

Novel visual stimuli activate a population of neurons in the primate orbitofrontal cortex

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Abstract

Neurons were found in the rhesus macaque anterior orbitofrontal cortex that respond to novel but not to familiar visual stimuli. Some of these neurons responded to all novel stimuli, and others to only a subset (e.g., to novel faces). The neurons have no responses to familiar reward- or punishment-associated visual stimuli, nor to taste, olfactory or somatosensory inputs. The responses of the neurons typically habituated with repeated presentations of a novel stimulus, and five presentations each 1 s was the median number for the response to reach half-maximal. The neurons did not respond to stimuli which had been novel and shown a few times on the previous day, indicating that the neurons were involved in long-term memory. The median latency of the neuronal responses was 120 ms. The median spontaneous firing rate was 1.3 spikes/s, and the median response to novel visual stimuli was 6.0 spikes/s. These findings indicate that the long-term memory for visual stimuli is information that is represented in a region of the primate anterior orbitofrontal cortex.

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1. Introduction

The cortex on the orbital surface of the frontal lobe includes Area 13 caudally, Area 11 anteriorly, and Area 14 medially, and the cortex on the inferior convexity includes Area 12 (see Fig. 8 and Carmichael & Price, 1994; Petrides & Pandya, 1995; Price, 1999). Visual inputs reach the orbitofrontal cortex directly from the

inferior temporal cortex in which representations of objects are found (Booth & Rolls, 1998; Miyashita, 1993; Rolls & Deco, 2002; Tanaka, 1996), the cortex in the anterior part of the superior temporal sulcus in which face-responsive neurons are found (Desimone, 1991; Hasselmo, Rolls, & Baylis, 1989; Hasselmo, Rolls, Baylis, & Nalwa, 1989; Perrett, Rolls, & Caan, 1982; Rolls, 2000c), and the temporal pole (Barbas, 1988, 1993, 1995; Barbas & Pandya, 1989; Carmichael & Price, 1995b; Morecraft, Geula, & Mesulam, 1992; Seltzer & Pandya, 1989). There are corresponding auditory inputs from the superior temporal cortex (Barbas, 1988, 1993), and somatosensory inputs from somatosensory cortical areas 1, 2, and SII in the frontal and pericentral operculum, and from the insula (Barbas, 1988; Carmichael & Price, 1995a). The caudal orbitofrontal cortex receives strong inputs from the amygdala (e.g., Price et al., 1991). The caudal orbitofrontal cortex contains the secondary and

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tertiary taste and olfactory cortical areas, and in these areas the reward value of taste and odour is represented (Rolls, 1999a, 1999b, 2000a, 2000b, 2002, chap. 23, 2004, 2005). The orbitofrontal cortex also receives inputs via the mediodorsal nucleus of the thalamus, pars magnocellularis, which itself receives afferents from temporal lobe structures such as the prepyriform (olfactory) cortex, amygdala and inferior temporal cortex (see Price, 1999). The orbitofrontal cortex projects back to temporal lobe areas such as the inferior temporal cortex, and, in addition, to the entorhinal cortex (or “gateway to the hippocampus”) and cingulate cortex (Barbas & Blatt, 1995; Insausti, Amaral, & Cowan, 1987).

Neurons with visual responses have been described previously in the orbitofrontal cortex (Rolls, Critchley, Mason, & Wakeman, 1996b; Thorpe, Rolls, & Maddison, 1983; Tremblay & Schultz, 2000a, 2000b). These neurons frequently respond to visual stimuli based on their association with either a rewarding or aversive taste (glucose vs. salt), and learn this association in as little as one trial (Rolls et al., 1996b; Rolls, 1999b; Rolls, 2002, chap. 23, 2005; Thorpe et al., 1983). In addition, another population of neurons in the orbitofrontal cortex responds to face visual stimuli (Rolls, 2005; Rolls, Critchley, Browning, & Inoue, 2005). These neurons are in the orbitofrontal cortex, and are separate from those described in the inferior prefrontal convexity cortex (O’Scalaidhe, Wilson, & Goldman-Rakic, 1997). In this paper we describe a new population of orbitofrontal cortex neurons that responds to novel visual stimuli.

The overall aim of this research is to advance understanding of the functions of the orbitofrontal cortex, because it is involved in emotion and its disorders (Rolls, 2005), and is a part of the brain frequently damaged in closed head injury in humans (Hornak, Rolls, & Wade, 1996; Rolls, 1999a, 1999b, 2000a, 2000b, 2004; Rolls, Hornak, Wade, & McGrath, 1994) though studied also in patients with discrete surgical lesions (Hornak et al., 2003, 2004).

2. Methods

2.1. Recordings

Recordings were made from single neurons in the orbitofrontal cortex in two rhesus macaques (*Macaca mulatta*) weighing 2.5–3.5 kg. The neurophysiological methods were the same as described previously (Rolls, 1976; Rolls, Yaxley, & Sienkiewicz, 1990; Rolls & Baylis, 1994; Scott, Yaxley, Sienkiewicz, & Rolls, 1986a; Scott, Yaxley, Sienkiewicz, & Rolls, 1986b; Yaxley, Rolls, & Sienkiewicz, 1990). All procedures, including preparative and subsequent ones, were conducted in accordance with the Policies on the Use of Animals and Humans in Neuroscience Research revised and approved by the Society for

Neuroscience in January 1995, and were licensed under the U.K. Animals (Scientific Procedures) Act 1986. The monkey was fed during the experiments and on return to its home cage and was allowed ad lib access to water. Glass coated tungsten microelectrodes were constructed in the manner of Merrill and Ainsworth (1972) without the platinum plating. A computer (Pentium) with real-time digital and analogue data acquisition collected spike arrival times and displayed on-line summary statistics or a peristimulus time histogram and rastergram. To ensure that the recordings were made from single cells, the interspike interval was continuously monitored to make sure that intervals of less than 2 ms were not seen, and also the waveform of the recorded action potentials was continuously monitored using an analogue delay line.

2.2. Localisation of recordings

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

2.3. Screening of neurons

2.3.1. Visual stimuli

Responses to visual stimuli were determined using a visual discrimination task to present images, views of objects, and faces on a video monitor (Rolls et al., 1996b), and by presenting real objects and faces through a large aperture (5 cm) shutter (Thorpe et al., 1983). The visual discrimination task involved the randomised presentation on a video monitor of one stimulus per trial for 2 s in a Go/NoGo paradigm. A 500 ms cue tone preceded the visual stimulus to enable the monkey to fixate the screen before the visual stimulus appeared. Lick responses to a rewarded visual stimulus during the stimulus were rewarded with the delivery of a fruit juice solution from the lick tube; a lick response on the NoGo trials (or in the intertrial interval of typically 5 s) was associated with the delivery of a mildly aversive saline solution. Because the monkeys could make multiple licks during the 2 s period, and more licks could be made if the monkey was already fixating the screen before the stimulus appeared (Rolls, Sanghera, & Roper-Hall, 1979), the monkey’s fixation of the screen was excellent. Further evidence for this was that the first lick to a rewarded stimulus was made within 350–500 ms, which is only

possible if no saccade is necessary before a response is made; and that the neuronal responses had sharp onset latencies at ≈ 100 ms to effective stimuli as illustrated in Fig. 1B. While searching for visual cells, the task was run with 12 images in a standard familiar set used every day that were rewarded, and one (the S $-$) that was associated with saline.

To test a cell for responsiveness to novel stimuli, one novel image was inserted into the set. If the neuron responded to this novel image, then the main data collection task was run. The images in this task consisted of four of the set of familiar stimuli, and four completely novel images (typically two face and two non-face). (The images were completely novel in that they had never been seen before by the monkey.) The four familiar stimuli included the S $-$, included to make sure that the monkey looked at and processed the stimuli on every trial. It is emphasized that all the novel and familiar stimuli (including the S $+$) were rewarded, and only one stimulus, the S $-$, was punished if licks were made when it was shown. The performance of the monkeys was always between 90% and 100% correct for both the rewarded and the non-rewarded stimuli, indicating that the visual stimuli were indeed being seen and discriminated. The stimuli could include faces and objects, and examples are provided by Rolls and Tovee (1995). All the other stimuli were associated with reward. On-line rastergrams and statistics enabled the determination of visual responsiveness. Use of this visual discrimination task ensured that on every trial the monkey looked at the video monitor, and perceptually processed the stimuli. Further evidence that the visual stimulus presentation was appropriate is that the receptive fields of inferior temporal cortex neurons, which provide the visual inputs to the orbitofrontal cortex, are typically 70° in diameter in the stimulus presentation conditions used here (Rolls, Aggelopoulos, & Zheng, 2003a); and that the neuronal responses had reliable short latencies, and continued throughout the 2 s visual presentation period, as illustrated in Fig. 1B. Once 6–8 trials for each stimulus had been run, the main data collection task was rerun several times with different familiar images from the standard set, and four further completely novel images. This enabled the neuronal responses after data collection to be compared to typically 8–12 familiar images, and 8–12 novel images. The monkey was trained on this visual discrimination task, but was never trained on any recognition memory task, that is a task in which differential behavioural responses had to be made to novel and familiar visual stimuli. Thus the neurons described in this paper could not reflect the training of different behavioural responses to novel and familiar visual stimuli.

To analyse the neuronal responses, the firing rate was measured in each trial in a 500 ms period starting after the neuron started to respond (as identified by cumulative sum tests). A one-way ANOVA was

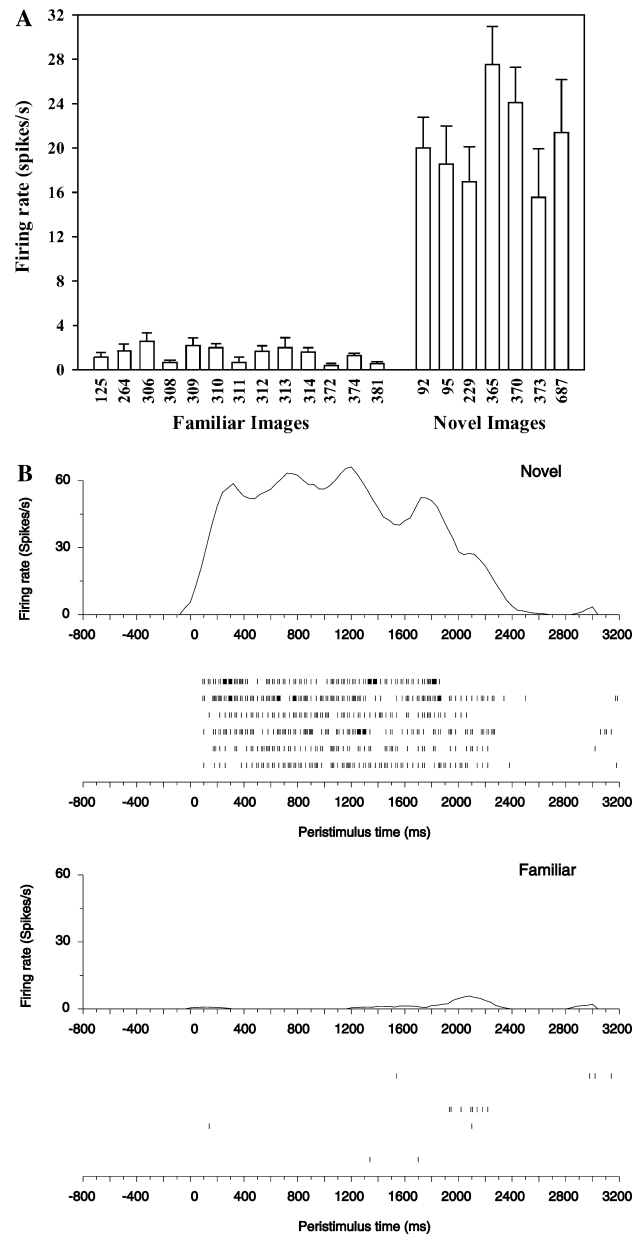


Fig. 1. (A) The activity of a neuron (be0281) that had no response to familiar visual stimuli, but which responded to all novel visual stimuli. The mean and standard error of the mean responses calculated across the responses to 4–6 novel and familiar stimuli are shown in this and the other figures unless otherwise stated. The rates were measured in a 2 s period starting at the onset of the 2 s visual stimuli in a visual discrimination task. Licks to all stimuli produced fruit juice reward apart from image 374, licks to which if made produced a taste of saline in the visual discrimination task. The numbers refer to different stimulus images. (B) Rastergrams and peristimulus time histograms of the same cell. The response latency was approximately 80 ms. The trials for the novel images are each to a different novel image. The trials to the familiar images are each to one of the set of familiar images. The peristimulus histograms are calculated from all novel trials (above) and all familiar trials (below).

performed, followed by post hoc tests, to identify significant responses, and differences between stimuli, using SPSS. This showed which responses were different, based

on the 4–10 trials of data available for each stimulus. To test the significance of the difference between the responses to novel and familiar stimuli, a Student's *t* test was performed using the responses to all novel stimuli and the responses to all familiar stimuli.

In addition to tests for visual responsiveness, tests were also performed to investigate whether the neurons described here responded to sensory inputs from other modalities, including taste, olfactory, and oral somatosensory stimuli. It is noted here that none of these orbitofrontal cortex neurons had taste, olfactory, or oral somatosensory responses, all of which have been found in other populations of orbitofrontal cortex neurons (Rolls et al., 1990; Rolls & Baylis, 1994; Rolls, Critchley, Wakeman, & Mason, 1996a; Rolls et al., 1996b; Rolls, 1999a, 1999b; Rolls, Critchley, Browning, Hernadi, & Lenard, 1999, 2000a, 2000b; Rolls, 2002, chap. 23; Rolls, Verhagen, & Kadohisa, 2003b; Thorpe et al., 1983).

2.3.2. Taste

The testing methods used were those described by Rolls et al. (1996a, 2003b, 1990) and shown to activate some orbitofrontal cortex neurons. The gustatory stimuli included 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 0.001 M QHCl (Q) and 0.1 M monosodium glutamate (M). The concentrations of most of the tastants were chosen because of their comparability with our previous studies, and because they are in a sensitive part of the dose–response curve. The monkey's mouth was rinsed with distilled water during the intertrial interval (which lasted at least 30 s, or until neuronal activity returned to baseline levels) between taste stimuli. The stimuli within a set were delivered in random sequence. The stimuli were delivered orally in quantities of 0.2 ml with a hand-held 1 ml syringe. For chronic recording in monkeys, this manual method for stimulus delivery is used because it allows for repeated stimulation of a large receptive surface despite different mouth and tongue positions adopted by the monkeys (Scott et al., 1986a, 1986b). The firing rates were measured in a 3 s post-stimulus delivery period, as this is the period in which taste neurons, and the neurons described here, were found to have their main responses. For additional comparisons, the neuronal responses were also tested to a range of foods including banana, orange, apple juice, milk, and 20% blackcurrant juice.

2.3.3. Oral somatosensory stimuli including fat

The testing methods used were those described by Rolls et al. (1999, 2003b) and shown to activate orbitofrontal cortex neurons. To test for the oral effects of fat on neuronal activity, a set of fat and fat-related stimuli were delivered in the same way with a pseudorandom sequence. The fat stimuli included “single” cream (cream) (18% fat), “double” cream (47.5% fat), triolein, groundnut oil, and half fat milk (milk) (1.8% fat). Trio-

lein (glyceryl trioleate) was used as a pure fat. Vegetable oil (59.5% monounsaturates, 34% polyunsaturates and 6.5% saturates) and groundnut oil were used as other natural high-fat stimuli. To investigate whether the neurons responsive to cream were in some way responding to the somatosensory sensations elicited by the fat, stimuli with a similar mouth feel but non-fat chemical composition were used. These stimuli included paraffin oil (pure hydrocarbon) and silicone oil ($\text{Si}(\text{CH}_3)_2\text{O}$)_{*n*}. To control for specificity of the somatosensory input which could activate these neurons, other, non-fat-related, oral somatosensory or motor responsiveness of neurons was screened for by allowing the monkey to chew on a short length of plastic tubing. Due to the tenacious nature of the oral coating resulting from the delivery of cream or oil, the interstimulus interval was prolonged (usually more than 2 min) and repeated rinses with water were given during this period.

2.3.4. Olfactory stimuli

Responses to odorants were determined either using a perfumer strip method or using an olfactory discrimination task (Critchley & Rolls, 1996a, 1996b; Rolls et al., 1996b). The criteria for olfactory responsiveness were a significant elevation of cellular firing above the spontaneous firing rate to an odorant (measured during a 5 s period of presentation in front of the monkey's nose of an cotton bud/perfumer strip saturated in odour vapour), and no response to an odourless cotton bud used as a control. The olfactory discrimination task involved the randomised delivery of odorant saturated air via a computer-driven olfactometer (Critchley & Rolls, 1996b). A cue tone preceded the delivery, following which the monkey was required to sample each odour to identify odours as part of a Go/NoGo task. A lick response to a rewarded odorant was rewarded with the delivery of a sweet aspartame solution from the lick tube; a lick response on the NoGo trials was associated with the delivery of a mildly aversive saline solution. On-line rastergrams and statistics enabled the determination of olfactory responsiveness. An air extraction apparatus was located above the monkey's head to remove odour (see Critchley & Rolls (1996b)).

3. Results

The data described here were obtained during 377 recording tracks in four hemispheres of two monkeys (109 in bk and 268 in be), in which 1037 (177 + 860) neurons were recorded in the orbitofrontal cortex, and 658 neurons were fully tested for responses to novel stimuli (593 in be, and 65 in bk). A population of neurons, found in both monkeys bk and be as shown in Table 1, responded to novel visual stimuli, with the properties described next.

Table 1
Orbitofrontal cortex novelty cell response properties

Cell	Spon.	Familiar (mean)	Novel (mean)	Novel (1st presentation)	S+ (mean)	S- (mean)	<i>p</i>	No. trials to 1/2 amplitude	Latency (ms)
Be019	0.34	0.55	4.68	7.76	0.45	0.38	9.21×10^{-6}	5	280
Be026	0.97	0.98	6.72	7.17	1.28	1.61	5.48×10^{-8}	>6	240
Be027	3.10	1.05	13.02	22.00*	1.4	2.48	2.96×10^{-13}	6	120
Be0281	0.46	1.52	20.58	38.92*	0.38	1.72	2.53×10^{-12}	>10	80
Be0282	0.08	0.26	2.90	11.39	0	0.26	5.72×10^{-3}	1	440
Be032	2.11	1.49	8.92	19.50	1.71	1.45	2.78×10^{-5}	6	120
Be033	0.24	0.12	1.17	2.61	0.03	0.30	0.023	>4	120
Be034	1.27	0.78	3.26	5.59	0.78	1.55	1.12×10^{-4}	8	200
Be046	1.72	0.65	3.23	6.00	0.74	2.12	2.32×10^{-3}	4	160
Be061	<0.5	0.78	3.60	5.50	0.53	0.96	1.09×10^{-3}	>6	120
Be064	1.36	1.52	6.04	6.25	0.76	0.90	4.20×10^{-5}	>7	200
Be068	1.23	1.00	6.04	9.38	0.92	1.29	1.76×10^{-9}	3	240
Be074	0.10	0.23	0.96	0.89	0.05	0.25	0.015	7	120
Be082	0.54	0.34	2.67	8.73*	0.18	0.43	6.7×10^{-4}	3	280
Be089	1.14	0.91	5.21	12.42	0.83	0.66	3.05×10^{-6}	3	120
Be091	8.83	7.46	22.56	22.06	6.70	11.76	6.89×10^{-11}	>6	120
Be094	0.58	0.81	2.30	4.93	1.26	0.25	3.88×10^{-3}	3	200
Be114	2.11	1.37	5.19	11.39	1.02	2.05	5.80×10^{-5}	3	160
Bk099-1	0.59	0.49	1.73	1.25	0.29	0.70	0.009	3	840
Bk099-2	16.14	11.62	4.22	3.96	10.28	13.01	8.21×10^{-20}	>7	80, dec.
Bk107	10.04	10.86	16.00	14.00	10.68	11.04	6.00×10^{-4}	>3	120
Bk108-1	0.12	0.32	1.52	1.68	0.21	0.42	<0.0001	>6	80
Bk108-3	6.68	5.50	3.42	3.75	4.50	6.50	0.0324	>3	120, dec.
Bk110-2	0.00	0.12	0.95	1.25	0	0.20	<0.0001	>3	680
Bk123	1.74	3.14	6.01	5.75	4.25	2.10	0.035	>6	80
Bk124	2.39	3.05	6.28	11.94	3.02	4.50	0.0012	5	120
Bk133	14.08	13.88	22.73	24.7	14.15	13.23	<0.0001	>4	120
Bk138-2	6.70	5.74	10.88	26.25	5.33	6.47	2.37×10^{-9}	4	280
Bk139-2	5.06	5.69	15.00	11.88	5.00	7.00	<0.0001	>3	200
Bk141	18.25	18.71	31.17	30.56	21.97	14.77	<0.0001	>7	120
Bk169	0.88	1.02	2.09	4.58	1.06	0.88	<0.0001	1	80

Note 1: *p*, the significance of the difference between novel and familiar stimuli.

Note 2: dec., a response that was a decrease from the baseline spontaneous firing rate.

Note 3: *, instances where the neuron did not respond to familiar visual stimuli, nor to the first presentation of novel visual stimuli. However, on the second presentation of a novel stimulus the neuron had a large neuronal response, and there was some response to novel stimuli for the next few presentations.

The activity of a neuron that had a low spontaneous firing of 0.5 spikes/s, and no response to familiar visual stimuli, but which responded with a firing rate of 20–28 spikes/s (on average) to all novel visual stimuli, is shown in Fig. 1. All the stimuli included in Fig. 1A were shown during the performance of the visual discrimination task, and included faces, objects, and scenes. The novel visual stimuli had not been seen before on any occasion (except where specified because the duration of the memory shown by the cells was being investigated). Rastergrams and a peristimulus time histogram are shown in Fig. 1B. The response latency was approximately 80 ms. Sixteen of the 31 neurons with responses to novel visual stimuli responded to all novel visual stimuli.

The activity of a different neuron which responded to only some novel visual stimuli is shown in Fig. 2. The novel visual stimuli to which the neuron responded were images of scenes (91 and 103), of parts of the body such as a hand (266), and of simple geometrical stimuli (376 and 377); and those novel images to which it did not respond included faces (345), body parts (126 and 133)

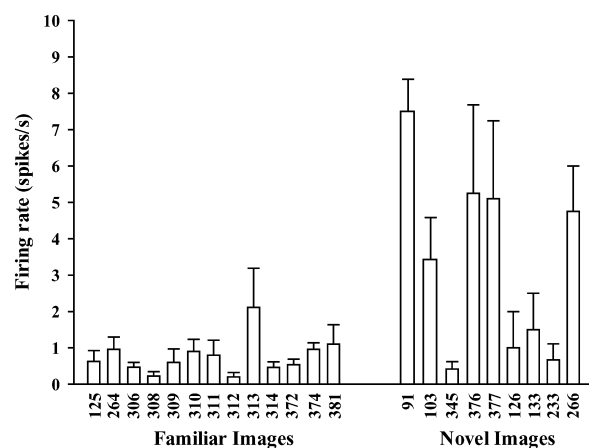


Fig. 2. The activity of a different neuron (be061) that responded to only some novel visual stimuli. Conventions as in Fig. 1. The spontaneous firing rate of this neuron was less than 1 spike/s.

and simple geometrical stimuli (233). The neuron had no response to familiar stimuli, with a mean firing rate to familiar stimuli of 0.8 spikes/s. Fifteen of the 31 neurons

with responses to novel visual stimuli responded to only some novel visual stimuli. The mean proportion of novel visual stimuli to which these neurons responded with more than 50% of the mean response to the most effective novel stimulus was 90%.

The activity of a different neuron which was influenced both by whether the stimulus was a face and whether the stimulus was novel is shown in Fig. 3. As shown, both effects had an influence on the firing rate of the neuron, averaged across the set of face and non-face, novel and familiar, stimuli, with the greatest response generally to novel faces. These effects were confirmed statistically in a two-way ANOVA, with significant main effects of both novelty ($F(1, 215) = 18.05, p < .0001$) and face vs non-face ($F(1, 215) = 27.78, p < .0001$), and a significant interaction ($F(1, 215) = 13.14, p < .0001$). One of the 19 neurons that were tested with novel faces and with novel non-face stimuli, and that had responses to novel visual stimuli, responded primarily to novel face visual stimuli. The responses occurred to all novel face stimuli that were tested.

The time course of the habituation of the response of a neuron (be089) to novel visual stimuli is shown in Fig. 4. Each point in the graph represents the mean response to 13 visual stimuli, which were novel on presentation 1. On each trial a stimulus was shown for 2 s. The neuron showed its major habituation over the first three presentations of the stimuli, but after this the neuronal response kept above the level of that to familiar visual stimuli, and had not reached the response level to familiar stimuli after 6–7 presentations ($t = 3.46, df = 38, p = .001$ for a comparison of the responses to novel and familiar stimuli on trials 6 and 7).

The time course of habituation of the responses of another neuron (be0282) that habituated in one trial are shown in Fig. 5. The mean response across nine novel visual stimuli is shown. The same neuron responded to novel visual objects simply shown to the monkey. In contrast, the responses of another neuron, be091, that

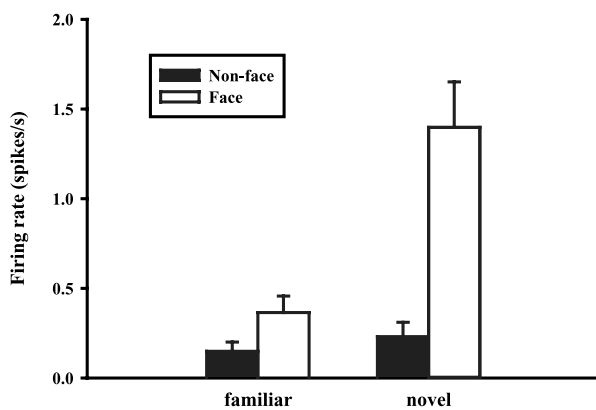


Fig. 3. The activity of a different neuron (be074) that responded more to face than to non-face stimuli, and more to novel than to familiar stimuli. Conventions as in Fig. 1.

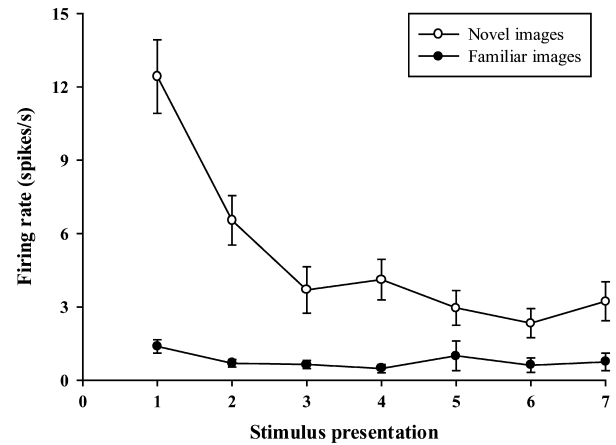


Fig. 4. The time course of the habituation of the response of a neuron (be089) to novel visual stimuli. Each point in the graph represents the mean response to 13 visual stimuli, which were novel on presentation 1. On each trial a stimulus was shown for 2 s.

did not habituate after even seven presentations of each novel visual stimulus, are shown in Fig. 6.

The number of trials to habituate to half the firing rate response to the first presentation of a novel stimulus for each neuron is shown in Table 1. In the table the symbol >6 indicates that the neuron was tested for six repetitions of each stimulus, and had not reached the half-maximal response by this number of repetitions. It can be seen from Table 1 that many of the cells took four or more trials to habituate to the half-maximal response, and that for 15 of the sample of 31 cells with responses to novel stimuli, the neuronal response had not habituated at all, or had not reached half the response to novel images, in six presentations of novel stimuli. Thus a variety of time courses of habituation was found in this population of neurons, with some of them still reflecting the relative novelty of the

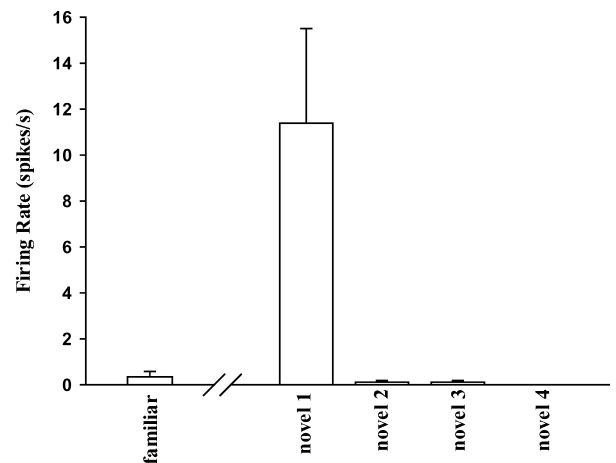


Fig. 5. The time course of the habituation of the response of a neuron (be0282) to novel visual stimuli. Each point in the graph represents the mean response to nine visual stimuli, which were novel on presentation 1 (novel 1). The second presentation of the novel stimulus is labelled novel 2, etc. On each trial a stimulus was shown for 2 s.

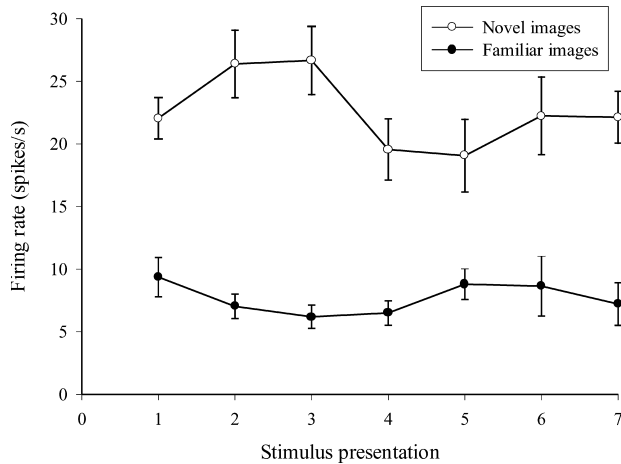


Fig. 6. The time course of the habituation of the response of a neuron (be091) to novel visual stimuli. Each point in the graph represents the mean response to nine visual stimuli, which were novel on presentation 1. On each trial a stimulus was shown for 2 s.

stimuli after six presentations. (The implication is that for the stimuli to be treated as familiar by 15 of the neurons, more than six 2 s presentations are needed.) Once the cells had habituated to a set of novel stimuli, no responses of the cells to these stimuli occurred later in testing on the same day. Nor did the neurons respond to a stimulus that had been shown as novel on the preceding day, showing that once the neurons had habituated, they reflected a long-term type of memory which lasted for at least 24 h. (To test this, while a neuron with responses to novel stimuli was being recorded in a new track on a particular day, stimuli that had been shown as novel on a preceding day were always shown. The fact that none of the novelty neurons described here responded to a stimulus that had been shown as novel on a preceding day shows that the responses of the novelty neurons described here reflect a type of long-term memory encoding that lasts at least for 24 h.) Nor did the neurons respond to any other stimuli that had been used in a familiar set on testing on previous days, even the first time such stimuli were seen during a day's testing. In these respects, the neuronal responses reflect a long-term memory.

The response of another neuron with a rather different time course of the habituation is shown in Fig. 7. The neuron did not respond to familiar visual stimuli, nor to novel visual stimuli the first time that they were presented. However, on the second presentation of a novel stimulus the neuron had a large neuronal response, and there was some response to novel stimuli for the next few presentations. Three different neurons with this property of the time course were found in the sample of 31 neurons with responses to novel stimuli (see Table 1).

These neurons did not respond differentially on the basis of whether a visual stimulus was associated with reward or punishment. This is shown in Table 1, in the columns S– and S+. The S– was a discriminative stimu-

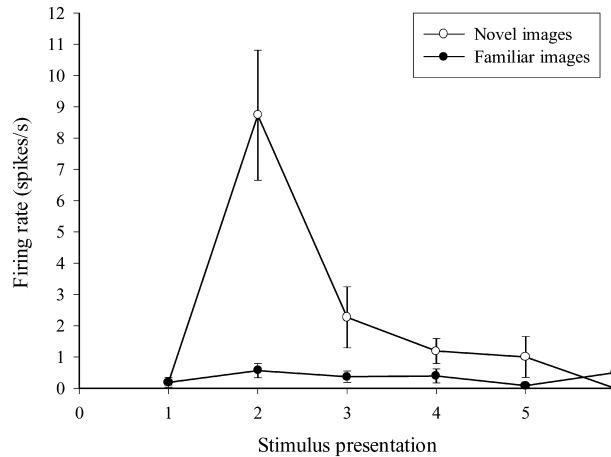


Fig. 7. The time course of the neuronal response to a novel stimulus followed by repeated presentations of the same novel stimulus of neuron (be082). Each point in the graph represents the mean response to 13 visual stimuli, which were novel on presentation 1. On each trial a stimulus was shown for 2 s.

lus (a black square) used in the task that informed the monkey that if a lick was made on that trial, a drop of aversive saline would be delivered. The S+ column in Table 1 shows the firing rate to stimuli in the task that were rewarded. For all cells with responses to novel stimuli, there were no significant responses to the S– and S+ stimuli, nor did the firing to the S– differ from that to the S+ stimuli. Further, the neurons did not code for the reward value of stimuli in that they responded to novel but not to familiar stimuli in the task, even though both were rewarded (in that they were discriminative stimuli to lick to obtain fruit juice reward). Thus this population of orbitofrontal cortex neurons encoded information about novel stimuli, and not about the reinforcement associations of visual stimuli.

The response latencies of the different neurons to novel visual stimuli are shown in Table 1, and for the majority were between 120 and 200 ms. For almost all the neurons the response to novel stimuli consisted of an increase in firing rate, but for two neurons, the response was a decrease from the baseline (see Table 1).

The sites at which these neurons were recorded are shown in Fig. 8, together with an indication of the region in which the sample of 658 neurons fully tested for responses to novel stimuli (593 in be, and 65 in bk) were recorded. The 31 neurons (4.7% of the sample of 658 neurons for which all the analyses described here were completed) were found in a restricted region in the middle part of the orbitofrontal cortex, with the majority 8–12 mm anterior to the sphenoid reference, and between the medial and lateral orbital sulcus, or close to the lateral orbital sulcus, in cytoarchitectonic area 13m, 13l and more anteriorly in 11l–12m (Carmichael & Price, 1994, 1996; Paxinos, Huang, & Toga, 2000). The neurons shown in Fig. 8 at 12A to sphenoid are probably in area 11l, and those in Fig. 8 at 8A to sphenoid are probably

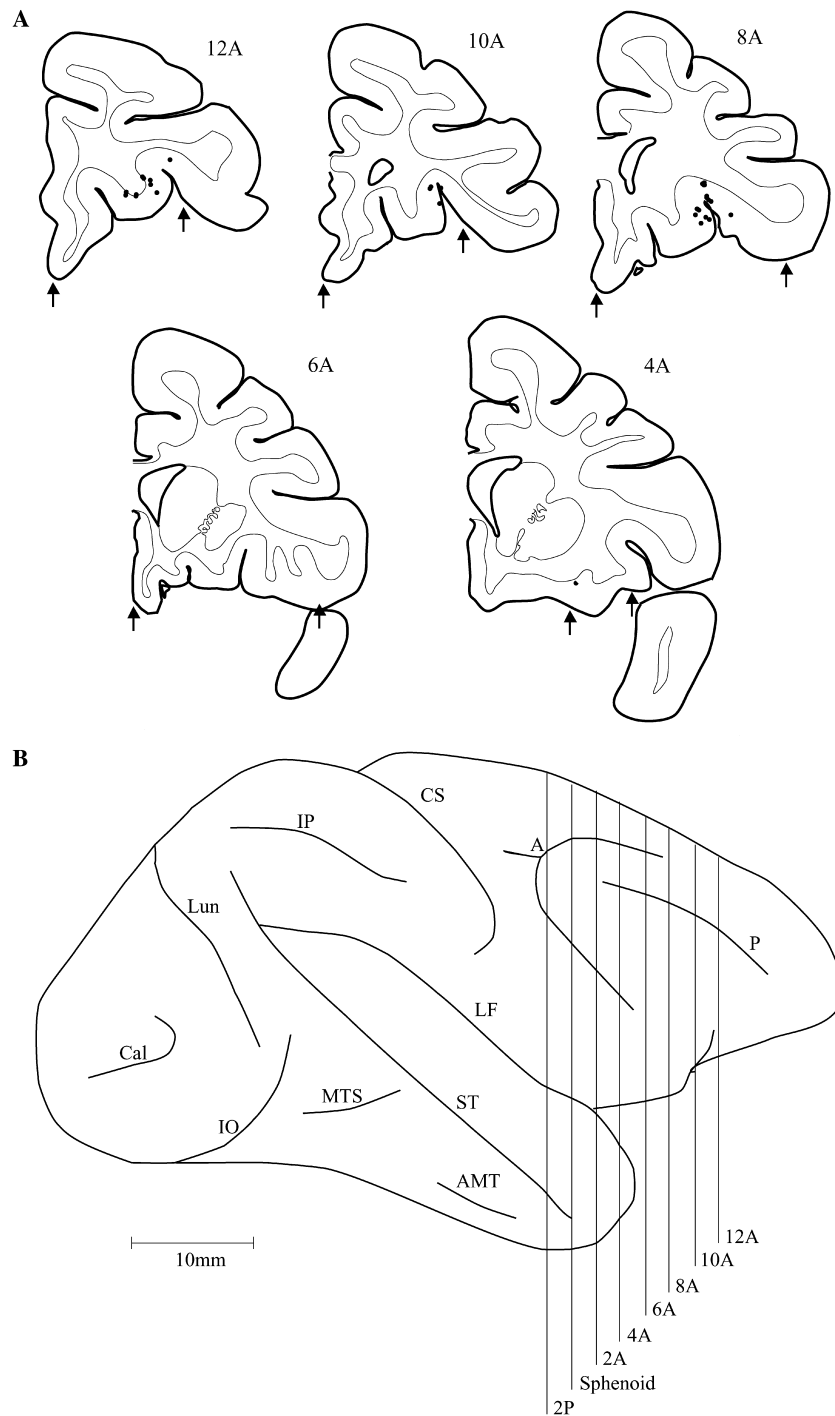


Fig. 8. (A) The recording sites of the neurons recorded in this investigation. The large circles show the recording sites of the neurons with responses to novel visual stimuli. (The sites are based on the X-ray data for every track and a standard atlas calibrated in X-ray coordinates.) The arrows indicate the regions within which neurons were sampled. (B) A lateral view of the macaque brain showing the levels with respect to sphenoid of the coronal sections shown in (A).

close to the border between area 11l and area 13. We note that none of these orbitofrontal cortex neurons had taste, olfactory, or oral somatosensory responses, all of which have been found in other populations of orbitofrontal cortex neurons (Rolls et al., 1990; Rolls & Baylis, 1994; 1996a, 1996b; Rolls, 1999a, 1999b, 2000a, 2000b, 2002, chap. 23, Rolls et al., 1999, 2003b; Thorpe et al., 1983).

The responses of the whole population of neurons, examples of which have been given above, are provided in Table 1. The number of neurons with significantly different responses to novel and familiar stimuli, as shown in Table 1, could not have arisen by chance statistical sampling of the 658 neurons analysed, as shown by a Fisher generalized significance test ($p = 4 \times 10^{-7}$) (Kirk, 1995).

4. Discussion

These results show that there is a population of neurons with responses to novel visual stimuli in the orbitofrontal cortex. The responses of individual neurons to novel visual stimuli are not only very highly statistically significant (see Table 1, where for individual neurons the results are as highly significant as $p < 10^{-19}$), but also as a population the significant results could not have arisen by chance at $p < 10^{-6}$ as shown by the Fisher generalized significance test, which assesses the likelihood that the probability values observed over the whole population of 658 neurons analyzed with the novel vs familiar analyses of variance might have arisen by chance. The interpretation is thus that the responses observed in this population of orbitofrontal cortex neurons are very highly statistically significant.

The responses were found in a part of the orbitofrontal cortex which has been designated as the “orbital prefrontal network,” a set of interconnected subareas of the prefrontal cortex that receive inputs (either directly or via another orbitofrontal prefrontal network subarea) from the inferior temporal visual cortex area TE, as well as from the primary olfactory and gustatory cortices, and from somatosensory areas such as SI, SII, and 7b (Barbas, 1993; Carmichael & Price, 1996). The neurons were found in area 11l and an area where area 11l borders area 13, a region that was little if at all sampled in the study of Xiang and Brown (2004), as is evident from their Fig. 2, and the categorisation of their neurons into a ventromedial prefrontal region that they termed PFCvm, and a ventrolateral prefrontal region that they termed PFCo. The region in which the neurons with responses to novel stimuli were found in the present study is illustrated in Fig. 8, and is in a region in between the areas into which they divided their ventral prefrontal cortex neurons. Further, most of the prefrontal cortex neurons with responses in a running recognition memory task of the type introduced for neurophysiology by Baylis and Rolls (1987) and Rolls, Perrett, Caan, and Wilson (1982) that were described by Xiang and Brown (2004) as having activity related to novel visual stimuli were quite different from the neurons described here, in that most of their “novelty” neurons responded more the second time a novel visual stimulus was shown than the first time it was shown, a type of response that might more simply be termed a short term familiarity or recency response. (0.6% of the neurons recorded by Xiang & Brown (2004) in their regions PFCvm and PFCo did have decremental responses to novel stimuli, but as just noted, these are different areas to the mid-orbitofrontal cortex area in which neurons with responses to novel stimuli described in the were found in the present study.) Part of the interest of the neurons with responses to novel stimuli described in the current paper is that they are found in a region which closely

corresponds to the rostral orbitofrontal cortex region, area 11, that is activated by novel images in humans, and in which the activation is higher if the subjects are asked to encode, that is remember, the images (Frey & Petrides, 2000, 2002; Petrides, Alivisatos, & Frey, 2002), as described below.

The latencies of the neuronal responses were typically in the range 80–200 ms, and had a median value of 120 ms (see Table 1). These latencies are too short to be influenced by any eye movements, which in for example a visual search task take approximately 200 ms to initiate (Rolls et al., 2003a), so that the shortest latency of neuronal response that might be affected by an eye movement would be 280–300 ms if the neurons has an inherent response latency of 80–100 ms. On this evidence, even if differential eye movements to novel vs familiar stimuli were to occur, they could not account for the responses of the neurons to novel stimuli described here. For comparison, the response latencies of neurons in different subareas of the inferior temporal visual cortex under similar testing conditions are 80–110 ms (Baylis, Rolls, & Leonard, 1987). Thus, the response latencies of the orbitofrontal cortex neuron that respond to novel stimuli are consistent with the hypothesis that they receive their inputs from the inferior temporal cortex visual areas. Further, consistent evidence is that the latencies at which the orbitofrontal cortex neurons discriminate between novel and familiar visual stimuli (shown in Table 1) are longer than those at which some inferior temporal cortex neurons discriminate between novel and familiar stimuli (Baylis & Rolls, 1987; Miller, Lin, & Desimone, 1993). However, the orbitofrontal cortex neurons with responses to novel stimuli are very different indeed from those in the inferior temporal cortex, which typically in short term memory tasks such as delayed match to sample habituate to the novel sample stimulus rapidly (typically within 1–2 presentations), and have their response reinstated when the same visual stimulus is shown as novel on a later trial (Baylis & Rolls, 1987). Although the responses of the neurons are not large in terms of high firing rates, the responses are extremely highly statistically significant, and there is every indication that they as a population provide much information about whether a visual stimulus is novel. Further, although the proportion of neurons with the type of response described here to novel stimuli is not large (4.7%) when considered over the whole sample of neurons recorded in the orbitofrontal cortex in this investigation, there is every reason to think that even small proportions with a given type of response in the orbitofrontal cortex are functionally important. For example, although there are only a several percent of orbitofrontal cortex neurons that respond selectively to faces or to auditory stimuli (Rolls et al., 2005), selective, discrete, surgical, lesions of the human orbitofrontal cortex can give rise

to voice expression and face expression identification deficits (Hornak et al., 1996; cf. Hornak et al., 2003). Also, for example, the proportion of neurons in the primate orbitofrontal cortex with responses specifically related to non-reward in a visual discrimination reversal task is 3.6% (Thorpe et al., 1983), yet selective, discrete, surgical, lesions of the human orbitofrontal cortex can give rise to visual discrimination reversal impairments (Hornak et al., 2004) (cf. Rolls et al., 1994). Further, the proportion of neurons with selective responses to novel stimuli within the subregion of the orbitofrontal cortex in which they were recorded, shown in Fig. 8, would be higher if calculated just within the subregion in which they were found.

The time course of the habituation of the responses of this population of neurons was relatively slow. In particular, many of the neurons still responded to novel stimuli after six presentations of novel stimuli each 1 s long. This is slower, for example, than the responses of a population of basal forebrain neurons which respond in the running recognition memory task to the novel presentation of each stimulus, but have very much less response to the second (familiar) presentation of a visual stimulus (Wilson & Rolls, 1990). The neurons also habituate more slowly than is typical of neurons with responses to novel visual stimuli recorded in the amygdala (Wilson & Rolls, 1993). In addition, the orbitofrontal cortex neurons described here are involved in a long-term memory system, in that once they have habituated to a novel stimulus on one day, they do not respond to the same stimulus when it is shown one or several days later. In support of the neurophysiological data described here, Meunier, Bachevalier, and Mishkin (1997) have shown that orbitofrontal cortex lesions in monkey can produce an impairment on the performance of delayed match to sample memory task. However, given the nature of the neuronal responses found in the orbitofrontal cortex to novel stimuli, it would be of interest to perform further lesion studies in monkeys with the following paradigm, and indeed to test humans with orbitofrontal cortex damage in the following paradigm. The paradigm would be one in which many trials of exposure to a completely novel stimulus were allowed on one day, and then the subject was required to choose the next day between that stimulus and a new completely novel stimulus. That is, the properties of the neurons described in this paper are suited to provide information that could last a long time about whether a stimulus has been seen a number of times previously, rather than about whether a stimulus has been seen recently in a short term memory task.

The neurons described here in the orbitofrontal cortex are very different to those in the amygdala that respond to novel stimuli and to rewarding visual stimuli (Rolls, 1999b, 2000d; Wilson & Rolls, 2005). That population of amygdala neurons increases its firing rate to the

reward-related visual stimulus in a Go/NoGo visual discrimination task that indicates that a lick can be made to obtain fruit juice reward, but does not respond to a punishment-associated visual stimulus that indicates that if a lick is made, the taste of aversive saline will be obtained. These particular amygdala neurons respond to novel visual stimuli. Given that these neurons respond to rewarding visual stimuli, this suggests that the responses of these amygdala neurons to novel visual stimuli are involved in the rewarding properties which novel visual stimuli have. The function of this reward value of novel stimuli is presumably to produce exploration of new stimuli (Rolls, 1999b). In contrast, the responses of the orbitofrontal cortex neurons described here to novel stimuli are independent of the reward value of visual stimuli, and provide a representation that would be useful for determining whether a visual stimulus is new or not. (The neuronal responses of these neurons were independent of the reward vs punishment association of stimuli in that they did not respond to the S+ or the S– in the visual discrimination task, nor to the sight of food. Further, the completely new stimuli introduced to test the responses of these cells were always reward-related, so that the difference of their responses when these stimulus were novel as compared with when they became familiar was not due to any difference of reward association.) The functions that might be implemented by such orbitofrontal cortex neurons include directing orientation and attention to new stimuli for further processing, remembering whether a stimulus has been seen before, and recency memory.

The findings described in this investigation are important for understanding the functions of the human prefrontal cortex in memory. The dorso-lateral prefrontal cortex is very clearly implicated in short term (or working) memory functions (Fuster, 1973, 2000, 2001; Fuster & Alexander, 1971; Goldman, Rosvold, Vest, & Galkin, 1971; Goldman-Rakic, 1996; Goldman-Rakic & Leung, 2002) which could be implemented in autoassociation attractor networks (Rolls & Deco, 2002; Rolls & Treves, 1998), and it is therefore generally thought that the prefrontal cortex is not involved in long-term memory (Kolb & Whishaw, 1996). However, the discovery described here of neurons in the orbitofrontal cortex that respond to a type of long-term memory, whether visual stimuli are novel, suggests that there is a role for this part of the brain in at least this type of long-term memory. In this context, it will be important to test whether patients who have damage to the orbitofrontal cortex are impaired in the type of long-term novel visual stimulus memory described in this investigation. Consistent with the proposal made here, it is known anatomically that there are connections to at least a ventral and medial part of the prefrontal cortex from posterior cortical areas involved in memory in the medial temporal lobe including the retrosplenial cortex, entorhinal cortex,

and even the hippocampus (Barbas, 1988; Carmichael & Price, 1995b; Carmichael & Price, 1996; Morris, Petrides, & Pandya, 1999; Petrides & Pandya, 2002). The large response to novel stimuli of some orbitofrontal cortex neurons as described here would be useful in detecting the difference between novel and familiar stimuli (as there would be a large response across a population of these neurons to novel stimuli), and the output of these neurons could be used for a number of functions, including behavioural orienting or alerting to novel visual stimuli, autonomic responses to novel visual stimuli, and, via the connections of the orbitofrontal cortex to medial temporal lobe areas (Barbas & Blatt, 1995; Insauti et al., 1987), memory storage.

The discovery of a population of neurons in the primate orbitofrontal cortex activated by novel stimuli is complemented by functional neuroimaging studies with positron emission tomography in humans showing that the right rostral orbitofrontal cortex (area 11) is activated by novel images (of abstract art), and that the activation is higher if the subjects are asked to encode, that is remember, the images (Frey & Petrides, 2000, 2002; Petrides et al., 2002). The same orbitofrontal region in humans is activated by novel faces when they are encoded (Frey & Petrides, 2003). The neurophysiological data presented here provides evidence on a number of properties of the system that have not or cannot be elucidated with functional neuroimaging, including how selective orbitofrontal cortex neurons can be for novel images (see, e.g., Figs. 1 and 2); that some neurons can convey information about novel faces relative to novel non-face stimuli (see, e.g., Fig. 3); that the response latencies of the neurons with selective responses to novel stimuli are quite short, with a median value of 120 ms and a value as short as 80 ms for some neurons (see Fig. 1B and Table 1); that the neurons as a population convey evidence about how novel a stimulus is, in that different neurons take different numbers of trials to habituate (typically in the range 1–10, see Table 1), and in that some neurons respond to the second and not the first presentation of a visual stimulus (see, e.g., Fig. 7, and Table 1).

While it is not suggested that the orbitofrontal cortex is the only brain region involved in discriminating between novel and familiar stimuli, the particular properties of the neurons described here make it very likely that they do have a role in some types of behavior in which novel and familiar stimuli are discriminated. These neurophysiological experiments have identified the presence of neurons in the orbitofrontal cortex which discriminate between novel and familiar stimuli, described their properties, shown that they are separate from other orbitofrontal cortex neurons that respond to stimuli in other sensory modalities or based on their reward value, and opened the way for future investigations of the functions they perform.

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References

- Aggleton, J. P., & Passingham, R. E. (1981). Syndrome produced by lesions of the amygdala in monkeys (*Macaca mulatta*). *Journal of Comparative Physiology and Psychology*, *95*, 961–977.
- Barbas, H. (1988). Anatomic organization of basoventral and medio-dorsal visual recipient prefrontal regions in the rhesus monkey. *Journal of Comparative Neurology*, *276*, 313–342.
- Barbas, H., & Pandya, D. N. (1989). Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *Journal of Computational Neurology*, *286*, 353–375.
- Barbas, H. (1993). Organization of cortical afferent input to the orbitofrontal area in the rhesus monkey. *Neuroscience*, *56*, 841–864.
- Barbas, H. (1995). Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. *Neuroscience and Biobehavioural Reviews*, *19*, 499–510.
- Barbas, H., & Blatt, G. J. (1995). Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. *Hippocampus*, *5*, 511–533.
- Baylis, G. C., & Rolls, E. T. (1987). Responses of neurons in the inferior temporal cortex in short term and serial recognition memory tasks. *Experimental Brain Research*, *65*, 614–622.
- Baylis, G. C., Rolls, E. T., & Leonard, C. M. (1987). Functional subdivisions of the temporal lobe neocortex. *Journal of Neuroscience*, *7*, 330–342.
- Booth, M. C. A., & Rolls, E. T. (1998). View-invariant representations of familiar objects by neurons in the inferior temporal visual cortex. *Cerebral Cortex*, *8*, 510–523.
- Carmichael, S. T., & Price, J. L. (1994). Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *Journal of Comparative Neurology*, *346*, 366–402.
- Carmichael, S. T., & Price, J. L. (1995a). Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. *Journal of Comparative Neurology*, *363*, 642–664.
- Carmichael, S. T., & Price, J. L. (1995b). Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *Journal of Comparative Neurology*, *346*, 403–434.
- Carmichael, S. T., & Price, J. L. (1996). Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *Journal of Comparative Neurology*, *371*, 179–207.
- Critchley, H. D., & Rolls, E. T. (1996a). Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. *Journal of Neurophysiology*, *75*, 1673–1686.
- Critchley, H. D., & Rolls, E. T. (1996b). Olfactory neuronal responses in the primate orbitofrontal cortex: analysis in an olfactory discrimination task. *Journal of Neurophysiology*, *75*, 1659–1672.
- Desimone, R. (1991). Face-selective cells in the temporal cortex monkeys. *Journal of Cognitive Neuroscience*, *3*, 1–8.
- Feigenbaum, J. D., & Rolls, E. T. (1991). Allocentric and egocentric spatial information processing in the hippocampal formation of the behaving primate. *Psychobiology*, *19*, 21–40.
- Frey, S., & Petrides, M. (2000). Orbitofrontal cortex: A key prefrontal region for encoding information. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 8723–8727.
- Frey, S., & Petrides, M. (2002). Orbitofrontal cortex and memory formation. *Neuron*, *36*, 171–176.
- Frey, S., & Petrides, M. (2003). Greater orbitofrontal activity predicts better memory for faces. *European Journal of Neuroscience*, *17*, 2755–2758.

- Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science*, *173*, 652–654.
- Fuster, J. M. (1973). Unit activity in prefrontal cortex during delayed response performance: neuronal correlates of transient memory. *Journal of Neurophysiology*, *36*, 61–78.
- Fuster, J. M. (2000). *Memory systems in the brain*. New York: Raven Press.
- Fuster, J. M. (2001). The prefrontal cortex—an update: time is of the essence. *Neuron*, *30*, 319–333.
- Goldman, P. S., Rosvold, H. E., Vest, B., & Galkin, T. W. (1971). Analysis of the delayed-alternation deficit produced by dorso-lateral pre-frontal lesions in the rhesus monkey. *Journal of Comparative and Physiological Psychology*, *77*, 212–220.
- Goldman-Rakic, P. S. (1996). The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philosophical Transactions of the Royal Society B*, *351*, 1445–1453.
- Goldman-Rakic, P. S., & Leung, H.-C. (2002). Functional architecture of the dorsolateral prefrontal cortex in monkeys and humans. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 85–95). New York: Oxford University Press.
- Hasselmo, M. E., Rolls, E. T., & Baylis, G. C. (1989). The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey. *Behavioural Brain Research*, *32*, 203–218.
- Hasselmo, M. E., Rolls, E. T., Baylis, G. C., & Nalwa, V. (1989). Object-centred encoding by face-selective neurons in the cortex in the superior temporal sulcus of the monkey. *Experimental Brain Research*, *75*, 417–429.
- Hornak, J., Rolls, E. T., & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia*, *34*, 247–261.
- Hornak, J., Bramham, J., Rolls, E. T., Morris, R. G., O'Doherty, J., Bullock, P. R., & Polkey, C. E. (2003). Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain*, *126*, 1691–1712.
- Hornak, J., O'Doherty, J., Bramham, J., Rolls, E. T., Morris, R. G., Bullock, P. R., & Polkey, C. E. (2004). Reward-related reversal learning after surgical excisions in orbitofrontal and dorsolateral prefrontal cortex in humans. *Journal of Cognitive Neuroscience*, *16*, 463–478.
- Insausti, R., Amaral, D. G., & Cowan, W. M. (1987). The entorhinal cortex of the monkey. II. Cortical afferents. *Journal of Comparative Neurology*, *264*, 356–395.
- Kirk, R. E. (1995). *Experimental design: Procedures for the behavioural sciences* (2nd ed.). Pacific Grove, CA: Brooks/Cole.
- Kolb, B., & Whishaw, I. Q. (1996). *Fundamentals of human neuropsychology* (4th ed.). New York: W.H. Freeman.
- Merrill, E. G., & Ainsworth, A. (1972). Glass-coated platinum-plated tungsten microelectrodes. *Medical and Biological Engineering*, *10*, 662–672.
- Meunier, M., Bachevalier, J., & Mishkin, M. (1997). Effects of orbital frontal and anterior cingulate lesions on object and spatial memory in rhesus monkeys. *Neuropsychologia*, *35*, 999–1015.
- Miller, E. K., Lin, L., & Desimone, R. (1993). Activity of neurons in anterior inferior temporal cortex during a short-term memory task. *Journal of Neuroscience*, *13*, 1460–1478.
- Miyashita, Y. (1993). Inferior temporal cortex: where visual perception meets memory. *Annual Review of Neuroscience*, *16*, 245–263.
- Morecraft, R. J., Geula, C., & Mesulam, M.-M. (1992). Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. *Journal of Comparative Neurology*, *232*, 341–358.
- Morris, R., Petrides, M., & Pandya, D. N. (1999). Architecture and connections of retrosplenial area 30 in the rhesus monkey (*Macaca mulatta*). *European Journal of Neuroscience*, *11*, 2506–2518.
- O'Scalaidhe, S. P., Wilson, F. A., & Goldman-Rakic, P. S. (1997). Areal segregation of face-processing neurons in prefrontal cortex. *Science*, *278*, 1135–1138.
- Paxinos, G., Huang, X.-F., & Toga, A. W. (2000). *The rhesus monkey brain in stereotaxic coordinates*. San Diego, CA: Academic Press.
- Perrett, D. I., Rolls, E. T., & Caan, W. (1982). Visual neurons responsive to faces in the monkey temporal cortex. *Experimental Brain Research*, *47*(3), 329–342.
- Petrides, M., & Pandya, D. N. (1995). Comparative architectonic analysis of the human and macaque frontal cortex. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 9, pp. 17–58). Amsterdam: Elsevier Science.
- Petrides, M., Alivisatos, B., & Frey, S. (2002). Differential activation of the human orbital, mid-ventrolateral, and mid-dorsolateral prefrontal cortex during the processing of visual stimuli. *Proceedings of the National Academy of Sciences of the United States of America*, *99*, 5649–5654.
- Petrides, M., & Pandya, D. N. (2002). Association pathways of the prefrontal cortex and functional observations. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 31–50). New York: Oxford University Press.
- Price, J. L., Carmichael, S. T., Carnes, K. M., Clugnet, M.-C., Kuroda, M., & Ray, J. P. (1991). Olfactory input to the prefrontal cortex. In J. L. Davis & H. Eichenbaum (Eds.), *Olfaction: A model system for computational neuroscience* (pp. 101–120). Cambridge, MA: MIT Press.
- Price, J. L. (1999). Networks within the orbital and medial prefrontal cortex. *Neurocase*, *5*, 231–241.
- Rolls, E. T. (1976). The neurophysiological basis of brain-stimulation reward. In A. Wauquier & E. T. Rolls (Eds.), *Brain-stimulation reward* (pp. 65–87). Amsterdam: North-Holland.
- Rolls, E. T., Sanghera, M. K., & Roper-Hall, A. (1979). The latency of activation of neurons in the lateral hypothalamus and substantia innominata during feeding in the monkey. *Brain Research*, *164*, 121–135.
- Rolls, E. T., Perrett, D. I., Caan, A. W., & Wilson, F. A. W. (1982). Neuronal responses related to visual recognition. *Brain*, *105*, 611–646.
- Rolls, E. T., Yaxley, S., & Sienkiewicz, Z. J. (1990). Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *Journal of Neurophysiology*, *64*, 1055–1066.
- Rolls, E. T., & Baylis, L. L. (1994). Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. *Journal of Neuroscience*, *14*, 5437–5452.
- Rolls, E. T., Hornak, J., Wade, D., & McGrath, J. (1994). Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology, Neurosurgery and Psychiatry*, *57*, 1518–1524.
- Rolls, E. T., & Tovee, M. J. (1995). Sparseness of the neuronal representation of stimuli in the primate temporal visual cortex. *Journal of Neurophysiology*, *73*, 713–726.
- Rolls, E. T., Critchley, H., Wakeman, E. A., & Mason, R. (1996a). Responses of neurons in the primate taste cortex to the glutamate ion and to inosine 5'-monophosphate. *Physiology and Behavior*, *59*, 991–1000.
- Rolls, E. T., Critchley, H. D., Mason, R., & Wakeman, E. A. (1996b). Orbitofrontal cortex neurons: role in olfactory and visual association learning. *Journal of Neurophysiology*, *75*, 1970–1981.
- Rolls, E. T., & Treves, A. (1998). *Neural networks and brain function*. Oxford: Oxford University Press.
- Rolls, E. T. (1999a). The functions of the orbitofrontal cortex. *Neurocase*, *5*, 301–312.
- Rolls, E. T. (1999b). *The brain and emotion*. Oxford: Oxford University Press.
- Rolls, E. T., Critchley, H. D., Browning, A. S., Hernadi, A., & Lenard, L. (1999). Responses to the sensory properties of fat of neurons in the primate orbitofrontal cortex. *Journal of Neuroscience*, *19*, 1532–1540.
- Rolls, E. T. (2000a). The orbitofrontal cortex and reward. *Cerebral Cortex*, *10*, 284–294.
- Rolls, E. T. (2000b). Taste, olfactory, visual and somatosensory representations of the sensory properties of foods in the brain, and their relation to the control of food intake. In H.-R. Berthoud & R. J. Seeley (Eds.), *Neural and metabolic control of macronutrient intake* (pp. 247–262). Boca-Raton, FL: CRC Press.

- Rolls, E. T. (2000c). Functions of the primate temporal lobe cortical visual areas in invariant visual object and face recognition. *Neuron*, 27, 205–218.
- Rolls, E. T. (2000d). Neurophysiology and functions of the primate amygdala, and the neural basis of emotion. In J. P. Aggleton (Ed.), *The amygdala: A functional analysis* (2nd ed., pp. 447–478). Oxford: Oxford University Press.
- Rolls, E. T. (2002). The functions of the orbitofrontal cortex. In D. T. Stuss & R. T. Knight (Eds.), *Principles of Frontal Lobe Function* (pp. 354–375). New York: Oxford University Press.
- Rolls, E. T., & Deco, G. (2002). *Computational neuroscience of vision*. Oxford: Oxford University Press.
- Rolls, E. T., Aggelopoulos, N. C., & Zheng, F. (2003a). The receptive fields of inferior temporal cortex neurons in natural scenes. *Journal of Neuroscience*, 23, 339–348.
- Rolls, E. T., Verhagen, J. V., & Kadohisa, M. (2003b). Representations of the texture of food in the primate orbitofrontal cortex: neurons responding to viscosity, grittiness and capsaicin. *Journal of Neurophysiology*, 90, 3711–3724.
- Rolls, E. T. (2004). The functions of the orbitofrontal cortex. *Brain and Cognition*, 55, 11–29.
- Rolls, E. T. (2005). *Emotion Explained*. Oxford: Oxford University Press.
- Rolls, E. T., Critchley, H. D., Browning, A. S., & Inoue, K., (2005). Face-selective and auditory neurons in the primate orbitofrontal cortex. In preparation.
- Scott, T. R., Yaxley, S., Sienkiewicz, Z. J., & Rolls, E. T. (1986a). Taste responses in the nucleus tractus solitarius of the behaving monkey. *Journal of Neurophysiology*, 55, 182–200.
- Scott, T. R., Yaxley, S., Sienkiewicz, Z. J., & Rolls, E. T. (1986b). Gustatory responses in the frontal opercular cortex of the alert cynomolgus monkey. *Journal of Neurophysiology*, 56, 876–890.
- Seltzer, B., & Pandya, D. N. (1989). Frontal lobe connections of the superior temporal sulcus in the rhesus monkey. *Journal of Comparative Neurology*, 281, 97–113.
- Tanaka, K. (1996). Inferotemporal cortex and object vision. *Annual Review of Neuroscience*, 19, 109–139.
- Thorpe, S. J., Rolls, E. T., & Maddison, S. (1983). Neuronal activity in the orbitofrontal cortex of the behaving monkey. *Experimental Brain Research*, 49, 93–115.
- Tremblay, L., & Schultz, W. (2000a). Modifications of reward expectation-related neuronal activity during learning in primate orbitofrontal cortex. *Journal of Neurophysiology*, 83, 1877–1885.
- Tremblay, L., & Schultz, W. (2000b). Reward-related neuronal activity during go-nogo task performance in primate orbitofrontal cortex. *Journal of Neurophysiology*, 83, 1864–1876.
- Wilson, F. A. W., & Rolls, E. T. (1990). Neuronal responses related to reinforcement in the primate basal forebrain. *Brain Research*, 509, 213–231.
- Wilson, F. A. W., & Rolls, E. T. (1993). The effects of stimulus novelty and familiarity on neuronal activity in the amygdala of monkeys performing recognition memory tasks. *Experimental Brain Research*, 93, 367–382.
- Wilson, F. A. W., & Rolls, E. T., (2005). The primate amygdala and reinforcement: A dissociation between rule-based and associatively-mediated memory revealed in amygdala neuronal activity. *Neuroscience*, in press.
- Xiang, J. Z., & Brown, M. W. (2004). Neuronal responses related to long-term recognition memory processes in prefrontal cortex. *Neuron*, 42, 817–829.
- Yaxley, S., Rolls, E. T., & Sienkiewicz, Z. J. (1990). Gustatory responses of single neurons in the insula of the macaque monkey. *Journal of Neurophysiology*, 63, 689–700.