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The Orbitofrontal Cortex: Neuronal Activity in the Behaving Monkey

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Summary. Single unit recording of neurons in the orbitofrontal cortex of the alert rhesus monkey was used to investigate responses to sensory stimulation. 32.4% of the neurons had visual responses that had typical latencies of 100–200 ms, and 9.4% responded to gustatory inputs. Most neurons were selective, in that they responded consistently to some stimuli such as foods or aversive objects, but not to others. In a number of cases the neurons responded selectively to particular foods or aversive stimuli. However, this high selectivity could not be explained by simple sensory features of the stimulus, since the responses of some neurons could be readily reversed if the meaning of the stimulus (i.e. whether it was food or aversive) was changed, even though its physical appearance remained identical. Further, some bimodal neurons received convergent visual and gustatory inputs, with matching selectivity for the same stimulus in both modalities, again suggesting that an explanation in terms of simple sensory features is inadequate.

Neurons were also studied during the performance of tasks known to be disrupted by orbitofrontal lesions, including a go/no go visual discrimination task and its reversal. 8.6% of neurons had differential responses to the two discriminative stimuli in the task, one of which indicated that reward was available and the other saline. Reversing the meaning of the two stimuli showed that whereas some differential units were closely linked to the sensory features of the stimuli, and some to their behavioural significance, others were conditional, in that they would only respond if a particular stimulus was present, and if it was the one being currently rewarded. Other neurons had activity related to the outcome of the animal's response, with some indicating that reinforcement had been received and others, that an error had been made and that a reversal was required.

Thus, neurons in the orbitofrontal cortex possess highly coded information about which stimuli are present, as well as information about the consequences of the animal's own responses. It is suggested that together they may constitute a neuronal mechanism for determining whether particular visual stimuli continue to be associated with reinforcement, as well as providing for the modification of the animal's behavioural responses to such stimuli when those responses are no longer appropriate.

Key words: Orbitofrontal cortex – Reinforcement – Feeding – Visual discrimination – Reversal – Frontal lobe

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Introduction

Frontal lobe damage in both man and animals results in a variety of cognitive, motivational and emotional changes (see Nauta 1971; Fuster 1980). However, the functions disrupted by damage to this region of the brain are still poorly understood. For example, frontal lobe damage in humans has been associated with behavioural perseveration, as seen for example in the Wisconsin Card Sorting Task (Milner 1964), and related problems are seen in monkeys with damage to the orbitofrontal cortex (OFC). However, despite considerable research, it is still not clear why damage to this part of the brain should result in such effects.

To gain an insight into the nature of the neural processes disrupted by frontal lobe damage, recordings were made of neuronal activity in the orbitofrontal cortex of monkeys while they were performing a task of a type known to be disrupted by orbitofrontal lesions, namely, a go/no go visual discrimination task

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with reversals. Orbitofrontal lesions disrupt the performance of a variety of tasks including go/no discriminations (Brutkowski et al. 1963; Lawicka et al. 1966, 1975; Iversen and Mishkin 1970), visual discrimination reversals (Jones and Mishkin 1972; Butter 1969; Iversen and Mishkin 1970), object alternations (Mishkin et al. 1969; Mishkin and Manning 1978), spatial reversals and alternations (Iversen and Mishkin 1970; Mishkin et al. 1969; Butter 1969), and the extinction of previously rewarded responses (Butter et al. 1963; Butter 1969). The impairment in the performance of all these tasks is evident as a failure to inhibit responses to stimuli which have previously been reinforced when such responses become inappropriate. By determining how orbitofrontal neurons respond during the performance of the go/no go visual discrimination task with reversals, which is an example of the sort of task disrupted by orbitofrontal lesions, it may be possible to determine why damage to this area produces such severe impairments in tasks of this form (see Rolls 1975).

A second aim was to determine what sorts of sensory inputs reach the orbitofrontal cortex, and to determine how such sensory inputs are coded. Anatomical studies have shown that the orbitofrontal cortex is a region in which pathways from various sensory areas converge. Firstly, there are major inputs from the visual and auditory cortical association areas in the rostral parts of areas 21 and 22 in the temporal lobe (Chavis and Pandya 1976), as well as from polysensory regions including the temporal pole and possibly the cortex in the superior temporal sulcus (Kuypers et al. 1965; Pandya and Kuypers 1969; Jones 1969; Jones and Powell 1970). Secondly, there are subcortical regions which could provide sensory inputs, including the medial pulvinar (Bos and Benevento 1975; Jacobsen et al. 1978) which could relay visual inputs from the superior colliculus, and the medial magnocellular region of the mediodorsal thalamus which could relay information from sensory association areas in the temporal lobe (Nauta 1972). Thirdly, olfactory inputs could reach the OFC via the mediodorsal thalamus (Benjamin and Jackson 1974; Yarita et al. 1980), via the hypothalamus (Tanabe et al. 1975), or via a recently described direct projection from the region around the prorhinal sulcus (Potter and Nauta 1979).

Thus, there is good anatomical evidence for visual, auditory and olfactory convergence in the OFC, and some neurophysiological evidence supports this, although most of this comes from studies in anaesthetised animals (Benevento et al. 1977). With the exception of some studies on olfactory inputs to OFC (Tanabe et al. 1975; Yarita et al. 1980), virtually nothing is known of the responses of orbitofrontal neurons to sensory inputs in the awake animal. Such studies may well be particularly important in view of the fact that OFC lesions change behavioural responses to food, non-food and aversive visual stimuli (Butter et al. 1968, 1970; Butter and Snyder 1972; Ursin et al. 1969; Butter et al. 1969). For example, after OFC lesions, monkeys select and place in their mouths non-food items as well as foods, and show increased aversion and decreased aggression to emotion-provoking stimuli. For these reasons, it was thought valuable to investigate how neurons in the OFC of the behaving animal respond when such sensory stimuli are presented.

A third purpose behind the present study was to investigate the role of the OFC in the control of feeding, as part of a long term study aimed at determining how different brain areas are involved in feeding. More specifically, since the OFC has efferent connections to the hypothalamus, and is implicated by the lesion evidence in responses to food, it could provide inputs to neurons in the lateral hypothalamus and substantia innominata which have responses associated with the sight of food (Rolls et al. 1976, 1979, 1980; Rolls 1981). For this reason, and in order that neuronal responses in the two areas could be directly compared, the tests used for OFC neurons included those used for hypothalamic neurons. A preliminary report of this work has appeared (Thorpe et al. 1979).

Methods

Recording

Three male rhesus monkeys, weighing 4.0–5.5 kg were implanted under thiopentone sodium anaesthesia with stainless-steel holders on which a Trent-Wells or Kopf adaptor for chronic single-unit recording could be fitted during recording sessions. After 1 or 2 weeks, daily recording sessions were initiated. Single unit activity was recorded using glass-coated tungsten microelectrodes (after Merrill and Ainsworth 1972, but without the platinum plating) while the monkey sat in a primate chair with head restraint to provide recording stability. The electrode was introduced into the brain through a guide tube whose tip was just below the surface of the dura.

The signal from the microelectrode was passed through a FET buffer amplifier mounted on the microdrive, amplified by conventional band-pass filtered amplifiers, and displayed on an oscilloscope. Data were analysed using an on-line PDP-11 computer, which was programmed to produce peristimulus time histograms as a dot display, each time a new trial was presented, or to compute the mean firing rate (and its S.E.) of neurons during stimulus presentations or control periods.

Analysis of Neuronal Responses

The testing procedures were similar to, or developed from those used previously (Rolls et al. 1976, 1979; Sanghera et al. 1979; Rolls et al. 1977). Two main types of testing were used. The first,

"clinical" type of testing was designed to allow analysis of neuronal responses related to feeding, or to the presentation of aversive objects. Various food, non-food and aversive objects were presented and brought towards the animal, and in the case of foods, fed to the animal. Measurements of the firing rate of the neuron were taken in consecutive periods according to the following standard protocol: (1) when the monkey was sitting quietly (spontaneous activity), (2) as the experimenter reached behind a screen to retrieve an object from a tray that was out of the monkey's sight, (3) as the experimenter's arm was gradually brought back into view, (4) as the object was introduced into the monkey's field of view at a distance of about 1 m, (5) as the object was gradually brought towards the monkey, (6) while the object was held close to the monkey's mouth, (7) as the monkey was fed the object (if it was food or delivered saline), and finally (8) as the object was removed. On some trials, the object was removed before the monkey had a chance to taste it. The objects tested included numerous foods such as bananas, peanuts, raisins and other fruits, breakfast cereals, and sweets, as well as a 2 ml syringe from which the monkey was fed blackcurrant juice. There was also a range of neutral stimuli such as gratings and laboratory objects, and aversive stimuli such as a 1 ml syringe from which the monkey was given mildly aversive hypertonic saline to drink.

The sequence of counts used in the standard protocol allowed the orbitofrontal neurons to be grouped into certain classes. For example, neurons with responses confirmed as visual in further testing (see below) responded as soon as the object was shown to the animal (count period 4). Neurons which did not respond in count period 4, but did respond as the object approached the mouth in the latter part of count period 5 and during count period 6, could have activity that was related to behavioural responses such as movement of the mouth. Neurons which responded only after food was in the mouth (i.e. in count period 7) were often found to have gustatory responses. This fixed protocol testing situation was supplemented with interactive "clinical" testing designed to analyse further the responses of the neurons. For example, movement-related responses occurred unconditionally in relation to movements, whether or not feeding was being tested, and gustatory responses to the delivery of glucose solution could be shown to be dependent on the concentration of the fluid in the mouth. Other tests were used to determine whether some neurons had activity related to extinction and reversal of a licking response made by the animal to obtain a fruit juice reward. In these tests, the monkey was initially able to get a 0.2 ml drop of blackcurrant juice each time he licked a tube positioned in front of his mouth. In the extinction test, the delivery of fruit juice was terminated, and neuronal activity measured during the period immediately following in which the monkey was making unrewarded licks. In the reversal test, after an initial period in which the animal received a reward for each lick, the monkey started receiving a small amount of aversive hypertonic saline if licks were made.

The second testing situation was designed to measure accurately the latency of neuronal responses to the presentation of visual stimuli, and during the performance of a go/no go visual discrimination task. A 6 cm diameter electromagnetically operated shutter (Compur 5FS) was positioned in a circular aperture in a screen 30 cm away from the animal, and was opened to reveal visual stimuli. The monkey's fixation could be observed by viewing the monkey through a peephole in the side of the screen. Correct fixation was usually obtained by providing a 0.5 s cue period immediately before the opening of the shutter, during which a 450 Hz tone sounded and a small red light (L.E.D.) mounted just above the shutter came on. In addition, the shutter open time was kept relatively brief (1.5 s), and in the 8.5 s intervals between stimuli the monkey could see only the screen. The latency of the neuronal responses was measured in a peristimulus time histogram relative to the time of opening of the shutter.

This computer-controlled shutter presentation system could be used to measure response latencies to a wide variety of visual stimuli presented through the shutter. It was also used in a go/no go visual discrimination task. In this task, the shutter opened to reveal one of the two stimuli. One of the stimuli indicated that if the monkey licked a tube positioned in front of his mouth, he would obtain a reward of approximately 0.2 ml of fruit juice. The other stimulus indicated that if he licked the tube he would obtain 0.2 ml of aversive hypertonic saline. The monkeys' response latencies, measured from the time the shutter opened to reveal the positive discriminative stimulus to the time of tongue contact with the lick tube were typically 350–450 ms. By licking on the appropriate trials the animal normally obtained between 1500 and 2000 rewards during a 4 h recording session. Several different pairs of discriminative stimuli were used, including a red and green plaque, coloured syringes and vertical and horizontal gratings. The stimuli themselves were mounted on the arms of a rotor which was moved under computer control to bring the appropriate stimulus into position behind the shutter before the start of each trial, according to a pseudo-random sequence.

A reversal of the go/no go visual discrimination was frequently performed in which the meaning of the two discriminanda in the task was reversed, so that the previously rewarded stimulus was now negative and vice versa. All three animals learned to reverse their behavioural responses quickly, so that if they obtained saline for licking to a stimulus which had previously been associated with reward, they subsequently only licked to the previously punished stimulus which now indicated that reward was available.

Localisation of Units

The positions of the neurons recorded in the present study were determined in two ways. First, at the end of every track, X-ray photographs were taken of the frontal and lateral views of the head to determine (to within 0.5 mm) the position of the tip of the recording electrode relative to permanently implanted reference electrodes, whose positions were later determined histologically. Second, at the end of the recording period, lesions were made through the tip of the recording electrode to mark typical units. This was done by passing either anodal or cathodal current of 60–100 μA for 100 s. Following tranquilisation with ketamine and then a lethal i.p. dose of pentobarbitone sodium, the animals were perfused with 0.9% saline followed by formal saline. After equilibration in sucrose-formalin, serial frozen 50 μm brain sections were cut and stained with thionin.

Results

A total of 494 neurons, anatomically verified as lying in the orbitofrontal cortex, was analysed in the present study. 64.7% of the neurons that were comprehensively tested were found to respond in one or more of the testing situations used. In the first part of this results section, neurons with responses to sensory stimulation will be considered. A later section will deal specifically with neuronal responses during the performance of the go/no go visual discrimination task.

Visual Responses

One hundred and sixty units, that is 32.4% of the total population, were classified as having visual re-

sponses. Neurons classified as visual either (a) responded to the presentation of visual stimuli in both the clinical and shutter situations, or (b) showed responses in the shutter situation which were consistent and selective for some stimuli. These neurons were grouped into four classes on the basis of the types of visual stimuli to which they responded.

Non-Selective Visual Responses. Of the 160 neurons with visual responses, 53 (33.1%) had responses which were relatively non-selective in that they would respond to a wide variety of visual stimuli. These neurons did not respond in one of the following situations in which visual stimulation was minimised or excluded: (a) when the shutter opened to reveal only a blank backscreen at the back of the laboratory (blank trials), (b) when it opened to reveal only a white card positioned on the laboratory side of the shutter (external block trials), or (c) if the inside of the shutter was covered by a card, so that the animal could not even see the shutter open (internal block trials). This last procedure allowed neurons which were responding to the noise of the shutter opening to be excluded from the neurons classified as visual.

Selective Visual Responses. Sixty-five of the neurons with visual responses (40.6%) had visual responses which were selective, but were not selective on the basis of whether the stimuli were aversive or food-related. Often, the basis of this selectivity was unclear in that a neuron would consistently respond to a small number of objects that had no clear characteristic in common. However, in other cases, neurons were found which responded selectively to particular classes of stimuli (e.g. faces, novel stimuli, etc.).

Visual Responses to Aversive Stimuli. Sixteen neurons (10% of those with visual responses), responded selectively to aversive visual stimuli. These neurons typically responded to a variety of aversive stimuli which were often physically very different. These stimuli, which all evoked behavioural signs of aversion, included a syringe from which the animal could be fed aversive hypertonic saline, a squeeze bulb which could be used to puff air into the monkey's face, a threat face made by the experimenter, and small model snakes and spiders of the type to which monkeys with orbitofrontal lesions show reduced aversion (Butter and Snyder 1972).

Other neurons apparently responded only to particular aversive stimuli. Examples of the responses of a neuron which was only seen to respond to an aversive saline-containing syringe, and not to other

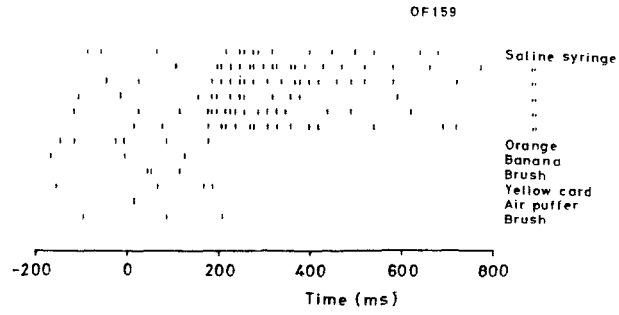

Fig. 1. Responses of a neuron with a visual response which was selective for the sight of a syringe which contained aversive hypertonic saline. Each action potential is indicated by a vertical line in the raster. The visual stimuli were shown at time 0 through a large aperture shutter, and were preceded by a 0.5 s tone to allow prior fixation

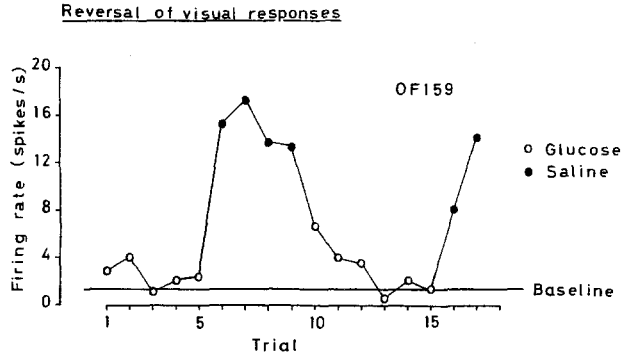

Fig. 2. Effects of alteration of the significance of the stimulus on the responses of the neuron illustrated in Fig. 1. On trials 1–5, no response of the neuron occurred to the sight of a 2 ml syringe from which the monkey had been given orally glucose solution to drink on the previous trial. On trials 6–9, the neuron responded to the sight of the same syringe from which he had been given aversive hypertonic saline to drink on the previous trial. Two more reversals (trials 10–15, and 16–17) were performed. The reversal of the neuron's response when the significance of the same visual stimulus was reversed shows that the responses of the neuron only occurred to the stimulus when it was associated with aversive saline and not when it was associated with glucose reward

aversive stimuli such as a puffer, are shown in Fig. 1. To determine whether the responses of the neuron were based solely on a physical property of the stimulus such as its colour, shape or component spatial frequencies, or whether it depended also on the aversiveness of the stimulus, the aversiveness of the stimulus was altered during the recording session as follows. Figure 2 shows that when the monkey was fed glucose solution from a 2 ml syringe, there was no change of firing rate associated with the presentation (count period 4) of the syringe. Then on trial 5, aversive hypertonic saline was fed to the monkey from the syringe. Note that on this trial there was still

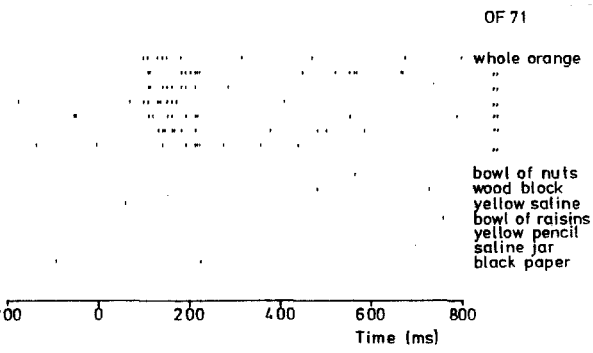

Fig. 3. Visual responses of a neuron which were selective for a particular food. Conventions as in Fig. 1. The neuron responded to the sight of a whole orange, but not to other foods or to control stimuli

no response to the sight of the syringe, as the animal had not yet had an opportunity to discover that the contents of the syringe had been changed. However, by trial 6, the neuron showed a clear response to the presentation of the syringe, from which the animal had just been fed saline, even though the syringe was unchanged in appearance. The neuron responded to the presentation of the syringe on every subsequent trial in the series in which saline was delivered, but gradually ceased to respond to the syringe from trial 9, after which glucose was again available from the syringe. Another reversal is shown after trial 15. It was possible to perform this type of experiment on three of the seven units with responses that were apparently specific for the saline-containing syringe, and it was shown that the neuronal responses of all three units depended on the aversive meaning of the stimuli. This strong dependence on the meaning of the stimulus, rather than its physical characteristics, is clear evidence that at least some neurons in the OFC have visual responses selective for certain classes of aversive stimuli.

Other evidence supporting the hypothesis that these neurons respond selectively to aversive stimuli comes from the finding that some receive convergent sensory inputs from other modalities. For example, one of the neurons which responded only to the sight of a saline-containing syringe, also responded to the taste of saline. Such bimodal responses are described later.

Food-Selective Visual Responses. Twenty-six of the 160 neurons with visual responses (16.25%) showed responses that were selective for food objects. Typically such neurons responded to a variety of different foods, but failed to respond to neutral and aversive stimuli. Since such neurons responded to a variety of physically very different stimuli it was very unlikely that the selectivity of the neuron was due to any one simple physical property such as colour or shape.

A number of these neurons apparently responded to only a few, or even to only one of the large number of foods tested. Figure 3 shows an example of a unit that responded selectively to orange. The unit responded equally well whether the orange was presented in the shutter or during clinical testing. Of the 26 food-selective visual units, 11 (42.3%) had responses that were apparently selective for particular foods. Four neurons had responses selective for orange, 4 for peanuts, 2 for banana, and 1 for raisins. Additional evidence that these neurons code for the presence of a particular food (rather than the presence of a particular pattern of colouration for example) was that 5 of the 11 neurons also had taste responses that were selective for the same food, as described later.

Latency. The latency of the earliest consistent response for all 160 visually responsive units is shown in Fig. 4. The majority responded with latencies between 80 and 200 ms, with a mean value of 152.4 ms (S.E. = 3.97). Interestingly, the group of neurons with non-selective visual responses had a mean latency of 132.3 ms (S.E. = 5.62), a value considerably shorter than either the selective, aversive or food-selective visual units (mean latencies 158.5, 167.5 and 169.2 ms, respectively). In each case, this difference was shown to be statistically significant ($p < 0.01$ using a two-tailed t-test).

Gustatory Responses

Thirty-six orbitofrontal units were classified as having gustatory responses. Thirty of these showed clear responses during feeding which were selective in that they did not occur to all the different types of food and fluids tested. This selectivity made it unlikely that the response was due to any simple mouth movement made during feeding, and this possibility was further excluded by testing whether neurons responded in relation to mouth movements made for example to an empty syringe.

For some of these neurons experiments were performed to investigate the relation between the concentration of the fluid in the mouth and the firing rate of the neuron. An example of a neuron which showed a monotonic increase of firing rate as a function of the concentration of the glucose being fed to the monkey is given in Fig. 5. Similar concentration-response relationships were found in three out of three neurons tested in this way. This finding provided additional evidence that the responses of

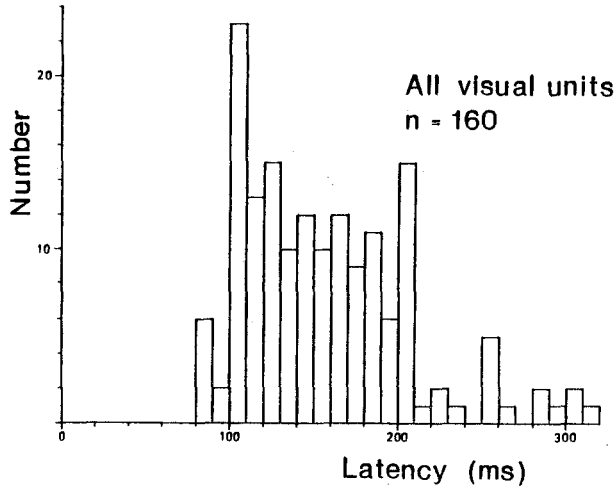

Fig. 4. Response latencies of orbitofrontal neurons with visual responses. The latencies shown are to the earliest consistent change from the prestimulus level (as shown by cumulative sum statistics

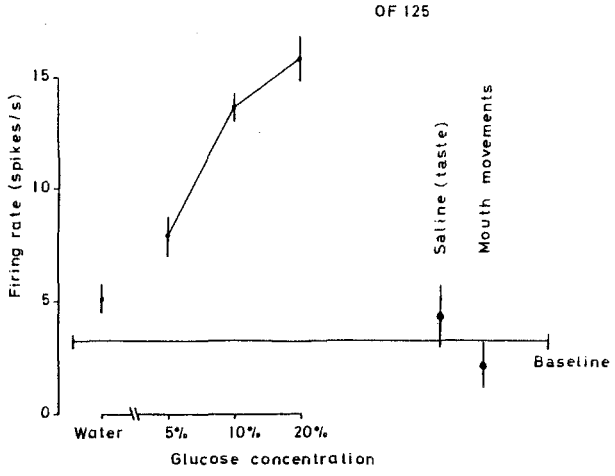

Fig. 5. Concentration-response relation for a neuron with a gustatory response. The firing rate (±SEM) is shown for different concentrations of glucose. No response occurred to the taste of saline or in association with mouth movements. The baseline spontaneous firing rate (±SEM) is also shown

these neurons were related to gustatory inputs and not to movements.

As with visual responses selective for food, a number of neurons were noted with gustatory responses which were only seen to particular foods. Nine such units were seen, with two selective for saline, four selective for peanuts, two selective for orange and one for banana. Six of these also had visual responses and are, therefore, considered in more detail in the section on bimodal responses.

Other Sensory Responses

Although special tests were not performed for responses to stimuli in sensory modalities other than vision and taste, a number of such responses were observed. Seven neurons were noted that responded to auditory but not to visual or gustatory stimulation. Three of these responded to the sound of the shutter opening with latencies of 20, 25 and 40 ms. A small number of other neurons had ill-defined responses to somatosensory stimulation, but generally also responded to stimuli in other modalities, so that it was difficult to rule out the possibility that the response was due to a non-specific arousal effect.

Bimodal Sensory Responses

Of the 160 visually responsive units, 13 also had gustatory responses. Of these 13 bimodal units, eight were selective for food-related stimuli, two for aversive stimuli, and three selective for other types of stimuli. No non-selective visual units were found which also responded to gustatory inputs.

Some of the neurons with bimodal responses had a high degree of correspondence between the inputs in the two modalities. An example is shown in Fig. 6. The first part (Fig. 6a) illustrates that the neuron showed a remarkably specific visual response in the shutter situation to the sight of a whole banana. By contrast no responses were seen to other foods or to simple controls for the colour of the banana. The latency of the visual response was 190 ms. In the second part (Fig. 6b), it is shown that the same neuron also responded vigorously (and independently, as the monkey could not see the banana in this test) to the taste of a banana, but did not respond to the taste of any of the other foods tested. Of the eight neurons with food selective visual responses, four showed specificities for foods presented visually which were matched in the taste modality by a specificity for the same food. No examples were seen of neurons whose selectivities in the visual and gustatory modalities were different.

Of the two bimodal units with visual responses selective for aversive visual stimuli, one showed specificities which corresponded in the two modalities. It responded only to the sight of a saline-containing syringe and only to the taste of saline during clinical testing. The other also responded to the taste of saline, but responded more generally to aversive visual stimuli.

Comparison of the visual response latencies of neurons with bimodal and unimodal responses shows that the bimodal units tend to respond with longer

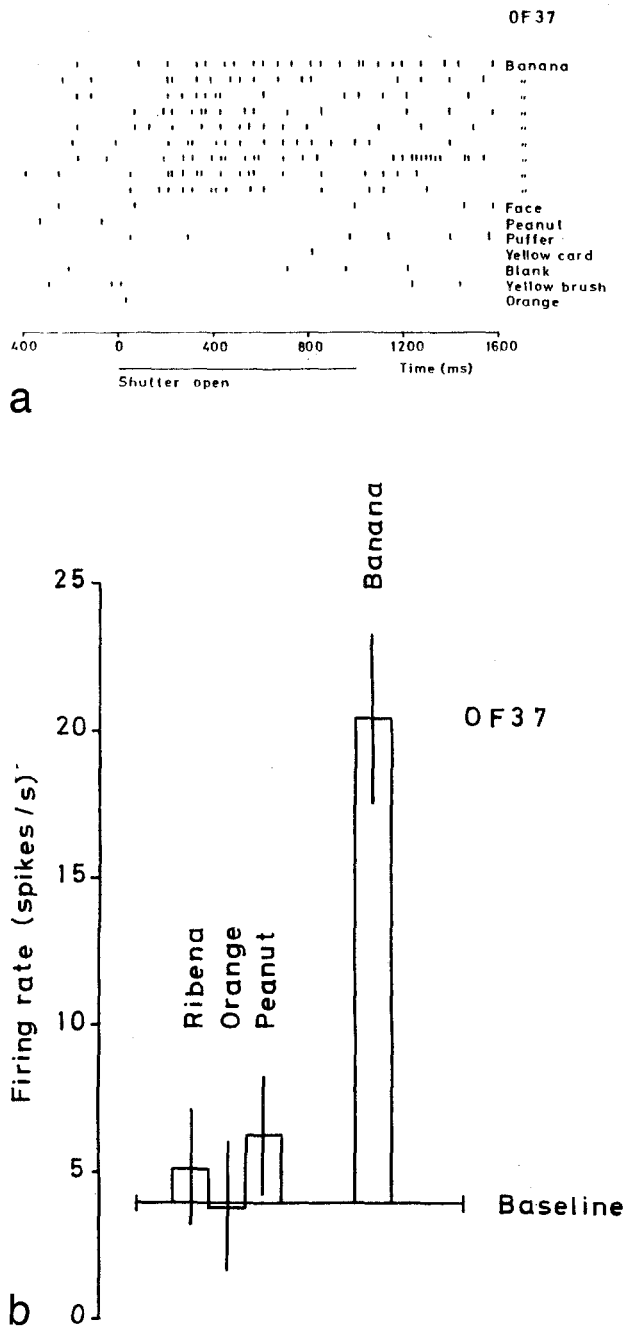

Fig. 6a, b. Responses of a bimodal neuron. **a** The visual responses had a latency of 190 ms and were selective for the sight of a banana. **b** The gustatory responses (measured without showing the food to the monkey, and while the food was in the mouth) were also selective for banana

latencies. The mean latency for all the food-selective visual units with no taste input was 156.1 ms, which was significantly shorter than the visual responses of the bimodal food-selective neurons whose mean latency was 198.7 ms ($p < 0.05$ using a two-tailed t-test).

Responses During Visual Discrimination and Reversal

In this section, neuronal responses during the performance of the visual discrimination task will be described. The total number of cells examined during the performance of the task was 463, of which 219 (or 47.3%) were found to be responsive. Different neurons were found to respond at different times during the performance of the task. For example, 68 neurons were found to respond during the 0.5 s cue period that preceded the opening of the shutter. Such neurons could be responding to the tone cue, the LED cue, or to both. To determine which was the critical event, 18 cells were tested separately with the individual cues, and it was found that the majority (13, or 72.2%) would respond to either cue. This lack of dependence on the modality of the cue, together with the relatively long response latencies (mean = 185.8 ms) suggest that the responses of such neurons are related more generally to task performance, and are not simple, unconditional sensory responses.

Other units (175, or 37.8%) had responses time-locked to the opening of the shutter. For some units, this shutter related activity was clearly related to visual or auditory inputs, and such responses have already been considered in earlier sections. In other cases, it was much less easy to specify the nature of the neuronal response to the shutter opening, and thus little can be said about their functional significance. However, one group of cells merits particular attention. These are the cells with differential responses, that is, they responded preferentially to either the S+ (the positive discriminative stimulus, which indicated that a lick could be made to obtain fruit juice) or to the S− (the negative discriminative stimulus).

Differential Units

Forty units (8.6% of the 463 tested) were found to have differential activity on reward and saline trials. Examples of the responses of such a neuron are illustrated in Fig. 7. The earliest consistent latencies at which these 40 neurons discriminated between the S+ and the S− (as determined using cumulative sum techniques (Woodward and Goldsmith 1964)) are shown in Fig. 8. Most of the neurons showed stronger responses to the positive stimulus, with 33 units responding more on reward trials (plotted above the baseline in Fig. 8), compared with seven responding more on saline trials (plotted below the baseline). It can be seen that the time of onset of differential activity varied widely between units, with the major-

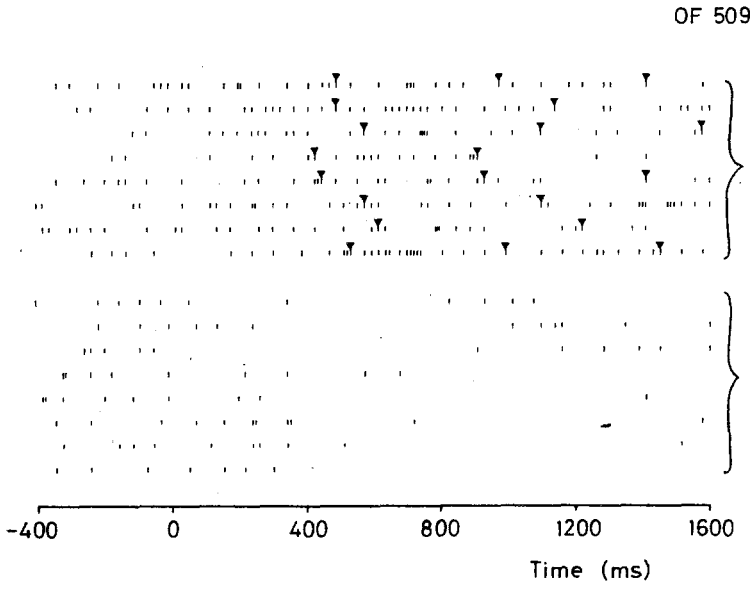

Fig. 7. An example of an orbitofrontal neuron which responded differentially in the visual discrimination task. The visual stimuli were shown at time 0. On the 8 reward trials, represented in the 8 top rows, the neuron continued firing (each vertical line represents one action potential) after the positive discriminative visual stimulus, and the monkey licked (indicated by the *triangles*) correctly to obtain fruit juice. On the 8 negative trials (lower 8 rows), the neuron stopped firing to the negative discriminative visual stimulus, and correctly the monkey did not lick, as saline would have been obtained. The trials were originally run in pseudorandom order

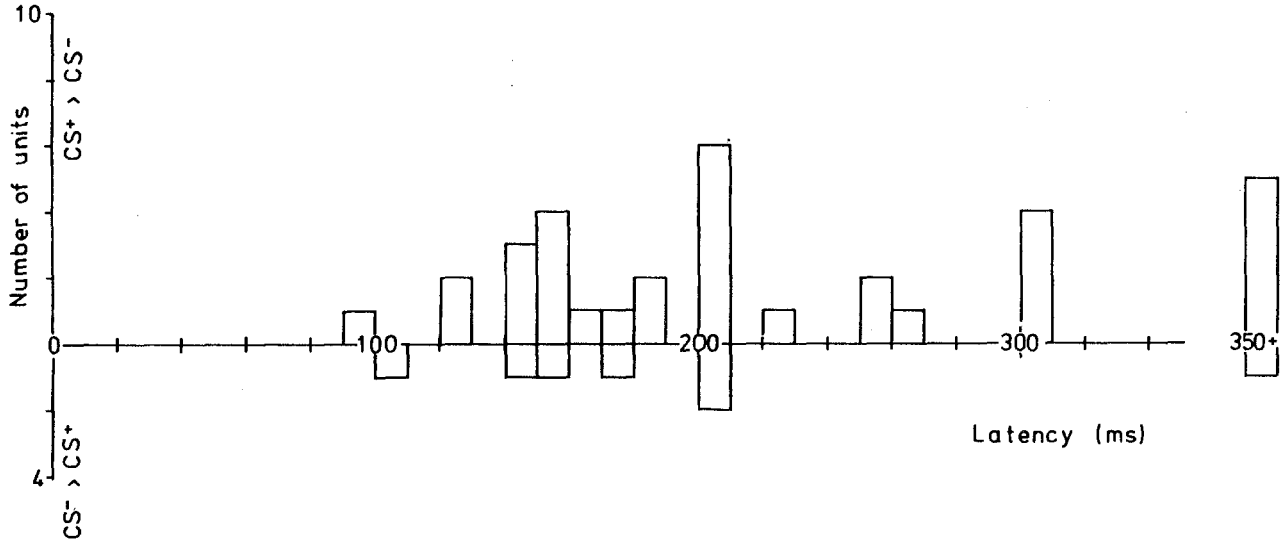

Fig. 8. The earliest consistent latencies at which 40 different orbitofrontal neurons responded differentially to the positive visual discriminative stimulus (CS+) and the negative visual discriminative stimulus (CS−) during the visual discrimination task. The response latencies of neurons which responded more to the CS+ are shown above the baseline, and the latencies of the neurons which responded more to the CS− are shown below the baseline

ity discriminating between 140 and 210 ms, but with values ranging from 90 to 500 ms. The neurons which had more activity on reward trials, and which had discrimination latencies of 300 or more ms, did not show a selective burst of firing on reward trials (as did most of the units that discriminated at shorter latencies), but rather showed maintained activity to the reward stimulus while showing a decrease in firing rate on saline trials.

To investigate why these neurons showed differential activity in the visual discrimination, the meaning of the two discriminative visual stimuli was reversed while the recordings continued. Twenty-one of the 40 units with discriminating responses were successfully tested during reversal. The majority (13, or 61.9% of those tested) were found to reverse their responses when the monkey reversed his behavioural responses in the visual discrimination. Thus, the responses of these neurons were related to the significance of the visual stimulus, in that for example their responses occurred to whichever of the two stimuli was associated with reward. Two neurons (9.5%) continued to respond selectively to the same stimulus, even after the animal had reversed his

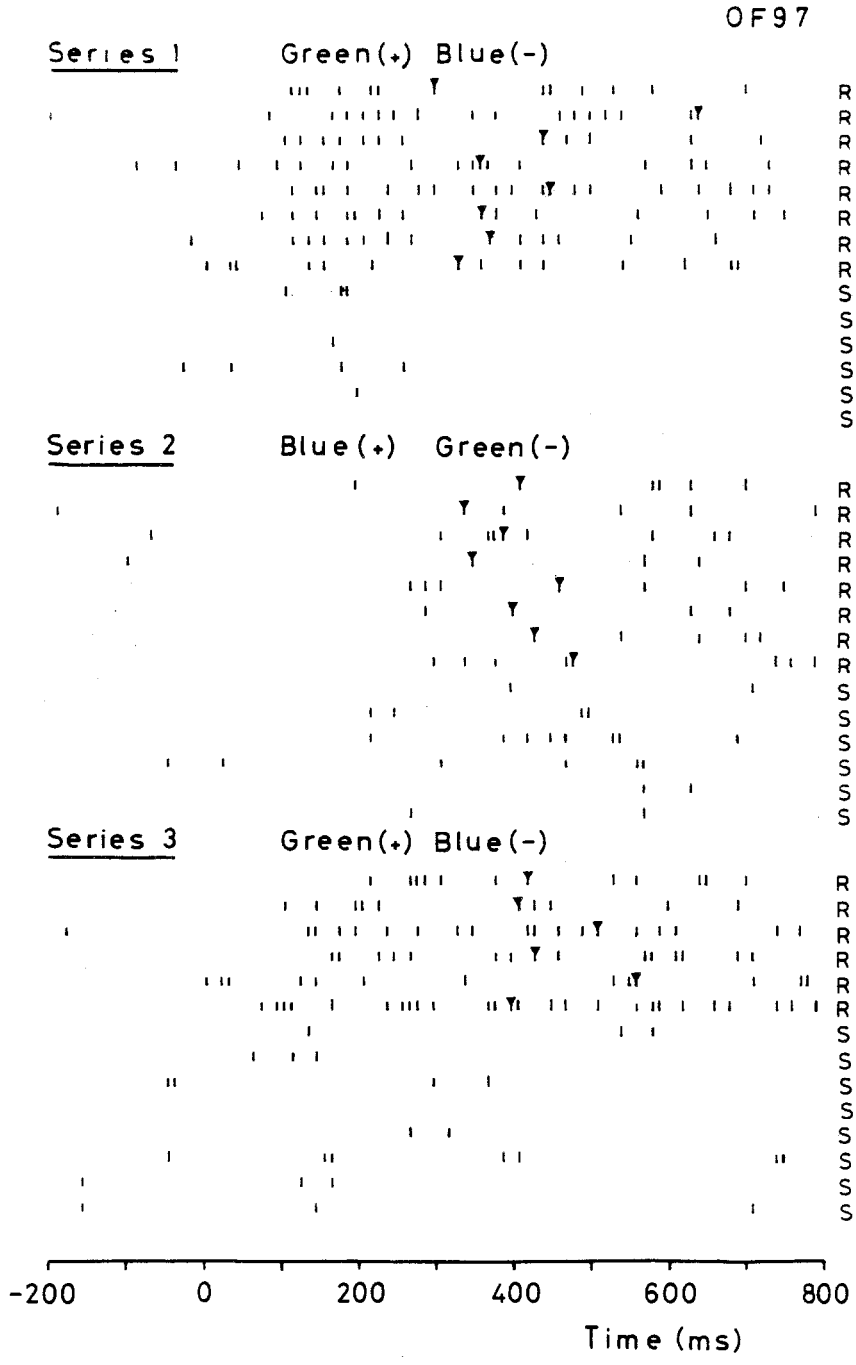

Fig. 9. Responses of a conditional differential neuron in the visual discrimination task. The neuronal responses occurred only to the green stimulus, and only when this signified reward (see text). Conventions as in Fig. 2. *R* – reward trials, *S* – saline trials. The trials within a series were run in pseudorandom order. The stimuli were shown at time 0

responses. This independence of these two neurons' responses from the motivational and behavioural "meaning" of the stimulus provided strong evidence that their selectivity was based on some sensory property of the stimulus such as its colour, and not on its association with reinforcement. Finally, six neurons (28.6%) had conditional differential responses in that they responded differentially only before reversal. Examples of the responses of such a neuron are shown in Fig. 9, in which the order of the trials has been rearranged for clarity. In series 1, it can be seen that the neuron only responded on reward trials, that is, to the green S+. The latency of the neuronal responses was approximately 90 ms. In series 2, the monkey had reversed his behavioural responses so that he was now only licking to the new blue S+. However, despite the fact that the monkey was performing the discrimination correctly on every trial, the neuron neither responded to the green S (which was now negative), nor to the reward-associ-

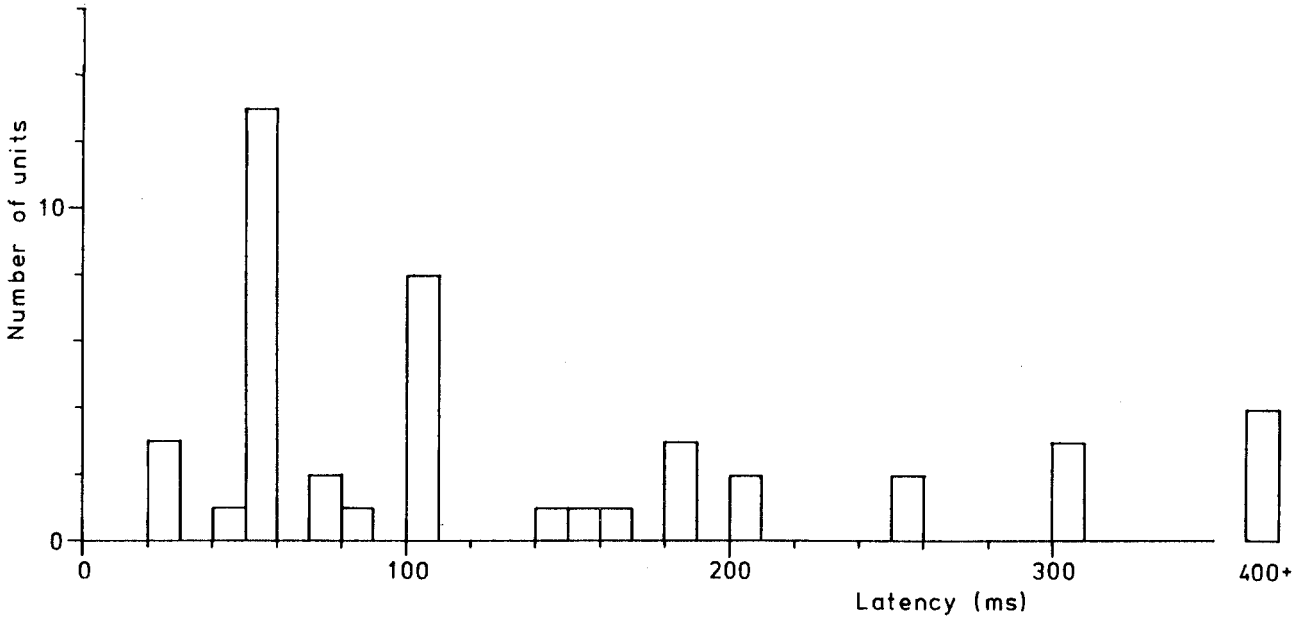

Fig. 10. Post-lick response latencies of the neurons with responses related to the lick response in the visual discrimination. The latencies are given relative to the time of the lick contact

ated blue S+. Series 3 shows that following a second reversal, the selective response to the green S+ was reinstated, and this pattern of responses was obtained from these cells for as many reversals as the experimenter performed. These findings show that these cells do not respond simply to a particular physical stimulus, nor to the association of any visual stimulus with reinforcement, but rather to a combination of both factors.

It is surprising to note that despite the fact that reinforcement value is an important factor in the differential activity of most of these orbitofrontal units, only two of them responded to other stimuli associated with reinforcement, such as the sight of food, and even these two units did not respond generally to all food objects. Reflecting the same point, only two of the 26 neurons with selective responses to the sight of foods responded differentially in the visual discrimination task.

Further information on the function of these three classes of differential neurons can be deduced by comparing the mean latencies at which they responded. Thus, the 13 neurons with responses which reversed had a mean latency for differential activity of 251.5 ms. The mean latency of the responses of the non-reversing neurons was 135 ms, and for the conditional differential units the mean response latency was 143.3 ms. Even though the numbers of units are small, the two latter groups had significantly shorter mean response latencies than the neurons which reversed ($p < 0.02$, two tailed t-test). Thus, neurons which retained information about the sensory properties of the stimuli responded with shorter latencies than neurons whose responses reversed and thus depended less on the sensory stimulus and more on the association of the stimulus with reinforcement.

Post-Lick Responses

A total of 45 neurons (9.3%) showed a change in firing rate after the monkey had licked in the task. The latencies at which different neurons responded relative to the time of the monkey's lick varied widely as illustrated in Fig. 10. Twenty-five of the neurons were separately tested with the delivery of reward and with the delivery of saline. Of these, 13 (52%) responded to both saline and reward delivery, and therefore, did not convey information about the occurrence of reinforcement. By contrast, eight neurons (32%) responded only if the monkey received reward, and not to the delivery of saline. Such neurons could simply be responding to the taste of the fruit juice. However, three of the eight neurons did not respond at all to the taste of the same solution outside the visual discrimination situation. One possibility, therefore, was that these neurons might signal that the animal's response in the task had been rewarded. Finally, four neurons responded only if the monkey received saline, and not to the delivery of reward, and did not respond outside the discrimination task to the taste of saline. Further observations on these neurons in relation to reversal are given below.

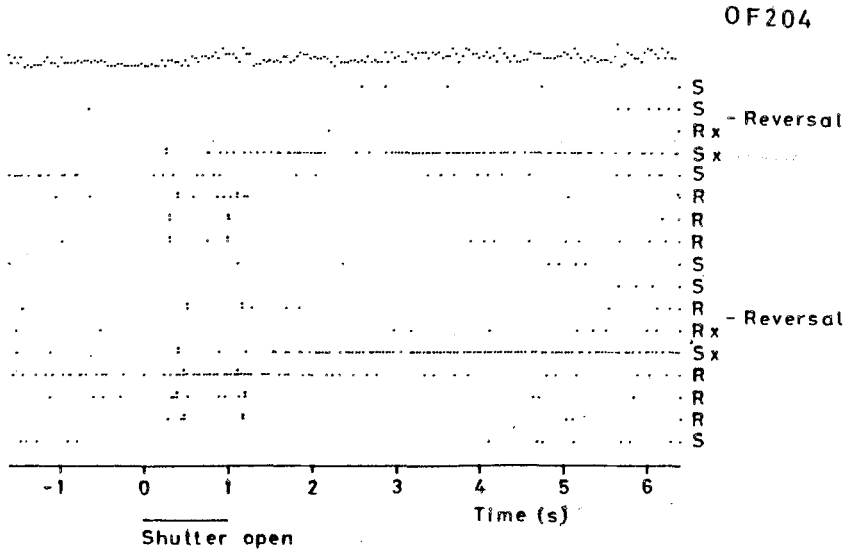

Fig. 11. Example of a neuron which responded with error-related activity in the reversal of the visual discrimination. The neuron did not respond during correct performance of the visual discrimination task (e.g. trials 1–5), but did respond on the reversal trial, trial 6, after the monkey had received saline when he licked to the previously rewarded stimulus (see text). *R* – reward trials, *S* – saline trials. Neuronal action potentials are represented by *single dots,* and the monkey's licks by *double dots.* The visual discriminanda were shown at time 0

Responses During Reversal

A total of 317 neurons was tested during the reversal of the visual discrimination task. Most (247 or 77.9%) were completely unaffected, but the minority of responsive units will be considered because of their relevance for understanding the effects of orbitofrontal lesions on reversal performance. Some of these responsive units have already been described in an earlier section. They are the neurons with differential responses on saline and reward trials whose response selectivity was altered as a result of the reversal.

In addition to these neurons, a small number of neurons were found with activity specifically related to the reversal procedure itself, rather than to the stimuli. These neurons showed strong activity after the monkey had made an error on the first saline trial after the reversal. The responses of one of these neurons are illustrated in Fig. 11. The first five trials demonstrate that while the monkey performed the visual discrimination normally, the neuron was almost inactive. However, following a reversal on trial six, the monkey licked to the previously rewarded stimulus, but because the meanings of the two stimuli had been reversed, received saline. At this point the neuron showed a prolonged burst of activity which started approximately 0.5 s after the error, and continued for 10 s until the start of the next trial. On the seventh trial the animal correctly licked to the new positive stimulus, and on subsequent trials continued to perform the new discrimination correctly. Clearly, a neuron responding in this way on error trials could simply be responding to the taste of saline, but other tests performed on the same neurons showed that neither this neuron, nor any of the three other neurons responding after an error in reversal, responded just because saline was in the mouth. Nor did these neurons respond simply because of arousal, in that there was no response during clinical testing to arousing or emotion-provoking stimuli such as the sight of a squeeze bulb from which air was puffed onto the monkey's face. Another interesting feature of this neuron is that it had a second burst of activity (of shorter duration) following the first rewarded lick after a reversal. It seems possible that this pattern of activity may be related to the fact that both the taste of saline on the reversal trial and the taste of reward on the subsequent trial indicate that a reversal is required.

The responses of a second neuron with error-related activity are illustrated in Fig. 12a. Although run randomly, the trials have been regrouped for clarity. The lower eight trials show that the neurons did not respond if the monkey correctly licked on reward trials (CS+ correct), or witheld licking on saline trials (CS− correct). However, as shown in the top five trials, if the monkey licked and obtained saline (CS− incorrect) for example on the first trial after a reversal, the neuron showed a clear burst of activity starting about 140 ms after the lick. As with the previous neuron, this response might have been simply due to the taste of saline. However, first, there was no response to the taste of saline during clinical testing. Second, the neuron also responded if the monkey licked on a reward trial but did not receive any fruit juice because the reward pump had been disconnected in extinction tests (Fig. 12a, trials labelled CS+ no delivery). Clearly, in this case the response could not have been due to the taste of aversive saline, but was related to the omission of the expected reward. The same neuron was found to also

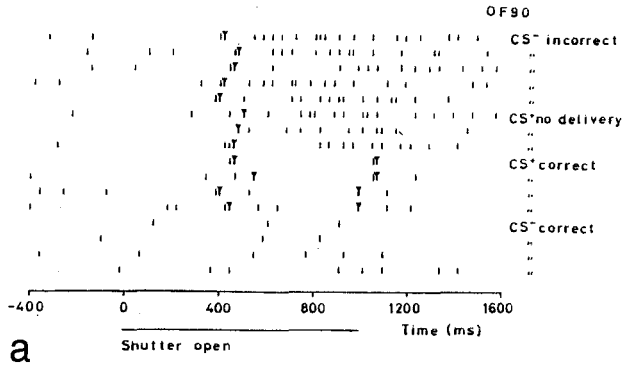

Fig. 12a. Example of another neuron which responded with error-related activity in the reversal of the visual discrimination (top 5 trials, CS – incorrect) and in the extinction of the visual discrimination (when no reward was delivered for a lick, see trials 6–8, CS+ no delivery) (see text). The neuron did respond during normal performance of the visual discrimination task (lower 8 trials). Conventions as in Fig. 3

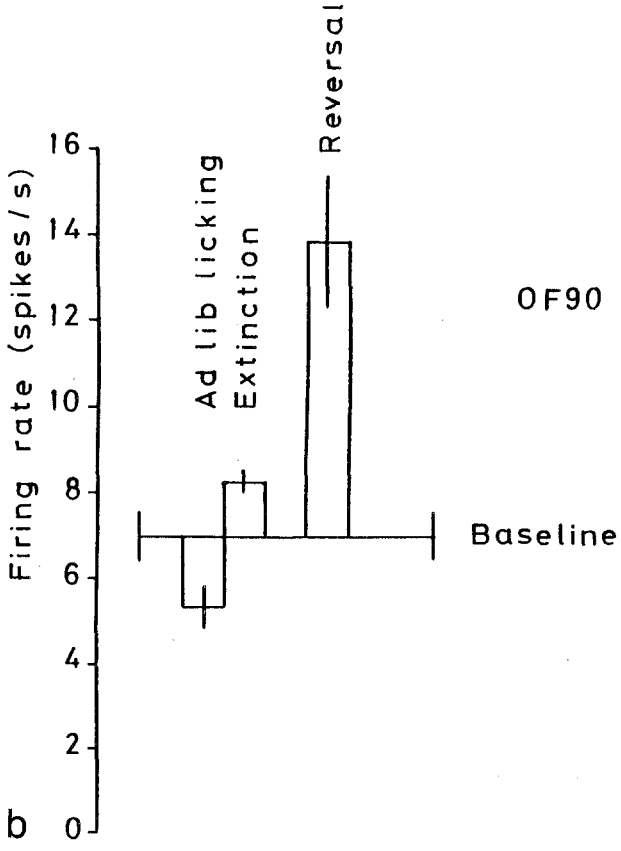

Fig. 12b. The same neuron did not respond in relation to ad libitum licking to obtain fruit juice, nor to the non-delivery of fruit juice in the ad libitum situation (extinction), but did respond if saline was unexpectedly given during ad libitum licking for fruit juice (reversal)

respond when the monkey was performing a simple licking response for ad libitum fruit juice reward if the animal was unexpectedly given saline, as illustrated in Fig. 12b. Four examples, that is, 1.3% of the number tested in reversal, were found of neurons which responded on error trials in the reversal of the visual discrimination.

One neuron had responses during reversal different from those already described. This neuron responded at about the time that the stimuli were shown, but only when the blue stimulus was associated with reward and the green stimulus with punishment. This activity disappeared when the discrimination was reversed such that the green stimulus was rewarded and the blue one punished. This is illustrated in Fig. 13 which shows the activity of the unit while the unit was reversed three times. During the first six trials, in which the blue CS was positive, it can be seen that the neuron showed a clear burst of activity starting just before the shutter opened (from about –100 ms), and continuing for about 250 ms. The response occurred irrespective or whether it was a reward or saline (S) trial. Then, the meaning of the two stimuli was reversed, but for three trials the monkey continued to treat the blue stimulus as positive. During this time the unit was still showing the characteristic perishutter activity. However, following an incorrect saline trial, the animal correctly reversed his response strategy and started treating the green stimulus as positive. This reversal of response strategy was associated with a cessation of the neuronal activity. Following a pause, the monkey started performing incorrectly in that he was again treating the blue stimulus as positive, and during this time the neuron again showed the perishutter activity. Later on, when the monkey started responding correctly (i.e. licking to the green stimulus), the neuron again stopped responding. Subsequently, the discrimination was reversed two more times, and it was confirmed that the perishutter activity occurred only on trials when the monkey was treating the blue CS as positive and the green CS as negative. This complex pattern of activity, which could not have been related to any simple sensory or motor events, will be considered in detail in the discussion.

Responses in Other Tests Related to Extinction and Reversal

In addition to neuronal responses related to the reversal or extinction of the visual discrimination (see Table 1), a number of neurons responded when, in the course of the ad lib licking task, saline was delivered instead of fruit juice in a passive avoidance

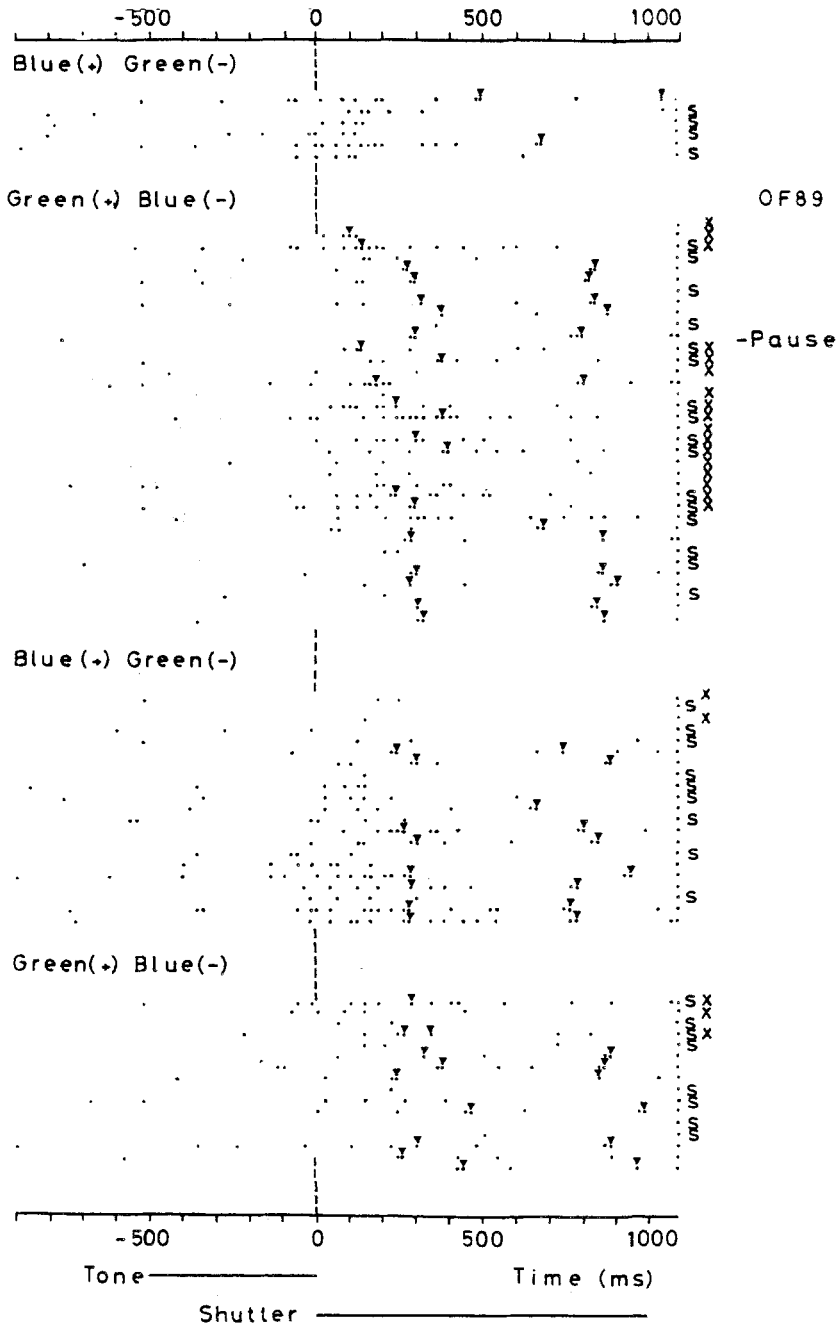

Fig. 13. Activity of a neuron which had peri-stimulus responses only when the blue discriminative stimulus was associated with reward and the Green discriminative stimulus was associated with saline (*s*), and the monkey was performing correctly (see text). The neuron did not respond when the Green stimulus was being treated as reward associated and the Blue stimulus as saline associated. Conventions as in Fig. 4. The gaps between the groups of trials (which were run sequentially) indicate when the significance of the stimuli was reversed

paradigm (Table 1, ad lib licking, reversal), or when the delivery of fruit juice reward was discontinued (Table 1, ad lib licking: extinction). Three such neurons were found, out of a total of 40 tested. In another test, which was part of the clinical testing protocol, some neurons were found which responded when objects such as food were brought close to the monkey's mouth, but were then gradually withdrawn from the animal. An example of this type of responsiveness in an orbitofrontal neuron is shown in Fig. 14. Although the neuron did not respond either to the sight or the approach of a fruit-juice containing syringe (or to the taste of the fruit juice), the neuron did respond when the syringe was taken away from the monkey. For five of the 13 neurons with responses related to object removal, including the neuron illustrated in Fig. 14, the responses only occurred if a rewarding food object was being used. One neuron had an especially sensitive response in that it responded not only if the food was removed, but also if the experimenter merely stopped moving the food towards the animal's mouth (see Fig. 15a).

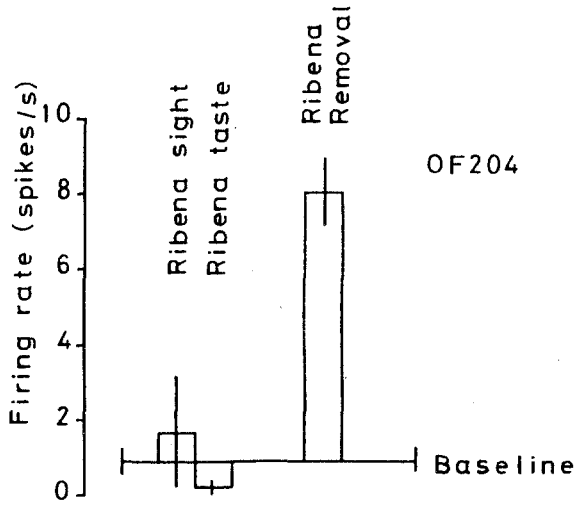

Fig. 14. An example of a neuron in the orbitofrontal cortex which did not respond to the sight or taste of fruit juice ('ribena'), but did respond when instead of being given to the hungry monkey, the fruit juice was removed. The mean and se of the mean responses and of the baseline firing rate are shown

This makes it very unlikely that the neuron responded because of eye-movements made by the animal such as divergence. Further, the same neuron failed to respond to the removal of the same stimulus (a clear 2 ml syringe) if the meaning of the stimulus was changed by replacing the glucose in the syringe with saline (Fig. 15b).

Altogether, 18 neurons (3.6% of those recorded) responded in relation to one or more of the reversal, extinction or object removal tests (see Table 1). The results summarized in Table 1 emphasise that none of these neurons responded in all of these non-reward/punishment situations, so that it must be concluded that the orbitofrontal cortex contains a population of neurons with responses selective for particular non-reward/punishment situations. It was also shown that only some of these neurons responded to aversive visual stimuli, and that none responded to all arousing stimuli. Thus, simple explanations in terms of fear, frustration or arousal are difficult to maintain.

Location of the Recording Sites

The locations of the 494 responsive and unresponsive neurons described in this study are shown in Fig. 16. All the units from both hemispheres of the three animals have been plotted on representative sections from the right hemisphere, and the three sections A, B, and C correspond to approximately 31, 28 and 25 mm anterior to ear-bar zero in the 4–5 kg monkey. Many of the units were recorded in area 13 between the lateral and medial orbital sulci, although a number were recorded more medially in the gyrus rectus and more laterally. No clear pattern in the distribution of the different classes of units was evident, although it was noticed that units with similar response properties were often clustered together on the same recording track.

Discussion

This investigation into the functional properties of neurons in the orbitofrontal cortex deals with two main problems. The first concerns the nature of the sensory input to the orbitofrontal cortex, that is, what modalities of sensory information are present, and what sort of sensory coding occurs. The second concerns the way in which orbitofrontal neurons respond in a number of behavioural situations, including for example the reversal of a visual discrimination task, which are known to be affected by orbitofrontal lesions. Hopefully, such an analysis will provide an insight into the functions being performed by this region of the brain, and will increase understanding of the causes of the disturbances associated with frontal lobe damage. In this discussion, we will first consider sensory coding by neurons in the orbitofrontal cortex, before looking at the responses of orbitofrontal neurons in the behavioural tasks.

A summary of the sensory responses shown by neurons in the orbitofrontal cortex is given in Table 2. A considerable proportion (32.4%) were classified as visual, and this high degree of visual responsiveness is consistent with the known projections to the orbitofrontal cortex from visual areas such as the inferior temporal cortex (Chavis and Pandya 1976). The response latencies are also consistent with such an input, in that the majority of orbitofrontal neurons responded with latencies of 100–200 ms (see Fig. 4), and typical response latencies of neurons in the inferior temporal visual cortex in the same testing conditions are 100–140+ ms (Rolls et al. 1977).

Neurons with visual responses have been found in other parts of the prefrontal cortex including the frontal eye fields (Mohler et al. 1973; Wurtz and Mohler 1976; Goldberg and Bushnell 1981), superior prefrontal convexity (Suzuki and Azuma 1977; Suzuki et al. 1979), dorsolateral prefrontal cortex (Kubota et al. 1974; Mikami et al. 1978; Mikami et al. 1979; Kojima 1980), in the cortex anterior to the arcuate sulcus of the macaque (Pigarev et al. 1979; Rizzolatti et al. 1981), and in the lateral orbitofrontal cortex of the anaesthetised monkey (Benevento et al. 1977). However, the present study is the first to describe such responses in the orbitofrontal cortex of

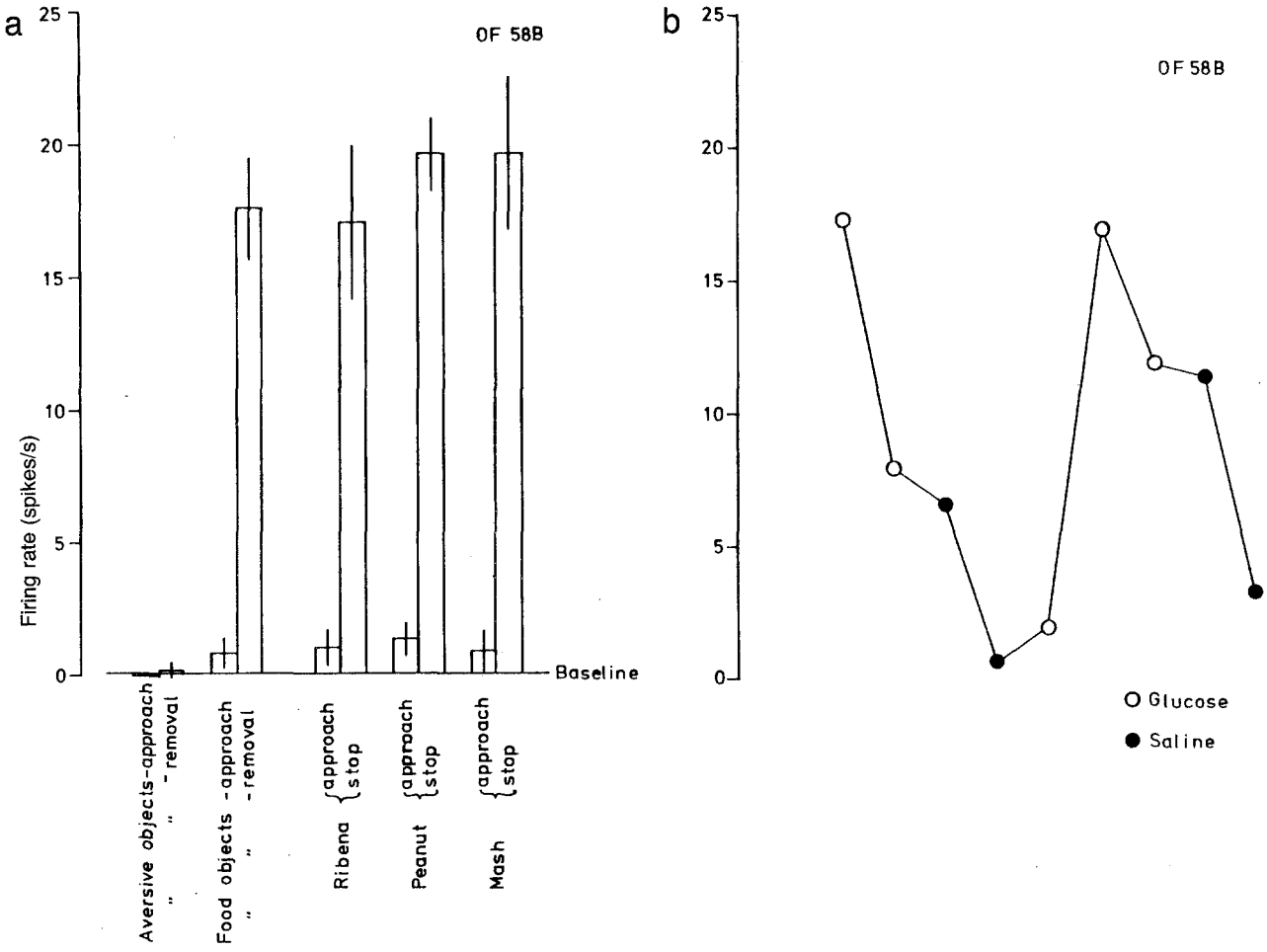

Fig. 15. Responses of a neuron which responded not only when food was withdrawn (**a**, removal), but also when the approach of food which was normally given to the monkey stopped. **b** Evidence that the same neuron responded to the withdrawal of food (glucose) but not of non-food (saline). If the monkey had been fed glucose from the syringe on one trial, then the neuron responded when the syringe was withdrawn on the next trial instead of being used for feeding (*open circles*). If the monkey had been fed saline from the syringe on one trial, then the neuron did not respond when the syringe was withdrawn on the next trial (*filled circles*)

Table 1. Tasks (rows) (see text) in which individual neurons (columns) responded (1), did not respond (0), or were not tested (blank)

	D 90	D 127	D 153	D 154	D 195	D 204	D 262	F 466	B 24	B 78	B 378	B 578	D 44A	D 48A	D 20	D 40	D 61	D 66
Visual Discrimination: Reversal	1	0	1	0	0	1	1	0						0				
Visual Discrimination: Extinction	1																	
Ad Lib Licking. Reversal	1	1		0	0	0		0	1									
Ad Lib Licking: Extinction	0	0		0	0	0		0	1									
Taste of Saline	0		0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Removal	0		0	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1
Visual Arousal	1		1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0

the awake monkey, under testing conditions in which the normal selectivity of the responses can be investigated, and using stimuli such as foods and aversive visual stimuli. Such stimuli are especially relevant for studying the responses of orbitofrontal neurons because, as pointed out in the Introduction, lesions to this region significantly affect the behavioural reactions of monkeys to such stimuli. In this study it was found that the majority (66.9%) of neurons showed some degree of selectivity, in that they would consistently respond to some stimuli, but consistently fail to respond to others. In many cases it was not possible to determine the basis for this selectivity, but it was possible to show that 16 units had visual responses that were selective for aversive visual stimuli, while a further 26 were selective for food-related stimuli.

Neurons with responses selective for aversive visual stimuli have previously been reported in the lateral hypothalamus and substantia innominata (LH/SI) and in the dorsolateral amygdala (Rolls et al. 1979; Sanghera et al. 1979). However, the neurons in the orbitofrontal cortex selectively responding to

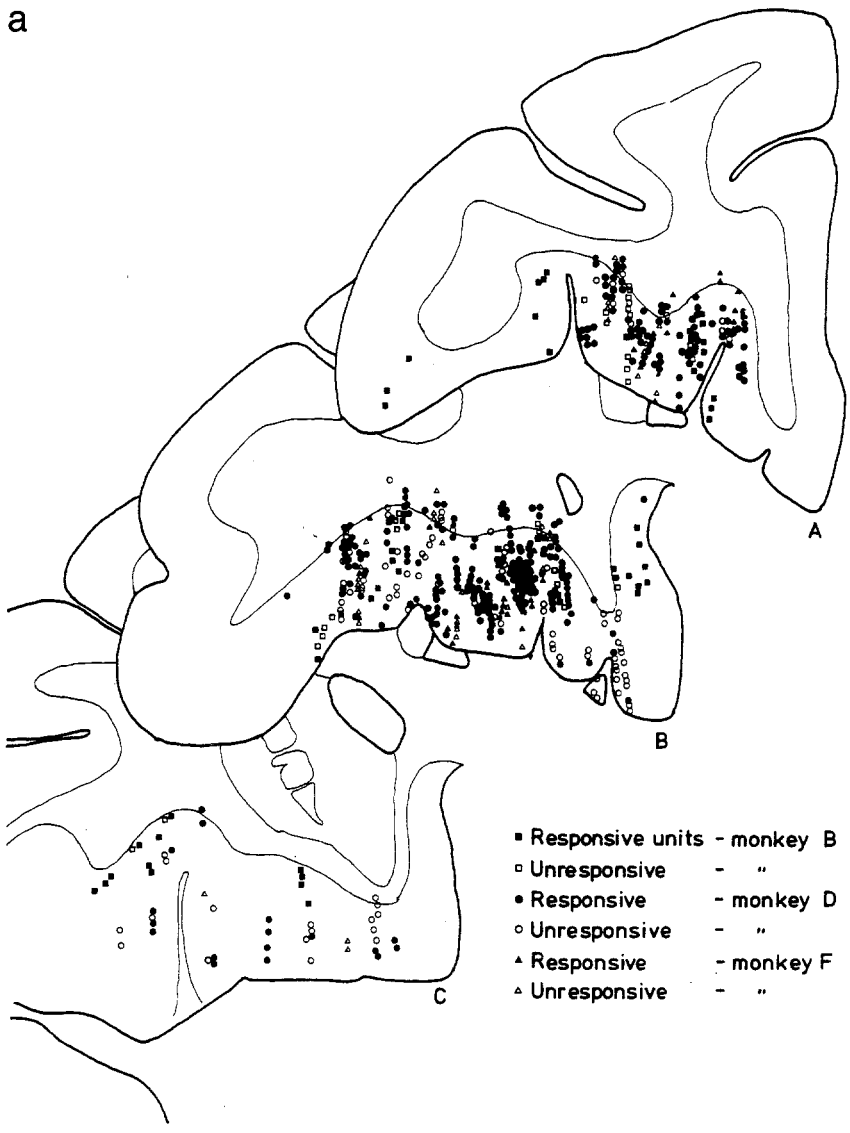

Fig. 16a. The locations of the 494 responsive and unresponsive orbitofrontal neurons recorded in three monkeys plotted on representative sections from one hemisphere. In these 4–5 kg monkeys, the sections A, B, and C corresponded to 31, 28, and 25 mm respectively anterior to stereotaxic zero

aversive visual stimuli seem to differ in a number of ways. First, the latency of the visual responses of some of the orbitofrontal neurons could be as short as 100 ms, a value shorter than that seen in any of the LH/SI units, which typically responded with latencies of 150–200 ms. Secondly, whereas the neurons in the LH/SI and amygdala tended to respond to a number of different aversive visual stimuli (and indeed, this was one of their defining characteristics), a number of orbitofrontal units showed considerable selectivity, with some (e.g. Fig. 1) responding only to particular visual stimuli. As described above, it is only because such highly selective units changed their responses during clinical reversal that it was possible to conclude that they were responding because the stimulus was aversive. The specificity with which some orbitofrontal neurons respond to particular aversive stimuli suggests that the coding in this part of the brain could indicate that a particular stimulus is aversive (or is not aversive, depending on recent reinforcement contingencies), rather than that any of many aversive stimuli has been presented, something which is more nearly reflected by the responses of some LH/SI neurons.

Similarly, neurons with visual responses selective for food have also been reported previously in studies of the lateral hypothalamus and substantia innominata (Rolls et al. 1976; Burton et al. 1976; Mora et al. 1976; Rolls et al. 1979). Here again, the responses of food-selective neurons in the orbitofrontal cortex appear different in some important respects. First, some of the orbitofrontal food-selective neurons had response latencies as short as 100 ms, compared with 140–200 ms for neurons in the LH/SI. Second, as with

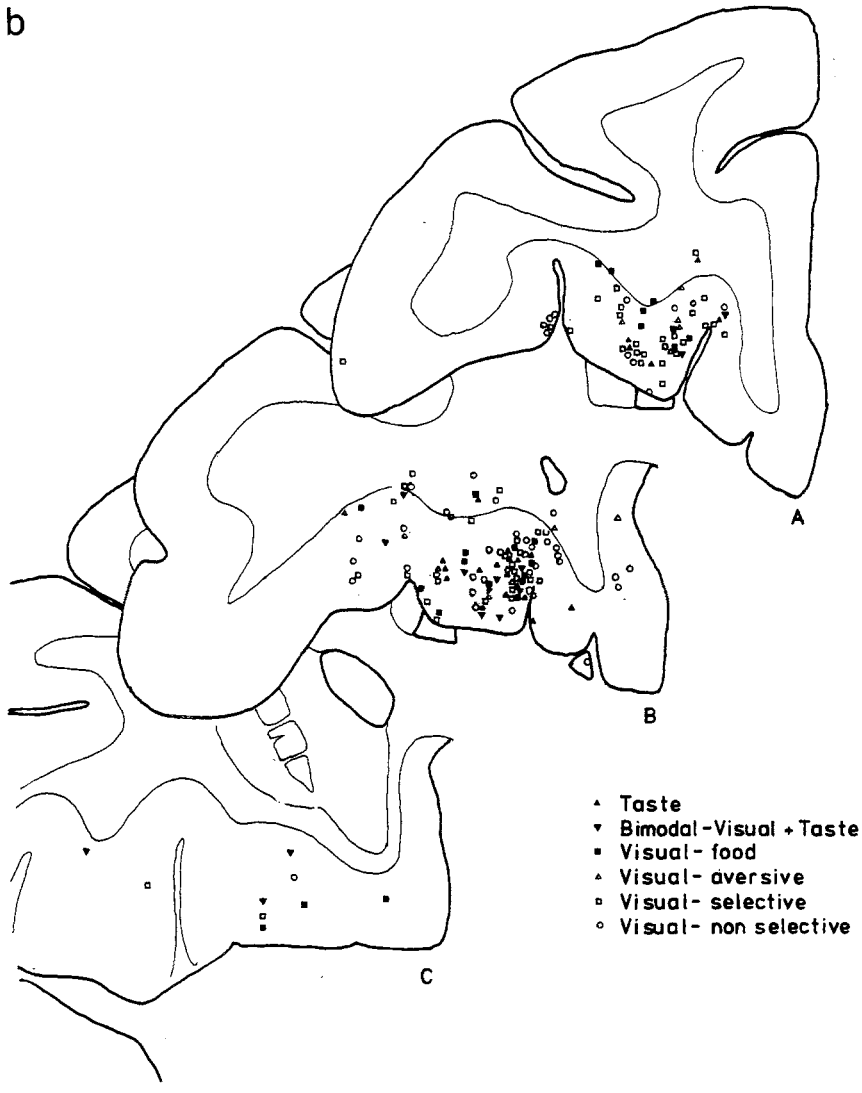

Fig. 16b. The locations of the orbitofrontal neurons with sensory responses

aversive responses, some orbitofrontal units showed a degree of selectivity not seen in any of the LH/SI neurons. Indeed, 11 of the 26 orbitofrontal neurons responded to only one of the food stimuli tested. These comparisons, together with the anatomically demonstrated connections from the orbitofrontal cortex to the hypothalamus (Nauta 1972), make it possible that the selective responses of some hypothalamic neurons to the sight of food may be due at least in part to inputs they receive from the orbitofrontal cortex. The generalised responses of hypothalamic neurons to the sight of food may arise by convergence of inputs from a number of different groups of neurons in the orbitofrontal cortex, each of which is selective for particular foods. Such an arrangement would have the considerable advantage that if a particular food-related stimulus was no longer associated with reward (as for example occurs in a reversal situation), the corresponding orbitofrontal neurons would no longer respond, and thus excitation from that particular stimulus would no longer influence hypothalamic feeding-related neurons. At the same time, the responses of hypothalamic neurons to other food-related stimuli (which are still associated with reward) would be unaffected.

The suggestion that the orbitofrontal cortex contains neuronal mechanisms which can independently code the reward value of different food-related and aversive stimuli can be related to the known effects of orbitofrontal lesions. Such lesions appear to interfere with the process by which the animal can learn that a particular stimulus is no longer associated with reinforcement. The evidence on the selective visual responses of orbitofrontal neurons, together with the dependence of many of these responses on the "meaning" of the stimuli, suggests that the influence of orbitofrontal neurons on hypothalamic feeding-

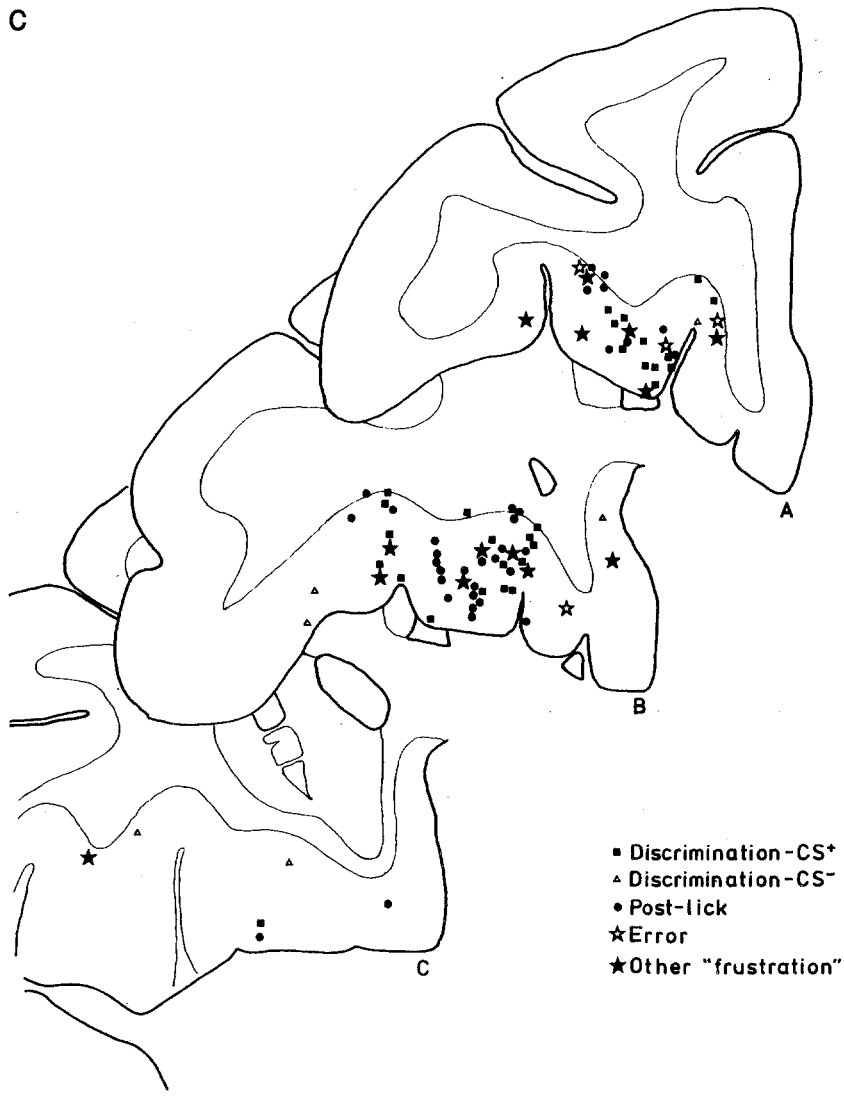

Fig. 16c. The recording sites of the differential, post-lick, error-related and other non-reward ("frustration") related neurons in the orbitofrontal cortex on sections 31, 28 and 25 mm anterior to the inter-aural plane

related neurons may be to ensure that they cease responding to a stimulus if that stimulus is no longer associated with reward.

In the present study 7.9% of the orbitofrontal units were classed as having gustatory responses, in that they responded only when the monkey was eating or drinking, and in that the responses could not be produced by mouth movements alone. A number of the neurons showed selectivity in that some would only respond to one of the foods tested. Little is known of how such gustatory information could reach the orbitofrontal cortex, but there is evidence that olfactory inputs reach part of the orbitofrontal cortex, and that these olfactory inputs can also be selective (Tanabe et al. 1975; Yarita et al. 1980; Potter and Nauta 1979). Although simple olfactory responses occurring before food entered the mouth were not noted in the present study, it is possible that the responses of some of the neurons with gustatory responses were at least partly dependent on olfactory information during feeding.

The present study clearly showed that some orbitofrontal units have auditory responses, and this finding is consistent with the known anatomical projections from the rostral part of area 22 to the area surrounding the lateral orbitofrontal sulcus (Chavis and Pandya 1976). Auditory responses have been reported previously in the lateral orbitofrontal cortex of the anaesthetised animal (Benevento et al. 1977), but the present study is the first to demonstrate such inputs in the alert animal. Although it was not a primary concern of this investigation, no clear evidence for somatosensory inputs was noted, and this is consistent with the lack of any obvious projection from somatosensory cortical areas.

The finding that some orbitofrontal units have clear bimodal responses is not unprecedented. In the lateral hypothalamus and substantia innominata, 19

Table 2. Types of sensory response shown by neurons in the orbitofrontal cortex

ORBITOFRONTAL SENSORY RESPONSES

	Number Tested	Number Responsive	%
TOTAL	494		
VISUAL	494	160	32.4%
Visual - non-selective	160	53	33.1%
Visual - selective	160	65	40.6%
Visual - food-selective	160	26	16.3%
Visual - aversive	160	16	10.0%
GUSTATORY	454	36	7.9%
Gustatory - selective	36	30	80.0%
AUDITORY		9	
BIMODAL			
Visual and Gustatory		13	
Visual and Auditory		2	

out of 33 neurons responding to taste also responded to the sight of food (Rolls et al. 1980). Furthermore, in the lateral orbitofrontal cortex of the anaesthetised animal, Benevento et al. (1977) reported that more than half the units with sensory responses to visual and auditory stimulation were bimodal. However, the present study provides the first evidence that the selectivity of the sensory responses of bimodal units can be matched in the two modalities. Thus, as illustrated in Fig. 6a and 6b, a unit which responded selectively to the sight of a whole banana independently showed the same selectivity for the taste of banana when tested clinically. It was shown that this selectivity was not due to a greater preference by the animal for a particular food, in that the responses of such selective neurons did not parallel the behavioural preferences of the monkey, and that in addition, different neurons had responses selective for different foods.

The observation that single neurons in the orbitofrontal cortex can have visual and gustatory inputs which are matched in their selectivity is difficult to explain by any simple hypothesis of sensory processing. There is no single sensory attribute such as colour, shape, size or spatial frequency which could account for the neuron's responses to both the sight and the taste of a particular food. As noted above, it is also unlikely that some motivational variable such as the reward value of the object could account for the matching selectivities in the two modalities, in that neurons selective for different foods were found. Given that such simple explanations appear inadequate, a parsimonious explanation is that neurons of this kind receive corresponding converging inputs as a result of the monkey learning that particular visual stimuli are associated with particular tastes. The discovery of units such as these constitutes the first evidence that higher level functions such as cross-modal matching could be achieved at the level of single neurons in the brain. This has considerable implications for such fundamental questions as how information is stored in the brain.

Task-Related Activity

The present study investigated the activity of orbitofrontal neurons during the performance of three tasks particularly affected by orbitofrontal lesions, namely, go/no go visual discrimination, reversal, and extinction. It was found that a considerable proportion (47.3%) had activity that was related to these tasks (see Table 3). Responses during the performance of the visual discrimination task can be considered in three major groups. First, there are those neurons with responses which occurred during the 0.5 s cue period which preceded the opening of the shutter (15.1%), together with those with non-differential responses in the period when the discriminative stimuli were shown (37.8%). Such neurons could play a role in the preparation of the monkey for the discrimination, or could code information potentially relevant to other visual discriminations, but clearly did not code discriminative information relevant to the performance of the task in progress. Second are those neurons which show differential activity on reward and saline trials in the visual discrimination (8.6%) and, therefore, do code information relevant to the performance of the visual discrimination in progress. Third, there are those neurons with post-lick responses (9.7%) which could code information about whether reinforcement has been given. These second and third groups of neurons will be considered in detail in the context of the functions of the orbitofrontal cortex.

The neurons with differential responses during the performance of the discrimination could be divided into three groups, depending on the effect that a reversal of the meaning of the discriminanda had on the differential activity of the neuron. Two units had differential responses that were apparently dependent on differences in the sensory properties of the two stimuli, in that they responsed to the same stimulus before and after reversal. Together with the

evidence presented earlier in this paper that a considerable number of orbitofrontal neurons have selective responses to visual stimuli, this finding shows that information related to the sensory aspects of visual stimuli reaches the orbitofrontal cortex and is reflected in the firing of some orbitofrontal neurons.

A larger number of differential neurons (13) were found to start responding to the other stimulus following a reversal of the meaning of the two discriminanda. Thus, such neurons showed a clear dependence on the reward value of the stimuli. However, these neurons did not in general respond to all visual stimuli associated with reward. Indeed, only two units with differential responses in the visual discrimination task also responded when food was shown to the monkey, and even these neurons did not respond to all foods. This finding again underlines the conclusion made earlier that there are differences between neurons in the orbitofrontal cortex and the feeding related units reported previously in the lateral hypothalamus and substantia innominata (Rolls et al. 1976; Rolls et al. 1979). Neurons with responses that occur to a wide range of foods, as well as to the rewarded stimulus in a visual discrimination task may be relatively common in the LH/SI, but they were virtually absent from the present sample of orbitofrontal neurons.

Further evidence that neurons in the orbitofrontal cortex respond to only some visual stimuli associated with reinforcement comes from the remaining six differential neurons, which had conditional differential responses when the meaning of the two visual discriminanda was reversed. Such neurons would respond differentially to one of the two discriminanda, but fail to respond to either stimulus after a reversal had been performed. This type of response has similarities with some of the other orbitofrontal neurons described earlier, which although clearly dependent on the rewarding or aversive nature of the stimulus, were nevertheless highly selective in the particular visual stimuli to which they would respond (see for example the neuron illustrated in Figs. 1 and 2 which selectively responded to only one of the aversive stimuli tested, namely, a saline-containing syringe, but was still clearly influenced by the aversiveness of the stimulus). There are also parallels with some units described by Watanabe (1982) which had responses in a conditional discrimination task which depended on the successive presentation of two particular cues, but as in the present study, could not be related to particular sensory or motor events.

The existence of such conditional units, which apparently require not only that a particular stimulus is present, but also that it should have a particular reinforcement association, poses an interesting problem of interpretation. Clearly, the responses of such units cannot be completely explained in terms of the sensory properties of the stimuli, since although the physical appearance of a stimulus is unchanged following a reversal of its meaning, the response of the neuron is completely different. However, other explanations, including the suggestion that the neuron might simply be coding the motivational significance of the stimulus, or that it might be related to some response made by the animal to rewarding stimuli, are also inadequate. Such explanations would require that the neuron responds to other stimuli associated with reinforcement, so that in the visual discrimination task, the neuron should respond to whichever stimulus is currently being rewarded. The fact that at least some orbitofrontal neurons do not show this behaviour strongly indicates that the processing being performed by the orbitofrontal cortex includes not only activity related to sensory and motor events, but also a degree of intermediate or "cognitive" processing.

Another type of unit found in the present study which defies simply sensory or motor explanations is the type illustrated in Fig. 13. The simplest description of the responses of this unit is that it showed activity at around the time that a decision whether to respond or not had to be made, but only when the animal was treating a particular stimulus, in this case the blue one, as positive. As with the conditional differential units, the activity of such a neuron cannot be simply related to any sensory event or to any motor response made by the animal. Rather, it would appear that the activity might reflect certain cognitive processes, related to the monkey's "central set" (Mishkin 1964). One possibility is that such neurons might act to gate the responses of sensory neurons, thus resulting in the sort of conditional neurons described in this paper which respond when a particular sensory input is present, but only when the animal treats that particular stimulus as positive.

Finally, there are the neurons with post-lick responses. Neurons with such "reward" or "reinforcement" related activity have been noted in a number of earlier studies of prefrontal unit activity in the behaving animal (Markowitsch and Pritzel 1976, 1978; Niki et al. 1972; Niki and Watanabe 1979; Rosenkilde et al. 1981; Watanabe 1982). In these earlier studies, it was not always clear what the basis of this activity was, whether for example the activity was related to the taste of the reward solution, or to non-specific stimulation associated with juice-delivery. In the present study, a number of such neurons

were tested with the delivery of both reward and saline solutions. Thirteen neurons (52% of those tested) responded to the delivery of either solution, and, therefore, could not carry any specific information about whether reinforcement had been given in the task. However, such neurons could indicate that contact with the lick tube had occurred, and such information could be useful in conjunction, with the absence of activity in taste-related neurons for the detection of extinction. Eight neurons (32%) responded to the fruit-juice but not the saline, and thus could convey information that reward had been received. Interestingly, not all these neurons responded to the taste of fruit juice delivered clinically, so that at least some could specifically be involved in coding that a response has been rewarded in the task.

Finally, there were four neurons which responded to the delivery of saline, but not to reward. These neurons have similarities to the small proportion of "error-related" neurons reported in other studies of the prefrontal cortex (Rosenkilde et al. 1981; Niki and Watanabe 1979; Watanabe 1982). In the present study it was also possible to test neurons in other "frustrating" situations, including the extinction and reversal of an ad lib licking response for fruit-juice reward, and the removal of food. A total of 18 neurons was found to respond in one or more such situations, but since none responded to all "frustrating" events, it seems unlikely that a simple unitary explanation in terms of an emotional state such as frustration could account for the responses of all these neurons. Rather, it seems that some of the error-related neurons recorded in the present study may be specifically involved in the performance of the visual discrimination reversal task.

Conclusions

The present study has clearly demonstrated that single neurons in the orbitofrontal cortex receive a considerable amount of sensory information, especially visual and gustatory. Much of this sensory information appears highly coded, in that some individual neurons respond selectively to particular types of stimuli, and in particular to foods and aversive stimuli. The loss of such neurons could well contribute to some of the behavioural changes that are reported to follow orbitofrontal lesions. To be specific, lesions are known to result in disturbances in food selection behaviour, and altered emotional responses to aversive visual stimuli such as model snakes (Butter et al. 1968, 1969, 1970; Butter and Synder 1972; Ursin et al. 1969), and such changes may reflect the loss of the highly coded sensory information about rewarding and aversive stimuli which appears to be present in orbitofrontal neurons.

One surprising finding was that some bimodal neurons having inputs from both gustatory and visual inputs showed matching selectivities in the two modalities, in that for example, a neuron would selectively respond to the same food in the two modalities. Such a result is difficult if not impossible to explain in terms of features of the stimulus in either the visual or gustatory modalities, and would appear to strongly favour the suggestion that high-level functions such as cross-modal matching can be achieved at the level of single neurons in the orbitofrontal cortex.

A further important finding is that a number of the apparently sensory responses of orbitofrontal neurons were highly dependent on the meaning of the stimulus. For example, the response of a neuron to the presentation of a 1 ml syringe was critically dependent on whether the syringe had recently been used to feed the animal rewarding fruit juice or aversive saline. Similarly, some neurons responding differentially to the sight of one of the visual discriminanda in a visual discrimination would only respond to that stimulus if it had been recently associated with reward. Thus, the orbitofrontal cortex seems to possess information on the reinforcement associations of particular stimuli, and seems able to rapidly modify this information in the light of the animal's recent experience. The loss of such an ability might well be expected to result in some the the effects of orbitofrontal lesions in monkeys, such as the perseveration of responding to previously rewarded stimuli.

Further insight into the nature of the orbitofrontal lesion effect is provided by the responses of neurons in the go/no go visual discrimination task. Here, a number of interesting response types were noted. First, there were neurons with differential activity to the visual discriminanda on reward and saline trials. Interestingly, by testing the effect of reversals on differentially active neurons it was possible to classify them into three separate groups; those linked closely to the sensory properties of the stimuli, those linked to the behavioural significance of the stimuli, and a third intermediate group whose responses were conditional upon both the sensory stimulus present and its behavioural significance. These three types of neuron could feasibly represent sequential stages in the processing of the sensory input, leading finally to response production. Disruption of this neuronal processing might well be predicted to impair performance on such tasks as visual

discrimination, as has indeed been observed after orbitofrontal lesions.

Particularly relevant for understanding the effects of orbitofrontal lesions are those neurons which respond after the monkey has made his response in the task. These neurons could code the outcome of the trial, that is, whether the animal received reward or punishment. Such information may be especially relevant in view of the fact that some orbitofrontal units with responses to the visual presentation of particular stimuli are extremely sensitive to the recent history of association with reward or punishment. It could be that these various types of neuron form part of a neuronal mechanism for rapidly altering the reinforcement association of individual stimuli as a result of experience. Such a mechanism would clearly be valuable if not essential for the performance of tasks which involve repeated reversals of the meaning of particular stimuli. Indeed, it is tasks such as visual and auditory discrimination reversals, object alternations, and spatial reversals and alternations which involve rapid changes in the reinforcement value of particular stimuli that are particularly disrupted by damage to the orbitofrontal cortex.

Finally, there is the question of how the orbitofrontal cortex achieves this rapid modification of the responses of neurons to particular stimuli as a result of recent experience. A clue is provided by the existence of neurons such as the one illustrated in Fig. 13 with activity correlated with the animal's "central set", in that activity was only seen when the animal was treating a particular stimulus as positive. Such activity could feasibly be used to gate the responses of other sensory neurons, to result in the sorts of conditional sensory responses which were seen in the present study.

The results of the present study have implications for understanding the effects of frontal lobe damage in man. Such damage is known to result in the characteristic phenomenon of perseveration in which patients continue to make the same response in a particular situation, even when that response is no longer appropriate. This effect is seen particularly clearly in for example the Wisconsin Card Sorting Task (Milner 1964). Such effects might be expected after damage to the orbitofrontal cortex which the present study has shown contains a wide variety of neurons, that between them can constitute a neuronal mechanism for monitoring the consequences of making responses in particular situations and to particular stimuli, and modifying subsequent behavioural strategies as a result.

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