant was increased to the level of the other, and in 7 of 12 cases the response to one odorant was decreased to the level of the other.

Comparison of the neuronal and behavioral changes to the olfactory stimuli

To elucidate the relationship between the time courses of neuronal and behavioral changes during the reversal, the numbers of trials following the reversal of the contingencies for the neuron and for the behavior to reverse are shown in Fig. 4. Because the number of trials to stop incorrect responses after the reversal (errors of commission) was often not the same as the number of trials to start correct responses (errors of omission), and these aspects of the reversal did not always evolve together, separate points indicate these two measures in Fig. 4. It was possible to show numbers of trials to the change after contingency reversal for 19 cases from the 17 cells that altered their responses during the

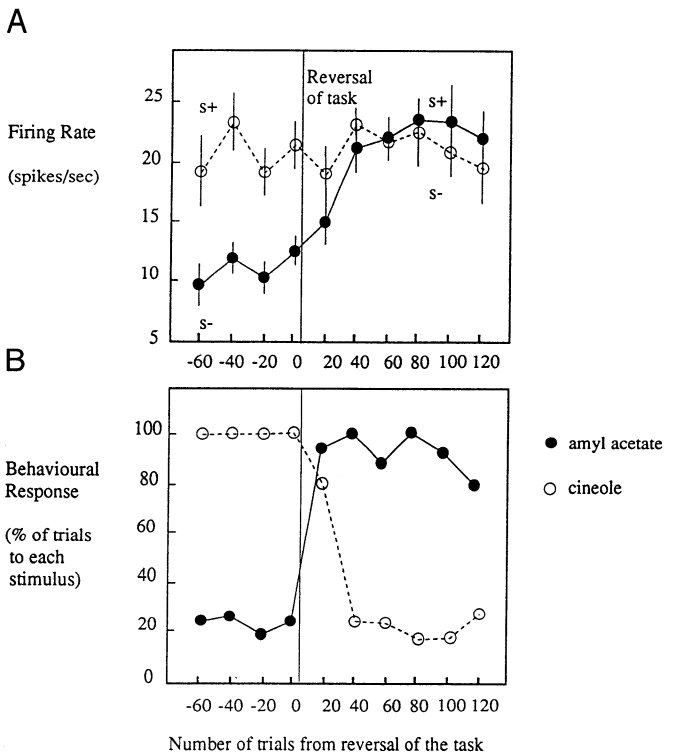

FIG. 3. *A* and *B*: activity of an olfactory neuron showing the conditional differential response to reversal of the discrimination task. The conventions are the same as for Fig. 1*A*. *B*: behavioral response of the monkey during the task.

reversal. (These were selected on the basis of having clearly defined times for both the neuronal and behavioral change after the contingency was altered. The criterion for neuronal change was the first set of 4 trials after which the neuronal response remained significantly different from its precontingency reversal level. The criterion for behavioral reversal was 85% correct performance.) In nine cases there was a concordance between the neuronal and behavioral change: the change in behavioral and neuronal responses occurred within the first 20 trials in six of these cases, and between 20 and 40 trials for one of these cases. In another eight cases, the change in the neuronal response to the odorant preceded the behavioral change in response by $\geq$20 trials (shown below and to the right of the diagonal reference line in Fig. 4). In two cases the neuronal change followed the behavioral change to the task odorant by >20 trials. These data show that in the majority of cases the neuronal change preceded or occurred at about the same time as the behavioral reversal, but that for two of these neurons the response persisted after the behavior had reversed.

Responses to odorants independent of reinforcement value

Further evidence for stability in the responses of some orbitofrontal olfactory neurons even when reinforcement contingencies changed was that some neurons were unaffected in the odor to which they responded when the reinforcement association of that odor changed. An example of such a neuron is shown in Fig. 5. The neuron responded differentially to the odorants, but did not change its relative responses to the odorants after reversal of the task. Before reversal the neuron responded more to the positively reinforced odorant cineole than to the saline-associated odorant amyl acetate. The monkey altered its behavior to the task within 40 trials after reversal of the reinforcement contingencies, yet this did not affect the preferential responses of the cell to cineole, even though after reversal the cineole became associated with saline. This neuron therefore encoded the sensory qualities of the stimuli and not the associated reward value. In a two-way ANOVA there was no significant interaction [$F(1,120) = 0.47$, $P = 0.49$], but in a one-way ANOVA there was a clear differential response between the stimuli [$F(1,120) = 62.14$, $P \ll 0.01$].

Of the 28 olfactory neurons with differential responses in

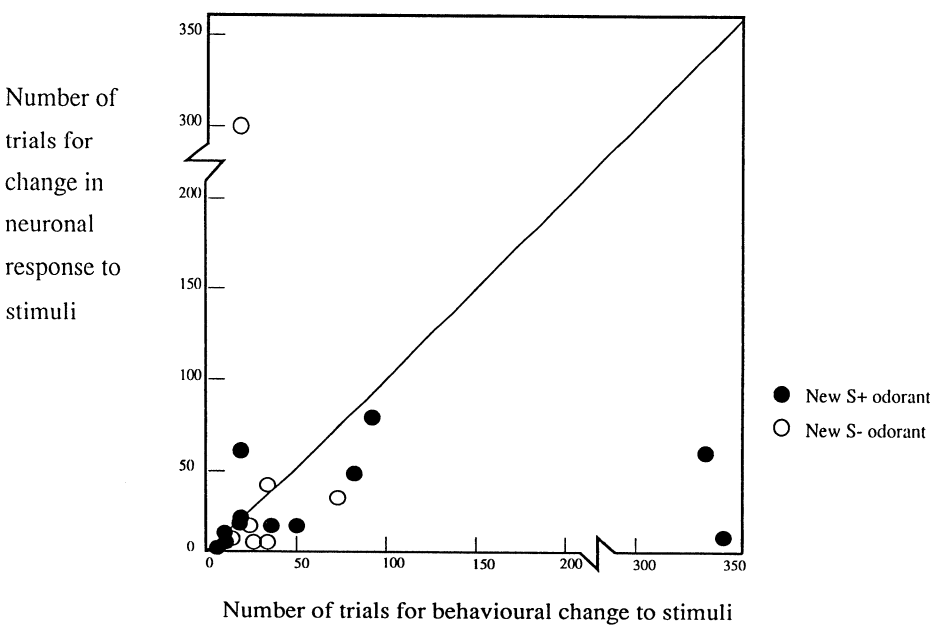

FIG. 4. Relationship between the number of trials taken to behaviorally change the response to odorant stimuli and the number of trials for the neuron to significantly change its responses to the same stimulus after task reversal. A reference line is given for when these are equal.

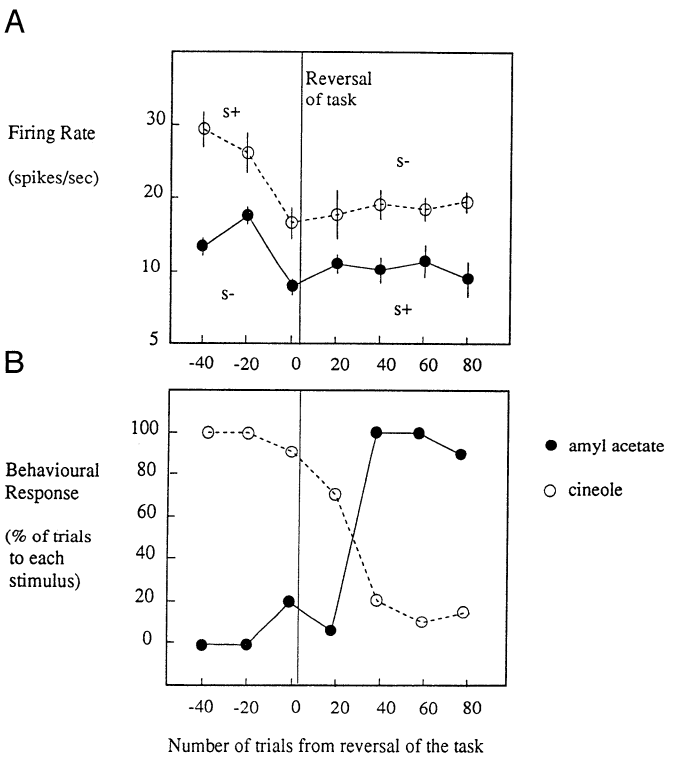

FIG. 5. *A* and *B*: activity of a differentially responsive olfactory neuron, whose responses to the odorants are unaffected by changes in the reinforcement value of the stimuli. This occurred despite a good behavioral reversal by the monkey (*B*).

the olfactory discrimination task in this study, 9 did not change their responses after the reversal of the olfactory discrimination task.

Neuronal responses in the visual discrimination task

Orbitofrontal visual neurons were examined for responses to a visual discrimination reversal task in the manner of the olfactory reversal experiments. The most common effect seen in neurons that responded differentially to the images (a triangle and a square) was a very rapid neuronal reversal of responses to the visual stimuli after the reversal of the taste reward associations of the visual stimuli. Figure 6 illustrates the responses of a visual cell to the task. Before reversal the neuron responded more to the reward associated stimulus, the square, but poorly to the triangle. Reversal of the stimulus associations resulted in a rapid behavioral learning of the new reinforcement contingencies. This was accompanied by an equally rapid change in the neuronal responses to the stimuli, so that the cell now responded to the triangle, associated with reward, but not to the square, which was now negatively reinforced. There was a significant interaction effect on a two-way ANOVA where one condition was before and after reversal and the other condition was the stimulus images [$F(1,156) = 134.6$, $P < 0.01$].

Figure 7 illustrates the activity of one of these rapidly reversing visual neurons during the visual discrimination reversal task, showing the neuronal responses separately for every trial. Before the task reversal, the neuron responded more to the reward-associated stimulus, a square. When the task was reversed, the next presentation of the square elicited the same neuronal response, but was associated this time with the taste of saline. The monkey continued to lick to the presentation of the square (now associated with saline) until trial 8 after the task reversal, but began to lick to the triangle on trial 6 after reversal (that is, after 3 errors of commission and 3 of omission). The neuronal response to the square decreased after the first error of commission, indicating one-trial learning at the level of the single neuron of the new taste association of this visual stimulus. This start of the neuronal reversal was clear before the reversal became clear in the behavior of the monkey.

Of 17 visual neurons examined in this task, full neuronal reversal was seen in 12 cases, with 4 other neurons showing the conditional differential effect (extinction) described above for olfactory cells and by Thorpe et al. (1983) for visual cells. One visual cell did not change its responses to the stimuli during the visual discrimination reversal.

Comparison of the neuronal and behavioral changes to the visual stimuli

In the manner of Fig. 4, the number of trials by which a change in the neuronal response to a stimulus was found was plotted against the number of trials for behavioral reversal in the visual reversal task. This was possible for 30 cases and is shown in Fig. 8. In 24 cases, both the neuronal and behavioral changes took place within the first 20 trials following reversal of the contingencies. For 23 cases, the change in the neuronal response preceded or occurred simultaneously with the change in the behavioral responses of the monkey to the new reinforcement contingencies. When compared

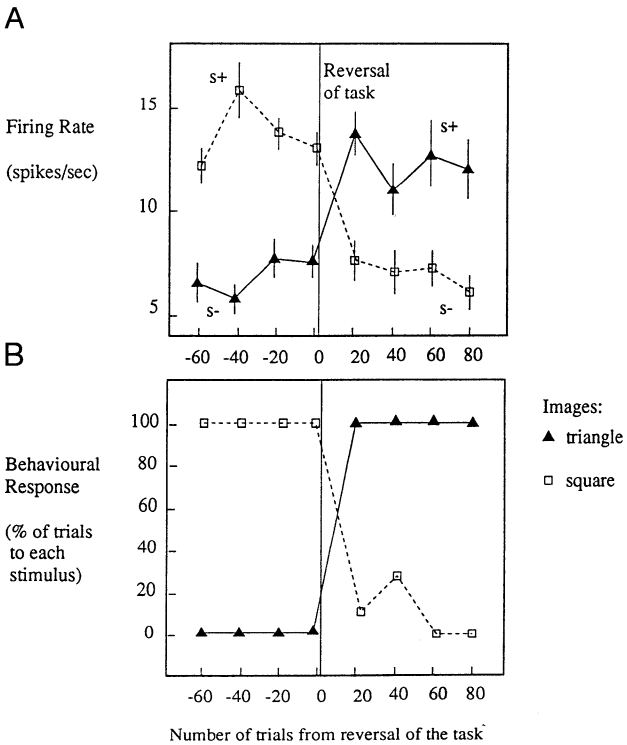

FIG. 6. *A* and *B*: activity of an orbitofrontal visual neuron during performance of a visual discrimination task and its reversal. Stimuli were a triangle and a square presented on a video monitor. The behavioral response of the monkey to the task is plotted in *B*. Conventions are the same as for Fig. 1.

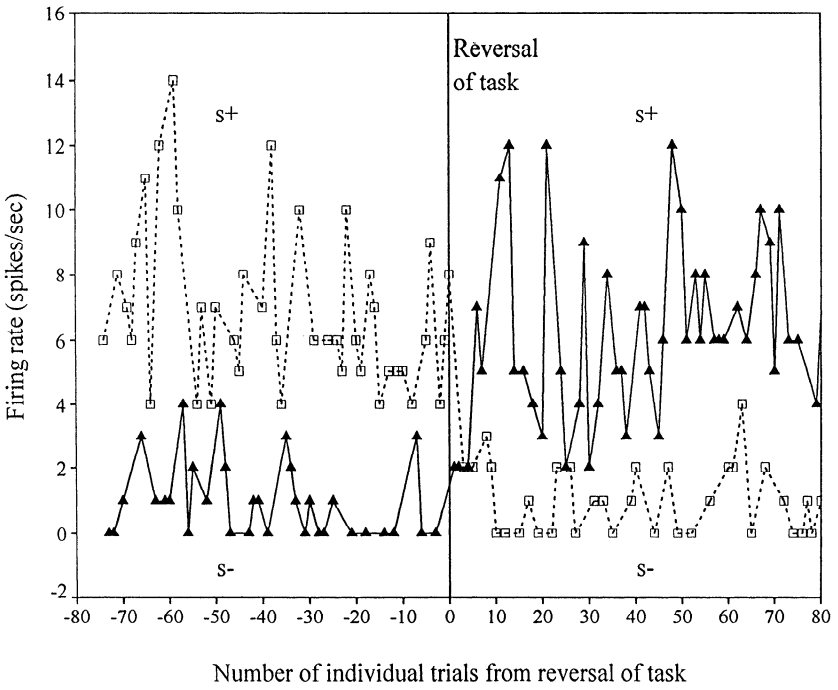

FIG. 7. Activity of a visual neuron during the visual discrimination reversal task, illustrating a rapid reversal of the neuronal responses after the task reversal. The responses of the neuron are shown separately for each individual trial.

with the data from the olfactory reversal experiments, it is evident that both the neuronal and behavioral learning of the reversal are considerably more rapid for the visual task than for the olfactory task. (In 6 of 19 cases (32%) illustrated for the olfactory neurons, both the behavioral and neuronal changes occurred within 20 trials after task reversal, compared with 23 of 30 (77%) of the cases for the visual reversal.) The data support the findings of Thorpe et al. (1983) that a population of orbitofrontal cortex visual neurons exists that shows very rapid changes in responses to the visual stimuli when the taste reinforcement association of the visual stimuli is changed.

Summary of neuronal population results

Table 1 summarizes the results for all the neurons in this investigation. Although a majority of the olfactory neurons was affected by the olfactory discrimination reversal, the most common change for olfactory neurons was extinction of the differential activity to the discriminative stimuli following reversal. For visual neurons, by far the most common effect produced by reversal of the reinforcement contingencies was full reversal of the differential neuronal activity. Statistical analysis showed that the difference between the olfactory and visual neurons in these respects was significant ($\chi^2 = 9.6$, df = 2, $P < 0.01$).

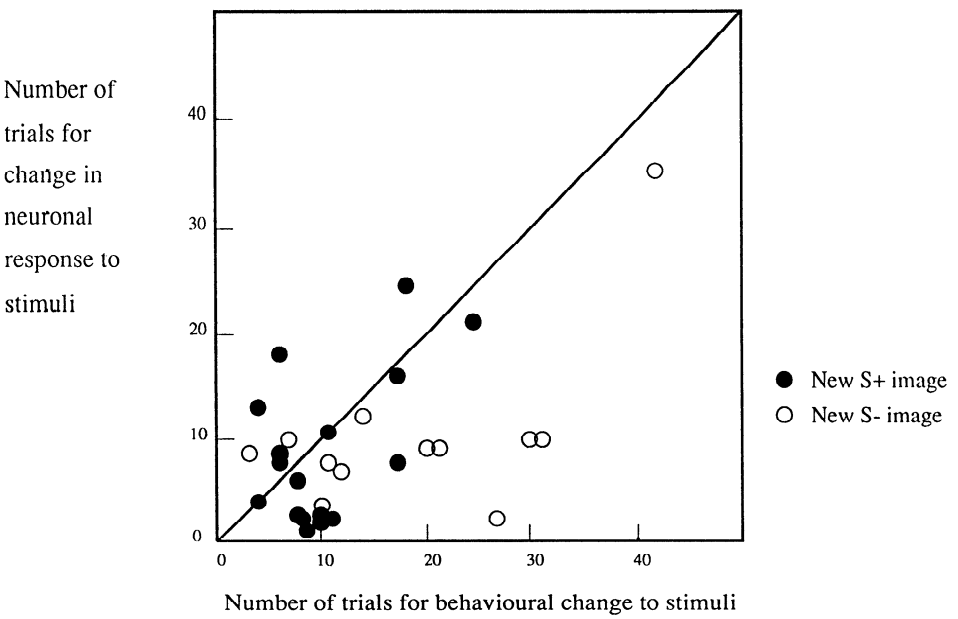

FIG. 8. Relationship between the behavioral change in response to the images and the neuronal changes activity to the images after reversal of the visual discrimination task.

TABLE 1. *Number and proportion of orbitofrontal cortex cells showing different types of modification during olfactory or visual discrimination reversal*

	Olfactory Cells		Visual Cells	
	N	Percent	*N*	Percent
Reversal	7	25.0	12	70.6
Extinction	12	42.9	4	23.5
No change	9	32.1	1	5.9
Total	28	100	17	100

Another difference between the visual and olfactory neurons was that whereas the visual neurons typically showed very rapid changes, within one to a few trials of the reversal of the reinforcement contingencies, the olfactory neurons usually took much longer to show any change (see Fig. 4), and when this change did occur, it was generally extinction, and even in cases when neuronal olfactory reversal was found, this was usually preceded by a period of nondifferential responding (extinction), as shown for example in Fig. 1.

Differences in the visual and olfactory behavioral reversal time courses were also found (cf. Figs. 4 and 6). The behavioral reversal of the visual discrimination was typically very rapid, frequently in several trials (mean 14 trials), indicating the acquisition of a reversal learning set for the visual reversal. In the case of the olfactory reversal task, even though this was being performed by the same monkeys, the behavioral reversal took much longer, with often 40–60 or many more trials (mean 75 trials) being needed for the behavioral reversal in the olfactory discrimination task. This difference was statistically significant ($t = 2.76$, df = 58, $P < 0.008$).

Location of neurons

Figure 9 shows the position of the neurons in this study, reconstructed from three subjects, but shown here in their relative positions on one hemisphere. The visually responsive neurons are shown as triangles, olfactory neurons as circles. The symbols are filled according to the response of the cell in the reversal task. The visually responsive cells in this study were generally located more laterally than the olfactory cells, a finding consistent with the anatomic inputs to orbitofrontal cortex, and confirming the findings of Rolls and Baylis (1994). Barbas (1988) showed that area 12 in the caudolateral orbitofrontal region receives direct inputs from the temporal lobe visual cortices. Price et al. (1991), Morecraft et al. (1992), and Barbas (1993) have all demonstrated direct inputs from primary olfactory cortex predominantly into area 13 of the central part of the orbitofrontal cortex. Although the olfactory cells tended to be found more medially in the orbitofrontal cortex than the visual cells (see Fig. 9 and Rolls and Baylis 1994, Fig. 15), there was no segregation apparent on the basis of whether or not the cells reversed (see Fig. 9).

DISCUSSION

Behavioral performance

The computer-driven tasks enabled the controlled delivery of stimulus and reinforcement in the absence of other cues. The study showed that very rapid behavioral reversal in the visual discrimination task occurred, and that the behavior in the olfactory discrimination task took much longer to reverse than in the visual discrimination task even for very experienced monkeys. This behavioral aspect of the reversal is consistent with findings in the rat, for although rats learn olfactory discriminations quickly (Eichenbaum and Otto 1993; Eichenbaum et al. 1986; Nigrosh et al. 1975; Slotnick and Katz 1974), they do not reverse them quickly, and do not appear to acquire olfactory reversal learning sets (Reid and Morris 1993).

Neuronal responses in the olfactory discrimination task

This study provides firm evidence that the responses of some orbitofrontal olfactory neurons can have their tuning influenced by inputs from another modality, in this case by taste inputs associated with the olfactory stimuli. Thus the representation of olfactory stimuli in the orbitofrontal cortex can be shaped by the taste inputs with which the olfactory stimuli are associated. A prior indication of this, that 35% of orbitofrontal olfactory neurons tend to categorize odors according to the taste with which they are associated (Critchley and Rolls 1996a), has been confirmed here by showing that the responses of some olfactory neurons alter when the taste associated with the odor is altered during the reversal.

Not all the olfactory neurons investigated here showed any change in their tuning when the taste reinforcement contingencies were reversed. This is consistent with the finding that 65% of the olfactory neurons investigated by Critchley and Rolls (1996a) did not appear to categorize the olfactory stimuli according to the taste with which they are associated. Such olfactory neurons responded independently of the reward association. Together, these findings show that the representation of olfactory information in the orbitofrontal cortex includes some neurons ("channels") that operate independently of reinforcement association, and taste. These other olfactory neurons can thus convey information about what olfactory stimuli are present, independently of whether they are rewarding or not.

The modification of the responses of some olfactory neurons by the reward value of the stimulus may occur as a result of convergence of olfactory and taste information onto the same neurons. The presence of taste-responsive neurons within the orbitofrontal cortex (Rolls et al. 1990), and the fact that some of them can also be activated by olfactory stimuli (Rolls and Baylis 1994), supports this possibility. In the study of Rolls and Baylis (1994), it was shown that converging information from these modalities often results in cross-modal correspondence. For example, some neurons responded to the same food in more than one modality, and some neurons responded to sweet taste and fruit odor, whereas other neurons responded to salt taste and salmon odor. Such specific encoding of foods is likely to arise as a result of the type of associative learning between olfaction and taste described in this study. The particular model we propose is that some neurons in this region are unconditionally driven by taste (that is, through nonmodifiable synapses), and that the same neurons receive olfactory inputs through modifiable synapses that learn by a modified Hebb

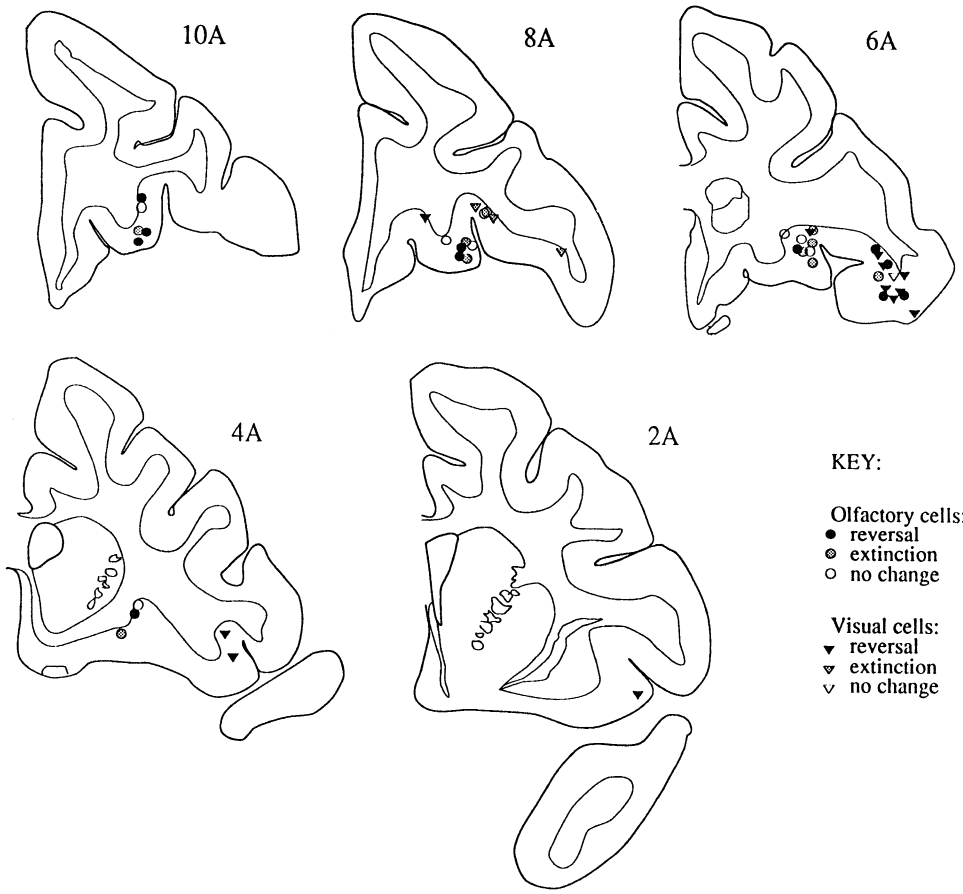

FIG. 9. Localization of neurons in this study. Distances are given in mm anterior to the anterior sphenoidal process. Triangles: visual cells. Circles: olfactory cells.

(associative) rule, thus implementing a pattern associator that can learn but also unlearn or reverse rapidly when the correlation between the olfactory and the taste inputs reverses (see, e.g., Rolls and Treves 1990).

The present study indicates that although the responses of some orbitofrontal olfactory neurons reverse, this reversal is not very rapid, and that the majority of the neurons showing a change show only extinction of the formerly differential response. The latter type of neuron would be useful for a system that learns reversal, for one population of such neurons could carry information about which olfactory stimulus is associated with reward when the discrimination task is run before reversal, whereas another population might only encode for the reward-associated olfactory stimulus after reversal. Such a system has been proposed to provide the basis for visual discrimination reversal in the orbitofrontal cortex (Thorpe et al. 1983), in which some visual neurons reverse, whereas others just extinguish, during behavioral visual discrimination reversal.

Comparison of neuronal activity to olfactory and visual reversal tasks

The visual cells in this study could reliably differentiate between the sight of a triangle and a square when differentially rewarded in this task. The reversal of the reward associations of the stimuli produced not only a rapid behavioral learning of the new reward associations, but also produced a reversal in the responses of 70% of the neurons to the visual stimuli. This tendency of neurons to fully reflect the reinforcement value of visual stimuli contrasts with the responses of olfactory neurons to task reversal. An explanation for this may be that objects in the visual environment may have very changeable reinforcement values. Although making appropriate behavioral response to ones environment depends greatly on the discrimination between stimuli of different reinforcement values, these must constantly be reevaluated and relearned for social, emotional, and motivational behavior to remain appropriate. Visual stimuli that require the rapid relearning of reinforcement contingencies need not be objects, familiar or otherwise, but gestures, colors, or shapes might convey reinforcement meaning (Rolls 1994; Thorpe et al. 1983). Convergence of taste and visual information occurs in the orbitofrontal cortex and can lead to cross-modal representation of foods (Rolls and Baylis 1994; Thorpe et al. 1983). The responses of at least a proportion of these food-selective visual neurons are able to reverse during behavioral reversal of visual discrimination tasks (Thorpe et al. 1983). This implies that the visual identification of foods serves as a rapidly modifiable, provisional guide to its reinforcement value.

The present study indicates that the responses of olfactory neurons are less flexible to changes in the taste association of the stimuli. This indicates a greater stability, and therefore a more permanent representation, of taste-odor associations. Flavors are derived from the integration of olfactory and taste information about substances placed in the mouth. Flavors are specific to individual foods and as such show con-

stancy of their perceptual quality. They are the ultimate means by which food is differentiated from nonfood, bad food from good food. Contributions from other senses such as the visual system, and even the olfactory system in the absence of taste, indicate the likelihood of a substance being edible, and thereby can serve as guides to appropriate feeding-related behavior. However, the final decision as whether to swallow a potential food rests with its flavor. In a microsmatic animal, where olfaction plays a very minor role in the exploration of the environment, the need for stable associations between odors and tastes for the representation of flavors is very important. The small amount of plasticity in these olfactory taste associations that is described here is needed to incorporate new flavors and allow for exceptional circumstances where odor-taste associations are not constant (such as in the olfactory reversal task). It is also needed to build representations of new flavors, which are formed by consistent pairing between an olfactory and taste component.

The implication of the findings described here is that it is by rapid associative learning by neurons in the orbitofrontal cortex that behavior can alter and even reverse very rapidly when the associations between visual stimuli and primary reinforcers such as taste reverse, and quite rapidly when the associations between olfactory stimuli and primary reinforcers such as taste reverse. Consistent with this, lesions of the orbitofrontal cortex do impair reversal and extinction learning (Butter 1969; Iversen and Mishkin 1970; Jones and Mishkin 1972; Mishkin and Manning 1970). Moreover, the inappropriate social and emotional behavior, and inappropriate food selection, that are produced by orbitofrontal cortex lesions (see INTRODUCTION and Baylis and Gaffan 1991; Butter and Snyder 1972), can all be understood as related to the failure of such a learning system that allows associations between previously neutral (e.g., visual) stimuli and primary reinforcers (e.g., taste) to be rapidly learned, but also rapidly adjusted and rapidly reset when reinforcement contingencies change. It is partly in the latter respect that the orbitofrontal cortex may differ from the amygdala, for although the amygdala is involved in stimulus-reinforcement association learning, it is particularly the ability to rapidly relearn and reset such associations that depends on the orbitofrontal cortex (Rolls 1986, 1990, 1995a). Evidence for this is that it is reversal and extinction, rather than initial acquisition, of stimulus-reinforcement associations that depends more on the orbitofrontal cortex than on the amygdala, and that amygdala neurons show much less propensity to show visual-taste reversal than do orbitofrontal cortex neurons (see Jones and Mishkin 1972; Rolls 1974, 1975, 1990, 1995a; Sanghera et al. 1979; Thorpe et al. 1983). Another factor that may contribute to the importance of the orbitofrontal cortex in primates is that it contains the secondary taste cortex (concerned with processing one important class of primary reinforcer), it contains the higher order olfactory areas (which often convey reinforcing signals, whether learned or unlearned), and it receives an important output of the "what" or "object representation" visual system, from the inferior temporal cortex, which converges onto neurons also activated by primary reinforcers such as taste (Rolls and Baylis 1994; Thorpe et al. 1983). Indeed, it has been suggested that in line with the cortical processing of these modalities performed by this cortical area, and because it may contain more powerful learning mechanisms than the amygdala in terms especially of rapid relearning and adjustment, the orbitofrontal cortex may come in primates to be relatively more important than the amygdala, in the way described (see Rolls 1990, 1992, 1995a).

Finally, the experiments described here provide further evidence on the stimulus-reinforcement associative learning that occurs in the orbitofrontal cortex. The findings emphasize that such learning can be very fast, includes olfactory-to-taste as well as visual-to-taste association learning, and has many of the needed signals for such a role, including inputs that convey information about primary reinforcers as well as about otherwise neutral stimuli such as visual stimuli. Indeed, the series of experiments one of which is described here have been important in the development of the hypothesis that some of the clinical changes seen in patients with damage to the orbitofrontal cortex, including emotional, social, and motivational changes, arise because of damage to such a rapidly modifiable stimulus-reinforcement learning system (Rolls 1990, 1994). In particular, this research led us to use an almost identical visual discrimination reversal and extinction test in such patients, and we found that these patients did have deficits in the reversal and extinction tasks (Rolls et al. 1994), providing further support for the hypothesis that stimulus-reinforcement learning difficulties may provide at least partly the basis for understanding the changes in these patients. In particular, the failure to respond normally to the changing rewards and punishments that are continually exchanged in social situations between humans and other primates appears to be a function performed by the orbitofrontal cortex, both when the rewards are simple, such as taste, as shown here, or more complex, such as facial expression (Hornak et al. 1996) or even instructions about changes to behavior. Indeed, in the study by Hornak et al. (1996), it was shown that patients with orbitofrontal cortex damage are impaired at identifying facial expression (which can be used as a reinforcer), but not at face recognition. The results of these investigations, which were performed in the light of the neurophysiological findings on the orbitofrontal cortex described here and elsewhere, have implications for the rehabilitation of patients with orbitofrontal cortex damage, which are considered elsewhere (Hornak et al. 1996; Rolls et al. 1994).

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