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THE PRIMATE AMYGDALA AND REINFORCEMENT: A DISSOCIATION BETWEEN RULE-BASED AND ASSOCIATIVELY-MEDIATED MEMORY REVEALED IN NEURONAL ACTIVITY

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Abstract—To investigate the role of the primate amygdala in stimulus-reinforcement association learning, the activity of single amygdala neurons was recorded in macaques during two memory tasks. In a visual discrimination task, a population of neurons (17/659) was analyzed which responded differentially to a visual stimulus which always indicated that the primary reinforcer fruit juice could be obtain if the monkey licked, and a different visual stimulus that indicated that the primary reinforcer aversive saline would be obtained if the monkey licked. Most (16/17) of these neurons responded more to the reward-related than the aversive visual stimulus. In a recognition memory task, the majority (12/14 analyzed) of these neurons responded equally well to the trial unique stimuli when they were shown as novel and the monkey had to not lick in order to avoid saline, and when they were shown a second time as familiar and the monkey used the rule that if he licked, fruit juice would be obtained. The responses of these amygdala neurons thus reflect the direct associations of stimuli with reinforcement, but do not reflect the reward value of the stimuli when this must be assessed based on a rule (in the recognition memory task, that a stimulus will be punished the first time it is shown, and rewarded the second). This finding also shows that these amygdala neurons respond to relatively novel stimuli in the same way as they do to stimuli that have become rewarding by stimulus-reinforcement association learning. This provides a neural basis for relatively novel stimuli to be treated as rewarding, and approached. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: stimulus-reinforcement association learning, reward, punishment, novelty, familiarity, learning.

The primate amygdala has been implicated in learning about the reinforcing attributes of sensory stimuli in monkeys since Weiskrantz (1956) showed that ablation of the amygdala and temporal pole altered the acquisition and extinction of conditioned avoidance and suppression behavior. A related hypothesis—that the amygdala is crucial for the formation of stimulus-reinforcement associations—was proposed by Jones and Mishkin (1972) in studies showing that damage to the amygdala and temporal pole impaired the acquisition and reversal of visual (object) discrimination tasks. More direct evidence for this hypothesis is that amygdalectomized monkeys were impaired in a test in which they had to learn during a single presentation whether or not a trial-unique object was paired with reward (Spiegler and Mishkin, 1981). The deficits in reinforcement association learning produced by amygdala damage may be particularly evident when the association must be made between a previously neutral (e.g. visual) stimulus and primary reinforcement (e.g. the taste of food). (When the testing is performed in a Wisconsin General Test Apparatus, amygdala lesions may not produce significant deficits partly because the neutral visual stimulus is being associated with a visual stimulus with secondary reinforcing properties, the sight of food; and partly because with spaced trials, a habit can be built up slowly over many trials, see Phillips et al., 1988.) Consistent with the hypothesis that the primate amygdala is involved in behavior to stimuli with learned associations with a primary reinforcer such as taste, monkeys with neurotoxic lesions of the amygdala showed abnormal patterns of food choice, picking up and eating foods not normally eaten such as meat, and picking up and placing in their mouths inedible objects (Murray et al., 1996). These symptoms produced by selective amygdala lesions are classical Klüver-Bucy symptoms. Further evidence relating the amygdala to reward-related behavior is that Malkova et al. (1997) (see also Baxter and Murray, 2002) showed that after amygdala lesions made with ibotenic acid when the reward value of one set of foods was reduced by feeding it to satiety (i.e. sensory-specific satiety, see Rolls, 1999, 2005), the monkeys still chose the visual stimuli associated with the foods with which they had been satiated. The aim of the study described here was to investigate whether amygdala neurons that respond to visual stimuli paired with primary reinforcers such as the taste of food, also respond when reward must be determined in a different way, based on a rule (namely "behavioral lick responses to familiar but not to novel visual stimuli will produce reward").

Another effect of damage to the monkey amygdala, emotional abnormality, is consistent with the hypothesis that it plays a role in stimulus-reinforcement association memory (Weiskrantz, 1956; Horel et al., 1975; Aggleton and Passingham, 1981b; Rolls, 1990, 1992, 1999, 2000, 2005). The emotional abnormality may reflect a failure to remember or to identify the reinforcing and affective attributes of sensory stimuli. Thus there are substantial reasons, including advancing our understanding of the neural basis of emotion and its abnormalities, to explore the relationship between the amygdala and associative learning.

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In a study designed to test the hypothesis that the responses of amygdaloid neurons depend on the reinforcing value of visual stimuli, Sanghera et al. (1979) found neurons in the dorsolateral amygdala that responded primarily to foods and to the reward-associated visual stimulus in a visual discrimination task, responses that could reflect learned associations between these visual stimuli and the primary reinforcement associated with them. However, these neurons also responded to some objects that were not associated with rewards. We show in this paper that these other stimuli are relatively novel stimuli, thus providing a potential neural basis for the treatment of novel visual stimuli as rewarding (Rolls, 1999). Sanghera et al. (1979) also found that the majority of the neurons tested (eight of nine) did not reverse the visual stimulus to which they responded in the reversal of a visual discrimination task for juice reward vs saline punishment (and for the remaining neuron the evidence was unclear), so these neurons may not rapidly reflect new learning about the reward value of visual stimuli.

The aim of the present experiments was to investigate further the role of the amygdala in the effects of reinforcers on behavior and reinforcement-related associative learning, and to provide evidence on the processing within the amygdala which subserves its functions. Monkeys were trained to perform two tasks that required the reinforcement value of visual stimuli to be determined. These tasks required assessment of the reinforcement value either by direct association of a visual stimulus with primary (unlearned) reinforcement (task 1), or by a rule rather than by previous experience that the stimulus had been associated with a primary reinforcer (task 1). The first task was a Go/NoGo visual discrimination task in which the monkey learned that a behavioral response to one visual stimulus always resulted in the delivery of fruit juice reward, while a response to the other stimulus resulted in the delivery of aversive saline. This task thus required associations to be formed from a visual stimulus directly to a primary reinforcer, food or saline delivered into the mouth. The second task was a recognition memory task in which the reinforcement contingency rule was that if lick responses were made to novel stimuli then saline punishment resulted, whereas lick responses to familiar stimuli elicited fruit juice reward. In this task, the stimuli were essentially trial-unique, that is they had not been seen within the last several weeks, and were only shown twice during recording, once as novel, and once as familiar. In order to obtain juice, the monkey had first to determine the novelty and familiarity of the stimuli and then use the rule to determine its reinforcement or reward value. The monkey could not perform this task by directly associating the stimulus with the experience of its primary reinforcing qualities, and using the direct association to guide behavior. We note that the amygdala itself is not necessary for the performance of recognition memory tasks, which is impaired by perirhinal cortex but not by amygdala lesions (Zola-Morgan et al., 1989).

EXPERIMENTAL PROCEDURES

Subjects, stimulus presentation, behavioral responses, and reinforcement

Two rhesus monkeys (*Macaca mulatta*) were used in this study and were trained on a visual discrimination task with stimuli that were always rewarded or punished, and on a recognition memory task. They performed these tasks with many hundreds of trials per day, five days a week, for periods of up to 14 months. When sitting in the primate chair the monkeys' view of the laboratory was limited to a circular aperture in an enclosure that surrounded the chair. Head support and the enclosure ensured that the field of view was restricted to visual stimuli presented in the aperture. The aperture allowed different types of visual stimuli to be presented as follows: First, three-dimensional objects were presented using a 6.4 cm aperture electromagnetic shutter (rise time approximately 10 ms) mounted on the enclosure 8–12 inches from the monkey. The shutter was used to present stimuli during the performance of the behavioral tasks. A tube mounted in front of the mouth delivered saline or juice reinforcement, dependent upon the behavioral responses. During the performance of the tasks, a tone cue of 500 ms duration preceded the visual stimuli, facilitating fixation of the stimuli. Visual stimuli were presented for 1.5 s and the inter-trial interval was generally 6 s. Lick responses in the intertrial interval usually resulted in the delivery of saline, although this contingency was sometimes disabled to encourage the monkeys to make lick responses in the absence of visual stimuli, serving as a control measure. Second, objects, foods such as fruit and nuts, and syringes used to deliver juice or saline to the mouth were presented and delivered to the monkey through the aperture throughout the experiment. Laboratory chow and *ad libitum* water was available after their return to their home cage. The monkeys gained weight steadily during the course of the experiments. All procedures, including preparative and subsequent ones, were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, were licensed under the UK Animals (Scientific Procedures) Act, 1986, and are described by Rolls et al. (2003). The procedures minimized the number of animals involved in the study and optimized their welfare by including, for example, the provision of group housing and environmental enrichments.

In preliminary training, the monkeys were brought to the laboratory and given food and juice delivered through syringes which were inserted in colored, square plaques in order to make them distinguishable. One syringe (the S+) was white and was used to deliver fruit juice; the black syringe was used to deliver saline (the S−). The monkeys learned to distinguish between these two stimuli in a few trials, and reached for the S+ but not for the S−.

The Go/NoGo visual discrimination task

In the visual discrimination task, an electromagnetic shutter was used to present one of two syringes mounted in square plaques of different colors, one per trial. Lick responses after the presentation of a syringe mounted in a black plaque (the S−) resulted in the delivery of aversive hypertonic saline, while responses to the syringe mounted in the white plaque (S+) resulted in the delivery of fruit juice reward. The monkeys licked to obtain fruit juice reward to the S+, and did not lick to the S− in order to avoid the taste of saline. The same plaques were always used in the visual discrimination task, indicated a fixed stimulus-reinforcement association, and were highly familiar to the monkeys.

The recognition memory task

The serial visual recognition memory task was adapted for neurophysiology by Rolls et al. (1982) from a paradigm described by Gaffan (1977) (see also Wilson and Rolls, 1990a). In the recognition memory task, lick responses during the presentation of

novel stimuli elicited aversive saline, while lick responses to familiar stimuli resulted in the delivery of rewarding fruit juice. Thus the monkeys had to determine the novelty or familiarity of the stimuli in order to obtain juice reward. The first (novel) presentation of a stimulus was followed by a second (familiar) presentation of the stimulus after zero to 16 other trials, with the number of intervening trials selected in pseudorandom order. A typical stimulus sequence was as follows: N1→N2→F2→N3→N4→F1 →N5→F4. In this example, the novel stimulus (N1) shown on trial 1 was shown again after four intervening trials as familiar (F1) on trial 6, while the novel stimulus (N2) shown on trial 2 was repeated with no intervening trials on trial 3.

In the recognition memory task, three-dimensional objects were presented using the electromagnetic shutter. Stimuli were handheld, but only the objects were visible against a white background. A given object, drawn from a population of approximately 2000 objects, was presented twice daily, once as novel and once as familiar. The entire stimulus set was presented once every 2 to 4 weeks. Thus a novel stimulus is operationally defined as a stimulus not seen for 14 or more days. The monkeys refrained from responding to stimuli that had not been seen for 2 weeks (i.e. the stimuli were treated as novel). Their performance on the recognition task was on average better than 90% correct.

Clinical tests

In order to establish the properties of differential neurons in a situation in which the monkeys did not have to make a behavioral response, foods, and the S+ and S− syringes used in the visual discrimination task, were presented through the aperture in the chair using a standard protocol in which counts of mean firing rate for a 2 s period were made by computer during each step in the protocol (Thorpe et al., 1983). The protocol consisted of (1) the presentation of the experimenter's arm viewed through the aperture; (2, 3) movements of the experimenter's arm to and from the stimulus to be presented, with the stimulus still out of view (these cues that a stimulus was about to be presented are powerful stimuli for neurons in the head of the caudate nucleus, as shown by Rolls et al. (1983)); (4, 5, 6) the sight of the stimulus, its approach and touching of the mouth to elicit mouth movements and somatosensory input; and (7) delivery of the stimulus resulting in taste stimulation and then chewing or drinking. The stimuli were presented without a preceding tone cue and the subsequent delivery of foods to the monkey was not contingent upon a behavioral response.

General experimental procedure

During the recordings the monkeys continuously and concurrently performed the visual discrimination and recognition memory tasks, so that on any trial novel and familiar objects, or the S+ and the S−, could be presented and interdigitated in pseudorandom order. In general, each neuron was tested for responsiveness to novel and familiar stimuli in the recognition memory task, and to the S+ and S−. If the neuron responded to the presentation of any of these stimuli, extensive testing for periods of up to 4 h continued in order to identify the properties of the stimuli that elicited the responses of the neuron.

Localization of the recorded neurons

X-radiographs taken at the completion of each microelectrode track served to identify the location of each track relative to permanently implanted stimulation electrodes and bony landmarks of the skull. Identification of the location of the recorded neurons was determined by small lesions made at the site of responsive neurons and by reconstructions of the electrode tracks based on coronal and sagittal X-radiographs taken of the microelectrode *in situ*. Measurements were taken of the position of the electrode tip relative to implanted stimulation electrodes and the sphenoid ridge (Aggleton and Passingham, 1981a), and large scale (×10) plots were made of the positions of neurons along the electrode tracks and regions in which neuronal activity was not recorded. These were overlaid onto large scale (×10) drawings of 50 μm histological sections stained with Cresyl Violet and positioned with respect to lesions and structures such as the anterior commissure in which neuronal activity was not recorded. Large scale (×10) drawings were made of the sections upon which plots of the positions of recorded neurons were superimposed (see Feigenbaum and Rolls, 1991).

Table 1. Summary of the responses of amygdaloid neurons

Differential and selective neurons	
Differential responses to the S+ and S−	17
Differential responses based on stimulus novelty	10
Selective responses to faces	10
Selective responses to food	6
Non-selective responses	
Responses during the shutter period	122
Responses during the tone period	72
Responses during the clinical tests	19
Responses during licking	12
Responses to auditory stimuli (e.g. to vocalisation by another monkey)	7
Responses to tactile stimuli (e.g. touch to the oral region)	2
Unresponsive neurons	382
Total number of recorded neurons	659

Data analysis

For each trial of the memory tasks the computer counted the number of spikes emitted during the period from 100 to 600 ms after stimulus onset. This period was used because (1) neuronal response latencies in structures afferent to the amygdala are of the order of 100 ms (Rolls and Deco, 2002), and (2) this is the period in which the monkeys make decisions about behavioral responses based on the presented stimuli. Data for the different trials (S+, S−, and novel and familiar in the recognition memory task) were compared using one way analysis of variance and post hoc Tukey tests (Bruning and Kintz, 1977). These comparisons were based on data collected from between eight and 18 presentations of each type of stimulus. A neuronal response was classified as differential if the response to the S+ was significantly different ($P<0.05$) from that to the S−.

The responses of differential neurons are shown as scatter plots in order to show how each neuron responded in the various conditions. These data points represent stimulus-elicited increases or decreases in firing rate from the spontaneous firing rate of each neuron, as determined by subtracting the spontaneous firing rate from the responses elicited by the stimuli. The latencies at which neurons responded differentially to the S+ and S− were determined with the use of cumulative sum techniques (Woodward and Goldsmith, 1964) implemented on a computer. Peristimulus time histograms were computed for each type of trial and subtracted from each other; the cumulative sum of this difference array was then calculated to allow estimation of the differential response latency.

RESULTS

A total of 659 neurons in 92 electrode penetrations were recorded in three hemispheres of two monkeys. The classification of all recorded neurons is found in Table 1. [The ten neurons in row 3 of Table 1 with responses only to novel stimuli have been described by Wilson and Rolls

(1993)]. Of the 659 neurons shown in Table 1, for 17 neurons it was possible to show that they had visual responses, discriminated between the reward- and punishment-associated stimuli in the Go/NoGo visual discrimination task, and to complete testing in both the visual discrimination and the visual recognition memory tasks. The reconstructed locations of these neurons that discriminate between reward-related and punishment-associated visual stimuli are shown in Fig. 1. The majority (12/17) of these neurons were located in the central or basal amygdaloid nuclei. Four differential neurons were in the basal nucleus and one was in the dorsal part of the lateral nucleus. All nuclei of the amygdala were well sampled in these 92 recording tracks, as shown by the recording sites of all 659 neurons shown in Fig. 1 of Wilson and Rolls (1993).

Visual discrimination task

The responses of one neuron with different responses to the reward and saline-associated visual stimuli in the visual discrimination task are illustrated in Fig. 2. The firing rate of the neuron increased on S+ (reward) trials with a latency of approximately 100 ms, and on S− trials (on which correctly the monkey did not lick) there was only a small transient response of the neuron on some trials, so that there was differential activity of the neuron to the S+ and the S− (occurring at 200 ms).

The majority (16/17) of these differential neurons responded with an increase in firing rate to the S+. To the S−, these neurons either had no response (n=4), had a decrease in firing rate (n=2), or had a transient increase in firing rate which was variable and lasted less than 100 ms (n=10). The differential response of the remaining neuron was expressed as more firing to the S− than to the S+. The magnitudes of the responses of the 17 differential neurons are shown in Fig. 3. In this scatter plot, each data point represents the mean response of a neuron to the S+ (ordinate) compared with its mean response to the S− (abscissa), following the subtraction of the spontaneous activity of each neuron from the responses elicited by the stimuli. Data points that cluster around the ordinate represent neurons with either no response to the S− or a decrease in firing rate to the S−. Data points located above the line of bisection and to the right of the ordinate represent neurons that responded with an increase in firing to the S+ with only a minor or transient response to the S−. The responses of each differential neuron to the S+, the S−, and novel and familiar stimuli were subject to an analysis of variance and Tukey tests, which in all cases showed significant differences between the responses to the S+ and S−. The responses of other neurons that yielded non-significant results were not included in this group of differential neurons.

Some of these differential neurons tended to respond to both the S+ and the S−, but with a more transient and smaller response to the S−. The mean latency of these responses to the visual stimuli by these 17 differential neurons was 131 ms, and the mean differential response latency (measured with the cusum technique) was 203 ms (range=90–380 ms) (which compared with the behavioral response latencies of 250–400 ms). The mean spontaneous firing rate of these differential neurons was 15 spikes/s (range=3–46 spikes/s).

The recognition memory task

The performance of the recognition memory task is guided by a reinforcement rule based on the memory of the familiarity of the stimuli: the presentation of a novel stimulus signals that aversive saline will be obtained if a lick is made, while the same stimulus shown again as familiar signals that fruit juice reward will be obtained if a lick is made. Therefore there is no direct reinforcement association to the stimulus that enables the task to be solved by remembering the previous association of the stimulus with reinforcement. This task was used to assess whether the responses of neurons that were identified by their differential activity in the visual discrimination task had responses which reflected the reward or reinforcement value even under conditions when there was no previous direct association of the stimulus with primary reinforcement.

The responses of neuron 339 to the novel and familiar stimuli presented in the recognition memory task are shown in Fig. 4. Although this neuron responded differentially to the S+ and S− in the standard (fixed) visual discrimination task with a high firing rate to the S+ and no response to the S−, the neuron had a high firing rate response to both the novel and the familiar stimuli in the recognition memory task (see Fig. 4), despite the fact that these stimuli differentially signaled the availability of aversive saline and juice reward. As all four types of stimuli (S+, S−, novel and familiar objects) were presented in pseudorandom order, the non-differential responses to novel and familiar stimuli cannot be attributed to changes in the stability and isolation of the neuronal recording with prolonged testing.

Twelve of the 14 neurons with differential activity in the standard visual discrimination task that were tested also in the recognition memory task did not respond differentially to the stimuli when novel (first presentation, leading to saline if a response was made) and when familiar (second presentation, leading to juice reward if a lick response was made) in the recognition memory task. An analysis of variance and Tukey tests provided the basis for the conclusion that there was no significant difference in the responses to novel and familiar stimuli, although there was a significant difference between the responses to the S+ and S− in the visual discrimination task. The responses of the 14 neurons tested in both tasks are shown in Fig. 5. In this figure a comparison is made between the mean response to the S+ (plotted along the ordinate) with the mean responses to novel and familiar stimuli (plotted along the abscissa). Many of the data points lie along the line of bisection, indicating that the responses to the S+, novel, and familiar stimuli are largely equal and large. (None of the neurons had large responses to the S−, as shown in Fig. 3.) In Fig. 5 the responses of each neuron to novel and familiar stimuli are shown joined by horizontal lines, illustrating the similarity for most of the neurons of their responses to these stimuli, even though the stimuli when

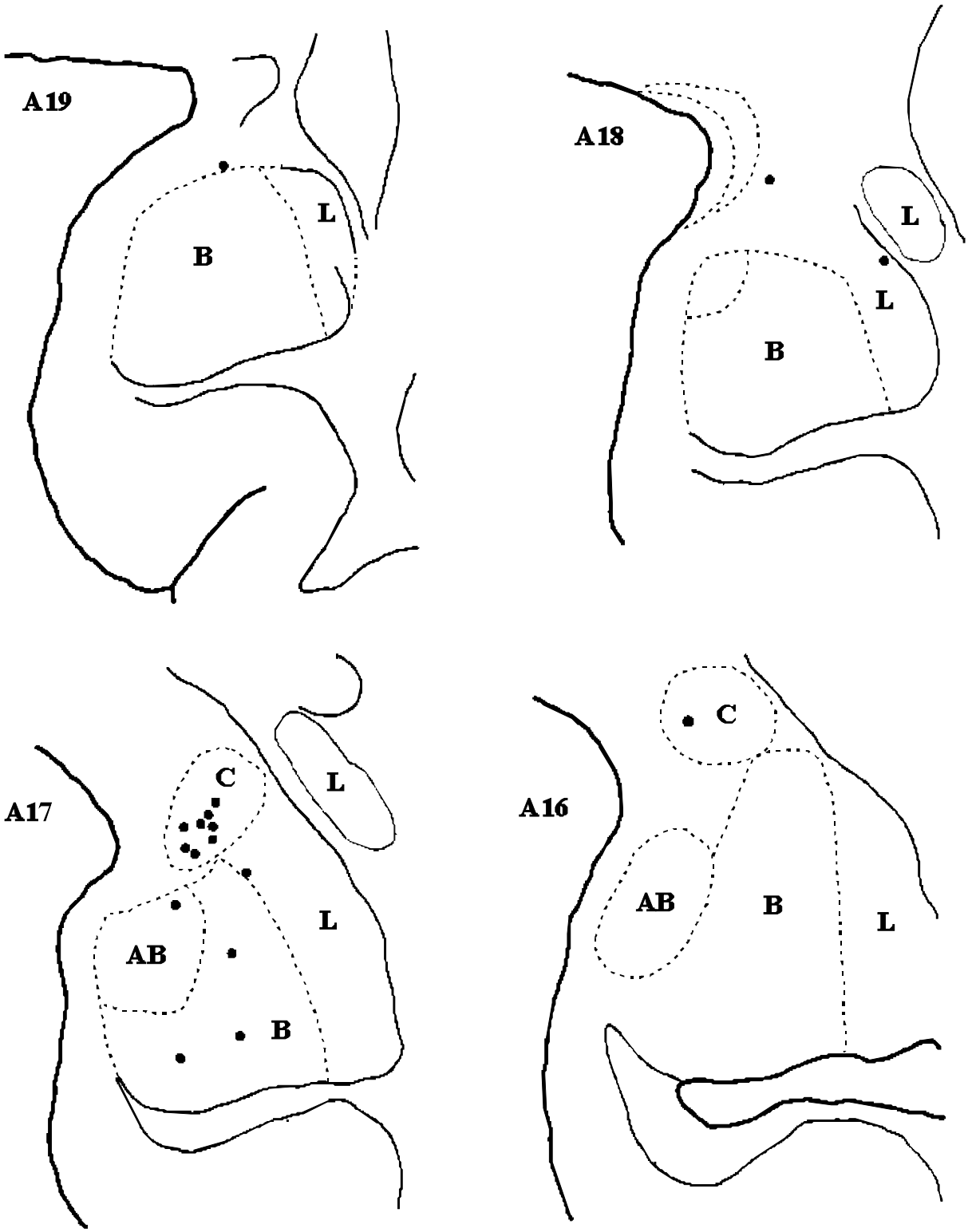

Fig. 1. The distribution of neurons with differential responses in the visual discrimination task. Each large dot represents the location of a differential neuron. Each drawing represents a section of brain 1 mm in extent, plotted anterior to the interaural line. The most posterior section is not shown. The locations of the neurons from three hemispheres are shown on a standard set of sections from the left hemisphere of one of the monkeys. Amygdaloid nuclei: AB, accessory basal nucleus; B, basal nucleus; C, central nucleus; L, lateral nucleus.

novel signified punishment and when familiar signified reward. It should be noted that the performance of the monkey was accurate during the recognition memory task, and it follows that the responses of these amygdala neurons

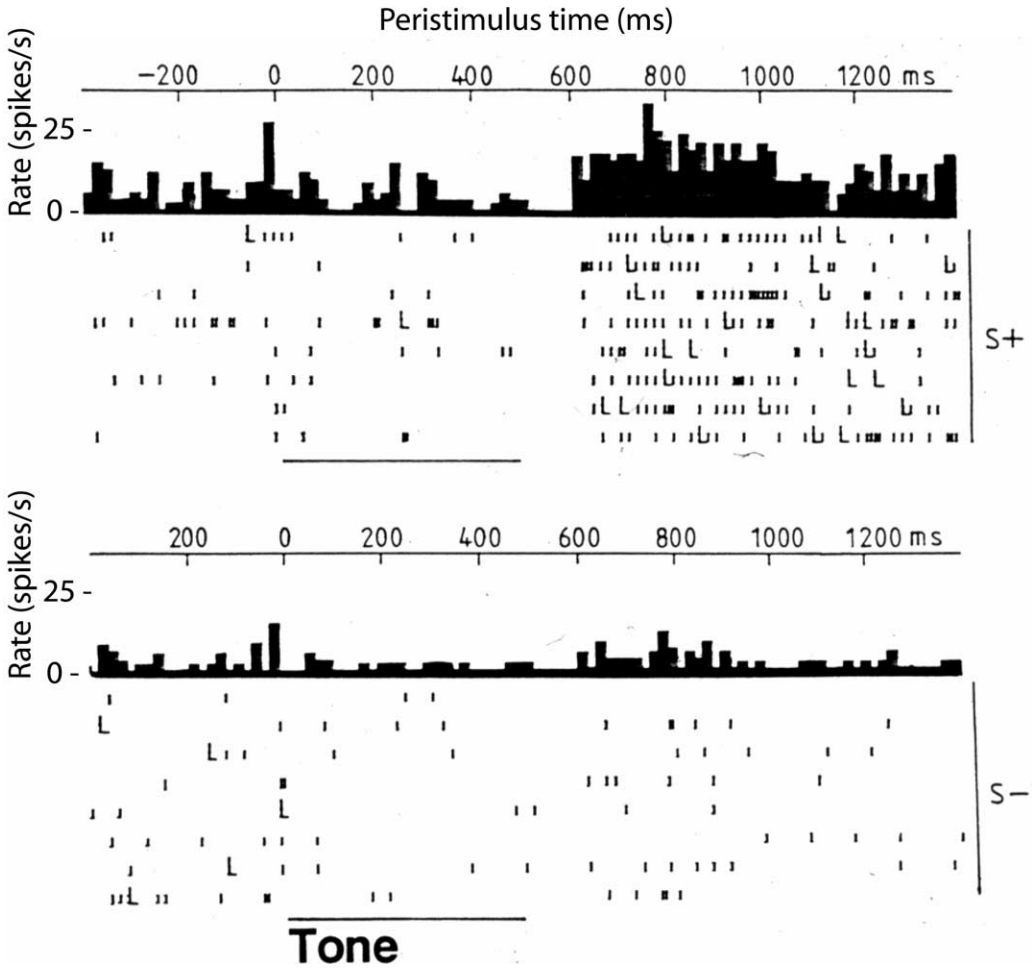

Fig. 2. Rastergrams and peristimulus response histogram showing the responses of a differentially-responsive neuron (339) in the visual discrimination task. Each tick represents the occurrence of an action potential; each row of ticks represents the firing of the neuron on a single trial to the presentation of the S+ or S−, with the visual stimulus presentation onset at time 0. There is an increase in firing rate at the presentation of the S+ stimuli. Presentations of the S+ and S− stimuli occurred in pseudorandom order but are grouped for clarity. The L indicates the occurrence of the lick response. The bin width in the histogram was 10 ms.

could not lead to the behavioral responses in the recognition memory task.

Although some of these neurons responded a little less the second than the first time each stimulus was shown in the recognition task (familiar vs novel in Fig. 5), in all cases this effect was non-significant, and contrasts with the responses of other amygdaloid neurons in which habituation was statistically significant (Table 1; Wilson and Rolls, 1993).

Clinical tests

In order to study other properties of differential neurons, foods and the S− syringe were presented to the monkeys through the aperture in the primate chair. During these tests counts of neuronal firing rate were taken during the sight and approach of stimuli toward the monkey, during the manipulation of the mouth with the stimulus, and during chewing and drinking. A neuron was taken to be responsive if the response to a stimulus was greater than a 50% change in the spontaneous firing rate of the neuron.

The majority of the neurons with differential responses in the visual discrimination task also responded to the sight of food (five of eight neurons tested), with fewer neurons responding while food was approaching the mouth (three of nine tests), touching the mouth (one of four tests), and during chewing (one of six tests). In all but one case the magnitude of the response to the sight of food was greater than responses to touching of the mouth and during chewing. Thus these neurons appear to be primarily activated by the visual appearance of foods, by the S+ in the standard visual discrimination task, and by relatively novel stimuli (i.e. on the first and second presentations) in the recognition memory task.

In six clinical tests in which the standard S− was presented outside the visual discrimination task, three differential neurons responded strongly to this stimulus. The neuronal responses to these presentations were increases in firing rate, compared with no change or a decrease in firing rate observed in the visual discrimination task. This responsiveness provides evidence that the lack of neuro-

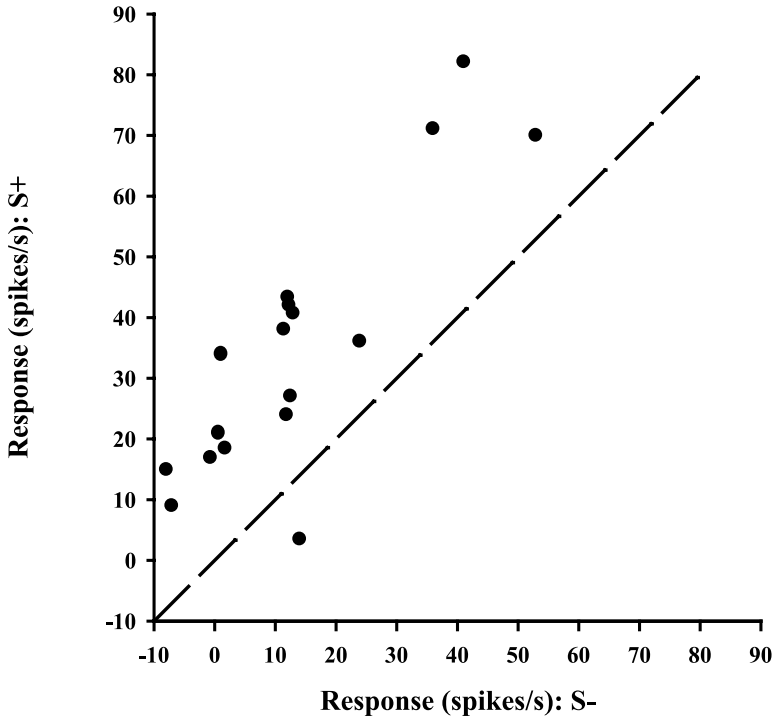

Fig. 3. Responses to the S+ and S− in the visual discrimination task. Each data point represents the mean responses (spikes/s) of one neuron to the S+ (ordinate) and the S− (abscissa). (The spontaneous firing rate of each neuron was subtracted to calculate its response.) Some neurons responded with increases in firing rate to the S+ and a smaller, transient response to the S−; other neurons respond to the S+, with no response or a decrease in firing to the S−. The firing rates were calculated over a 500 ms period starting 100 ms after stimulus onset.

nal responses to the S− in the standard visual discrimination task reflect a highly trained stimulus–reinforcement association, and that the neurons do not adapt flexibly to other situations.

Responses during the tone cue

A 500 ms tone cue preceded the presentation of all visual stimuli in the discrimination and recognition tasks. This cue

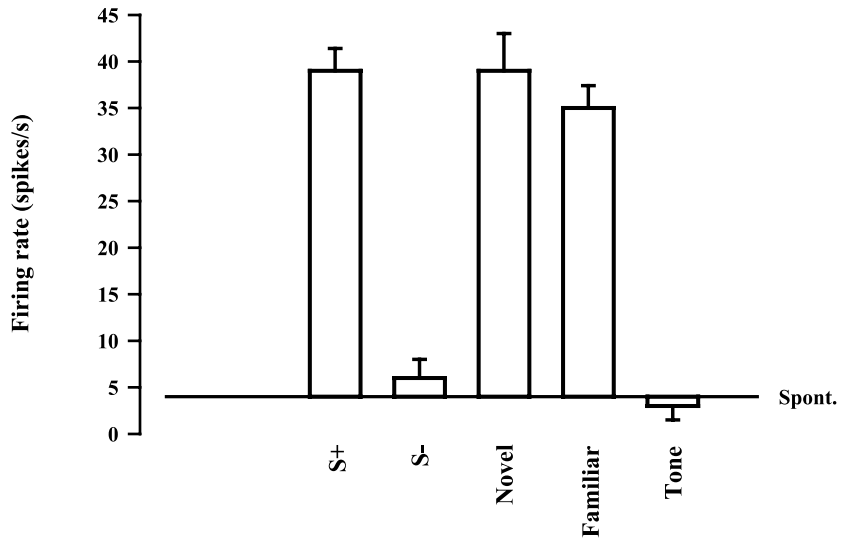

Fig. 4. Neuron 339 responded strongly to the S+ but not the S− in the standard visual discrimination task, and responded to both the novel and familiar stimuli in the recognition memory task, even though the novel stimuli signified saline if a lick response was made, and the familiar stimuli signified fruit juice reward. The means and standard errors of the neuronal responses are shown. (The responses to many novel stimuli were measured, on the first presentation when denoted novel and on the second presentation when denoted familiar, in the running recognition memory task.) The neuron did not respond to the tone cue which preceded the visual stimuli in both tasks. The means and SEM of the neuronal responses are shown. The spontaneous firing rate of the neuron is also shown (Spont).

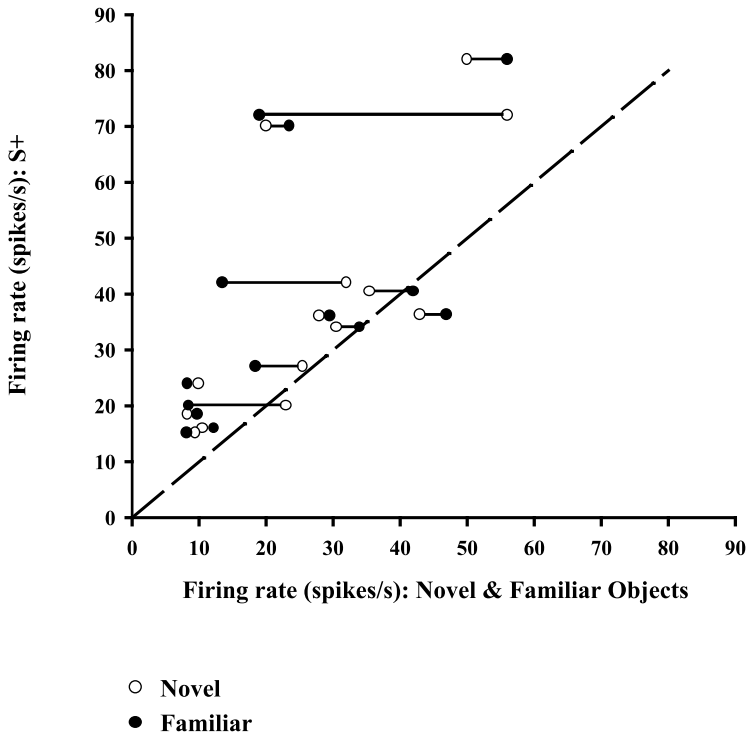

Fig. 5. Comparison of the responses to the S+ with the responses to novel and familiar stimuli. Each data point represents the mean responses (spikes/s) of one neuron to the S+ and to novel stimuli (open circles) or to familiar stimuli (filled circles). Responses to the S+ and novel/familiar stimuli are plotted along the ordinate and abscissa respectively. Each data point represents the neuronal responses after the spontaneous firing rate of the neuron has been subtracted. This transformation shows the magnitude and direction of the neuronal responses. Horizontal lines connect data points representing responses to novel and familiar stimuli compared with the S+ for a particular neuron. It is notable that the responses to novel and familiar stimuli are very similar. Data points along the line of bisection would indicate equivalent responses between the S+ and other stimuli; responses to the S+ tend to be slightly greater than to novel and familiar stimuli, as indicated by the distribution of the points above the line of bisection.

was used to facilitate fixation on the visual stimuli, and was a cue that signaled the appearance of salient visual stimuli such as the S+ and S−. The tone cue indicated that, relative to the intertrial interval, the probability of obtaining reward had increased (to 0.5), and it was of interest to determine whether the responses of these neurons reflected this alteration in reinforcement probability signaled by the tone cue. To use a term from neuroeconomics, the tone signaled an expected utility of 0.5, if the reward value of the fruit juice is taken as 1 (Glimcher, 2003). Fig. 6 shows that most of the neurons, although responding to the S+ (or in one case to the S−), did not respond to the tone cue. Only four of the 17 differential neurons responded to the tone cue and to the S+; three of these data points are located along the line of bisection, indicating equality of the responses to the tone and to the S+, with one neuron responding more strongly to the tone than to the S+. Thus these amygdala neurons did not track the expected reward value (Glimcher, 2003; Rolls, 2005).

Non-differential neuronal activity

Approximately half of all recorded neurons responded to the visual stimuli presented in the tasks. Extensive testing of these neurons indicated that only a minority responded differentially in the visual discrimination task as described above. Other groups of neurons (see Table 1) responded differentially in the recognition memory task on the basis of the novelty of the stimuli (as described by Wilson and Rolls, 1993), or selectively to food or face stimuli (cf. Leonard et al., 1985), or had significantly different responses ($P<0.05$) as tested by ANOVA to auditory or tactile stimuli (see for full paper Kadohisa et al., 2005) as shown in Table 1. However, the majority of responsive neurons responded non-selectively to the different visual stimuli shown in the tasks, during the tone cue period, or during the clinical tests. The basis of these non-selective responses could not be determined within the constraints of the testing protocols.

DISCUSSION

Amygdala neurons and associations between visual stimuli and primary reinforcers

The present results show the following. First, a population of amygdala neurons responds differentially to rewarding and aversive stimuli in a visual discrimination task with which the monkeys have had many thousands of trials of experience. This population of neurons typically responds more to the S+ than the S−. This confirms the finding of Sanghera et al. (1979), and the data of Nishijo et al. (1988) are consistent with this. The fact that there are many amygdala neurons that respond more to a visual stimulus

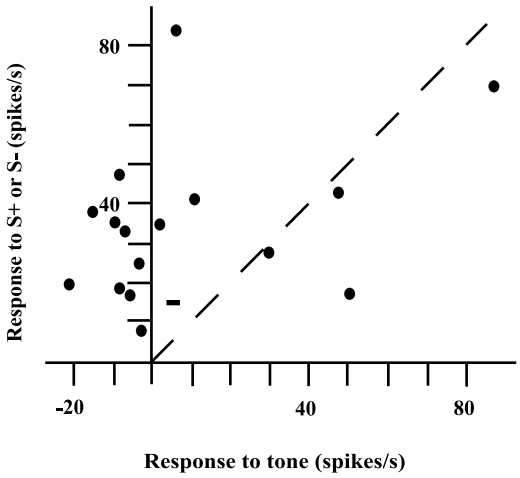

Fig. 6. A comparison of neuronal responses to the tone cue, the S+ and the S−. Each data point represents the mean responses (spikes/s) of one neuron to the tone cue plotted along the abscissa and the sight of the S+ (filled circles) or the S− (−) on the ordinate. The spontaneous firing rate of each neuron was subtracted from the responses to show the magnitude and direction of the neuronal responses. Most neurons responsive to the S+ did not respond to the tone cue and these data points are clustered around the ordinate. Four neurons responded to the tone cue and these data points are located on or to the right of the line of bisection. The one differential neuron that responded to the S− is indicated by the dash (-).

associated with a reward than with a punishment is of importance given the emphasis that has been placed on functions of the human amygdala in the effects elicited by aversive stimuli such as faces with fear expressions (Adolphs et al., 1994; Young et al., 1995, 1996). Consistent with the neurophysiology described here that reward-related stimuli can activate the amygdala, in fMRI studies we have found that the human amygdala is activated perfectly well by the pleasant, rewarding, taste of a sweet (glucose) solution (O'Doherty et al., 2001), providing evidence that reward-related primary reinforcers do activate the human amygdala (see also Rolls, 2005).

Second, the results show that these neurons do not respond to a stimulus on the basis of reward or reinforcement value when the reinforcement value is indicated by a rule rather than by direct previous association of the stimulus with reinforcement. This was shown by the finding in the visual recognition memory task with essentially trial-unique stimuli that these neurons responded equally to a novel stimulus which by rule indicated that aversive saline would be obtained, and to the same stimulus when repeated as familiar which indicated by rule that juice reward would be obtained. (In the recognition memory task the monkey's responses to familiar stimuli cannot be guided by direct associations between the stimulus when novel, and primary reward, e.g. taste, for when seen as novel, the stimulus indicated punishment by aversive saline if a lick response was made.)

Third, the results confirm the finding (Sanghera et al., 1979) that although the responses of these neurons occur in a visual discrimination task more to the S+ than the S−, and tend to respond to other visual stimuli consistent with this reinforcement association, the responses of this population of amygdala neurons do not occur to all stimuli with a given reinforcement value, and do not occur only to stimuli which have a given reinforcement value. This is shown in the present study by the findings that these neurons do not respond to stimuli in a visual recognition memory task based on the reinforcement signaled by the stimuli; that these neurons may respond in clinical tests to some stimuli which are not associated with reward, and may not even fully reflect in clinical tests the learned association of the S+ with reward; and that these neurons usually do not respond to the tone cue used in the tasks even though this signals that the probability of reinforcement has increased. This is in contrast to a population of basal forebrain neurons, some analyzed in the same monkeys, which have responses that reflect the reinforcement value of stimuli in all these situations (Mora et al., 1976; Rolls et al., 1976, 1979; Wilson and Rolls, 1990a,b).

There is another situation in which primate amygdala neurons do not reflect the reward value of visual stimuli, and this is during the reversal of a visual discrimination task (Sanghera et al., 1979). In that study, eight of nine neurons tested did not reverse their responses during visual discrimination reversal, and for one neuron the result was unclear. Two of the present set of amygdala neurons were also tested in visual discrimination reversal, and did not reverse their responses (Rolls, 2005). This finding is different to that for certain populations of neurons in the caudal orbitofrontal cortex and in a region to which it projects, the basal forebrain, which do show very rapid (in one or two trials) reversals of their responses in visual discrimination reversal tasks (Thorpe et al., 1983; Wilson and Rolls, 1990b; Rolls et al., 1996). On the basis of these findings, it is suggested that the orbitofrontal cortex is more involved than the amygdala in the rapid readjustments of behavioral responses made to stimuli when their reinforcement value is repeatedly changing, as in discrimination reversal tasks (Thorpe et al., 1983; Rolls, 1990, 1992, 1999, 2000, 2005). The ability to flexibly alter responses to stimuli based on their changing reinforcement associations is important in motivated behavior (such as feeding) and in emotional behavior, and it is this flexibility which it is suggested the orbitofrontal cortex adds to a more basic capacity which the amygdala implements for stimulus-reinforcement learning (Rolls, 1990, 1992, 1999, 2005).

It is unlikely that non-specific factors such as differences in the sensory properties of the stimuli, the go/no-go responses, eye movements, and task difficulty can account for the present results. First, it is unlikely that properties of the S− (e.g. shape and color) account for differences in the responses to the S− compared with the S+ and objects shown in the recognition memory task. The evidence for this is that in the recognition memory task many visual stimuli, some of which shared the color or the general shape of the S+ and S−, were presented, yet the neurons responded to novel and familiar stimuli in the recognition memory task and to the S+, but responded differently (usually very little) to the S−. Second, although the neurons responded very differently to the S− and novel stimuli, the monkeys made precisely the same (no-go) response to these two types of stim-

uli. In contrast, the monkeys' lick responses were made differentially to the S+ and novel stimuli, yet the neurons generally responded equally well to these stimuli. Third, eye movements do not account for these data as they are largely identical for all types of trial during the period in which neuronal data were collected (Wilson and Rolls, 1990a), and are usually initiated at a latency that is substantially longer than the average differential response latency of these amygdaloid neurons (Wilson and Goldman-Rakic, unpublished observations). Fourth, in a parallel study in which the subjects were the same monkeys used in the present study, we found that neurons in the basal forebrain, a major efferent target of the amygdala, responded differentially in the visual discrimination, reversal and recognition memory tasks, and therefore encoded the learned reinforcement value of the stimuli (Wilson and Rolls, 1990a,b). Thus differences in the difficulty of the various tasks cannot account for the amygdaloid neuronal responses, which are dissociable from those in the basal forebrain.

Our conclusion, with respect to associative learning, is thus that the responses of these neurons could reflect the association of a stimulus with a primary reinforcer, when the association is established in the long term with repeated stimulus–reinforcement association pairings. However, amygdala neurons in primates do not reflect the reinforcement association of stimuli rapidly when it changes in the reversal of a visual discrimination task, nor do these amygdala neurons reflect the reinforcement value of a stimulus when this must be determined on the basis of a rule (e.g. "familiar but not novel stimuli are rewarding").

To highlight the differences between the amygdala and orbitofrontal cortex in rapid reversal, we note that Deco and Rolls (2005) have proposed that the orbitofrontal cortex may implement rapid, one trial, visual discrimination reversal by holding the current rule (e.g. "the triangle is currently associated with reward") in a short term memory attractor network which can be rapidly switched from one state to another. (The switch occurs using quenching via inhibition of the current attractor state implemented by the error neurons described by Thorpe et al. (1983), and then the opposite attractor emerging because of partial adaptation in the synapses supporting the previously active attractor.) The rule attractor then switches the current mapping from stimuli to reward in a way analogous to that described by Deco and Rolls (2003). It is suggested here that this mechanism may not be implemented in the amygdala because, unlike the cerebral neocortex, highly developed recurrent collateral connections capable of supporting short-term memory-implementing attractors may not be present in the amygdala. This is a new computational hypothesis to account for the greater ability of the orbitofrontal cortex than the amygdala to implement rapid stimulus-reinforcement reversal learning.

Amygdala neurons, the reinforcing effects of novel stimuli, and approach/avoidance behavior

It was notable that these amygdaloid neurons responded to the S+ in the visual discrimination task and to the novel and familiar visual stimuli in the recognition memory task, but did not respond to the S− in the visual discrimination task. We suggest that the lack of response to the S− was because it had been presented on many occasions without reinforcement, or with negative reinforcement, so that the monkey had no tendency to explore or approach it further. In contrast, the novel and familiar stimuli in the trial-unique recognition task had not been seen before on novel presentations, and for only 1.5 s on familiar presentations, and with this limited degree of exposure, the monkeys were likely to still be interested in the stimuli, and to wish to explore them further (Humphrey, 1972). The S+ stimuli still elicited approach because of their association with reinforcement. The hypothesis we propose is that the responses of these amygdala neurons reflected the tendency of the monkeys to explore and/or approach the stimuli, and reflect two different processes that influence whether a stimulus is approached, that is, whether it has reward value. One process is that relatively novel stimuli are approached. The second is that stimuli that have been previously associated with primary reward are approached. These two processes would result in no approach if the stimuli were familiar, and had not previously been associated with a primary reward, or had been associated with punishment. In line with this suggestion, in a discrimination task, amygdala lesions would impair performance by impairing the normal ability of monkeys to *stop approaching visual stimuli if they have been seen long enough to become familiar*, and have not been paired with a primary positive reinforcer. It is thus suggested that these amygdala neurons respond to relatively novel stimuli (for at least the first several presentations), and that this responsiveness is the mechanism by which relatively novel stimuli are found reinforcing to explore. We note that the findings in the recognition memory task show that these amygdala neurons do not represent reward value when it is based on a rule, that a novel stimulus is rewarded, and when shown a second time, it is punished. Nor do these amygdala neurons reflect reward value when it changes rapidly during visual discrimination reversal.

Localization of these neurons in the amygdala

Neurons with differential responses in the visual discrimination task were mainly located in the central and basal nuclei of the amygdale, as shown in Fig. 1. Other studies have also reported regional differences in the distribution of responsive neurons recorded during the performance of operant tasks for food reinforcers (Nakano et al., 1986; Nishijo et al., 1988), and for neurons that are selectively responsive to the presentation of faces (Leonard et al., 1985; Rolls, 1992). The basis of this localization may be due to the anatomical organization of the amygdala, for the projection fields of the sensory-specific association cortices and their subregions are largely separated within the amygdala (Herzog and Van Hoesen, 1976; Turner et al., 1980; Iwai and Yukie, 1987), but converge in the dorsal part of the amygdala in the region of the central nucleus (Aggleton, 1985). Thus the differential neurons may reflect the convergence of intrinsic connections within the amygdala. It is notable that the central nucleus projects mas-

sively to the brainstem, connections which may influence the autonomic mechanisms often associated with amygdala function (Bagshaw and Benzies, 1968; Pascoe and Kapp, 1985; Rolls, 1999) and with affective reactions.

The representation of information in the responses of amygdala neurons

The small proportion of amygdala neurons activated by each stimulus or even class of stimulus was notable. This seems to be a consistent finding in neurophysiological studies of the amygdala. The differential neurons described in this paper comprised 2.6% of all recorded amygdala neurons; other neurons responded maximally to novel stimuli, or to foods, or to faces (Table 1). Sanghera et al. (1979) found 22/1754 (1.3%) amygdala neurons that responded mainly to the sight of foods; Nishijo et al. (1988) found that 14/585 (2.4%) of their sample were selectively driven by food stimuli; and Kadohisa et al. (2005) found that 44 (3.1%) of 1416 macaque amygdala neurons responded to oral stimuli. One reason for these low proportions may be that, to some extent, the different sensory modalities are separated within the amygdala. The differential neurons in the present study responding both to visual and auditory stimuli may reflect a convergence of sensory modalities in the central nucleus. Of course, as expressed as proportion of the neurons recorded in the relevant part of the amygdala, the proportion will be higher, as is evident from Fig. 1 and the fact that the amygdala was widely sampled in this study, with the recording sites of all neurons shown in Fig. 1 of Wilson and Rolls (1993). A second reason is that many amygdala neurons may require the presence of specific stimulus attributes that are different for different neurons. Amygdala neurons, if they are activated, often appear to exhibit a graded response to the various stimuli that are presented, in some cases responding to a small number of stimuli or even to a category of stimuli such as foods or faces (Table 1). The value of maintaining the proportion of neurons which respond to any one stimulus to a low value is discussed by Rolls (1989) and by Rolls and Treves (1990, 1998). This is particularly important in brain systems which are involved in associative memory, for under most conditions, this increases the memory capacity of the system.

The relationship between the activity of these neurons and emotion

Jones and Mishkin (1972) elaborated the hypothesis that many of the symptoms of the Klüver-Bucy syndrome produced by damage to the amygdala, including the emotional changes, could be a result of a deficit in learning stimulus-reinforcement associations (see also Mishkin and Aggleton, 1981; Rolls, 1990, 1999). For example the tameness, the hypoemotionality, the increased orality, and the altered responses to food would arise because of damage to the normal mechanism by which stimuli become associated with reward or punishment. Consistent with this, in a study of subtotal lesions of the amygdala, Aggleton and Passingham (1981b) found that in only those monkeys in which the lesions produced a serial reversal learning deficit was hypoemotionality present. According to the hypothesis which has been developed, a role for the amygdala in emotions, which can be considered as states elicited by reinforcing stimuli, is to lead to affective behavioral responses to stimuli which are reinforcing because they have a history of being associated with primary reinforcement, or because they are still relatively novel (Rolls, 1990, 1992, 1999). (Instrumental reinforcers are stimuli which if their occurrence, termination, or omission is made contingent upon the making of a response, alter the probability of the future emission of that response.) These affective responses include not only instrumental and approach behavior directed toward the stimulus, but also autonomic responses elicited by the stimuli, and there may be separate output pathways from the amygdala for these functions (Rolls, 1990, 1992, 1999). This hypothesis is now extended here and elsewhere (Rolls, 1992, 1999, 2005), by adding, consistent with the neuronal responses described in this paper, that a role for the amygdala in emotions, is to lead to affective behavioral responses (including approach) to stimuli which are reinforcing either because they have a history of being associated with primary reinforcement, or because they are still relatively novel.

In conclusion, the amygdala neurons described reflect reward value when it is based on well-learned direct associations between visual stimuli and rewards, but not when the reward value is based on a rule, or when the expected reward value increases during a trial as a result of presenting a cue that the trial will start. The amygdala neurons do reflect reward value when it is based on visual stimuli being relatively novel, so that they are approached and explored.

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