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Perirhinal cortex neuronal activity related to long-term familiarity memory in the macaque

Christian Hölscher,* Edmund T. Rolls and Jianzhong Xiang
University of Oxford, Department of Experimental Psychology, South Parks Road, Oxford OX1 3UD, UK

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Abstract

Lesion studies suggest that the perirhinal cortex plays a role in object recognition memory. To analyse its role, the activity of single neurons in the perirhinal cortex was recorded in three rhesus monkeys (*Macaca mulatta*) performing a delayed matching-to-sample task with up to three intervening stimuli. A set of familiar visual stimuli was used. Some neurons had activity related to working memory, in that they responded more to the sample than to the match image within a trial, as shown previously. However, when a novel set of stimuli was introduced, the neuronal responses were on average only 47% of the magnitude of the responses to the familiar set of stimuli. Moreover, it was shown in eight different replications in three monkeys that the responses of the perirhinal cortex neurons gradually increased over hundreds of presentations of the new set of (initially novel) stimuli to become as large as with the already familiar stimuli. The mean number of 1.3-s presentations to induce this effect was 400 occurring over 7–13 days. These results show that perirhinal cortex neurons represent the very long-term familiarity of visual stimuli. A representation of the long-term familiarity of visual stimuli may be important for many aspects of social behaviour, and part of the impairment in temporal lobe amnesia may be related to the difficulty of building representations of the degree of familiarity of stimuli.

Introduction

The perirhinal cortex receives connections from the inferior temporal visual cortex, from olfactory and somatosensory cortical areas, and also from some other areas such as the orbitofrontal cortex (Suzuki & Amaral, 1994a,b). Damage to the perirhinal cortex produces impairments in recognition memory tasks in which several items intervene between the sample presentation of a stimulus and its presentation again as a match stimulus (Zola-Morgan *et al*., 1989, 1994; Malkova *et al*., 2001). Indeed, damage to the perirhinal cortex rather than to the hippocampus is believed to underlie the impairment in recognition memory found in amnesia in humans associated with medial temporal lobe damage. Moreover, the functions of the perirhinal cortex are different from those of the inferior temporal visual cortex (IT, area TE) (see Buckley *et al*., 1997, 2001).

Neurophysiologically, it has been shown that many inferior temporal cortex (a term we use to refer to area TE) neurons (Rolls, 2000; Rolls & Deco, 2002) respond more to the first than to the second presentation of a stimulus in a running recognition task with trial-unique stimuli (Baylis & Rolls, 1987). A small proportion of neurons respond more to the familiar (second) than to the novel (first) presentation of each visual stimulus. In this task, each visual stimulus is shown twice, and the monkey makes different responses the first and the second time each stimulus is shown. In the inferior temporal cortex this memory spanned up to 1–2 intervening stimuli between the first (novel) and second (familiar) presentations of a given stimulus (Baylis & Rolls, 1987), and as recordings are made more ventrally, towards and within the perirhinal cortex, the memory span increases to several or more intervening stimuli (Wilson *et al*., 1990; Brown & Xiang, 1998; Xiang & Brown, 1998). In a similar task, though typically performed with non-trial-unique stimuli, a delayed matching-to-sample task with up to several intervening stimuli, some neurons respond more to the match stimulus than to the sample stimulus (Miller *et al*., 1998), and this short-term memory is reset at the start of the next trial (Hölscher & Rolls, 2002). In other studies of the functions of the perirhinal cortex it was shown that in paired association learning tasks, the ability of inferior temporal cortex neurons to reflect new associations between picture pairs was lost after disruption of projections from the rhinal to the inferior temporal cortex (Miyashita *et al*., 1996, 1998).

In the experiments described here, a much longer type of familiarity or recognition memory was investigated for the first time. Recordings were made from perirhinal cortex neurons while macaques performed a delayed matching-to-sample task with up to three intervening stimuli. The new aspect of the experiment was that the responses of each neuron were compared with a set of stimuli that were very familiar because they had been used on hundreds of trials in the task, and to a set of novel stimuli that were introduced into the experiment. It was found that the perirhinal cortex neurons responded much less to the less familiar images than to the very familiar stimuli. We then used the same initially novel stimuli for many days, and were able to follow the increase in the responses of perirhinal cortex neurons over hundreds of repeated presentations of the initially novel set of stimuli over the following 1–2 weeks. This leads to the suggestion that whereas one property of area TE neurons in the inferior temporal visual cortex is

Correspondence: Professor Edmund T. Rolls, as above.
E-mail: Edmund.Rolls@psy.ox.ac.uk
Web: www.cns.ox.ac.uk

Present address: Tübingen University, Department of Cognitive Neuroscience, Auf der Morgenstelle 28, 72076 Tübingen, Germany.

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object selectivity (see reviews by Rolls, 2000; Rolls & Deco, 2002), a property that the perirhinal cortex represents explicitly in its firing rate responses is a representation of the long-term familiarity of visual stimuli, in some cases at the expense of high object selectivity. Taken together, area TE and the perirhinal cortex may thus provide a representation of both the object and its long-term familiarity.

Methods

The activity of single neurons was investigated in the perirhinal cortex in three rhesus monkeys (*Macaca mulatta*, average weight 3 kg) performing a delayed matching-to-sample task. Single-cell recordings were conducted during daily recording sessions using single-neuron tungsten microelectrodes (tip size less than 10 μm) insulated with epoxylite except for the tip (FHC, USA). The microelectrodes were stereotaxically guided, and the location of the microelectrodes was reconstructed on each track using X-rays and subsequent histological reconstruction using microlesions made on selected tracks. The anatomical boundaries of the perirhinal cortex were defined by reference to Amaral *et al*. (1987) and the stereotaxic atlas of Paxinos *et al*. (1999). The recordings were made mainly in an area 1–8 mm posterior (P) to the sphenoid bone and 11–18 mm laterally from the midline (L/R), with extensive sampling of the perirhinal cortex achieved as shown in Fig. 5 by moving the microelectrode 1 mm between tracks. A recording system filtered and amplified the signal and stored spike waveforms, which were later sorted and cluster cut off-line using the Datawave (Longmont, CO, USA) Discovery software. The basic criteria for identifying the waveform for a single cell that were utilized with this software were: a signal-to-noise ratio of >3; a waveform shape and size that differed by less than 20%; and in addition that the spikes for a single cell never showed an interspike interval of < 2 ms, as such small intervals only occur when the spikes are from different neurons. The neurophysiological methods used here have been described in detail elsewhere (Booth & Rolls, 1998). The recording well was implanted after narcotization with i.m. ketamine (0.1 mL/kg) under anesthesia with thiopentone sodium i.v., and followed by the analgesic buprenorphine hydrochloride. All procedures, including preparative and subsequent procedures, were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals, the guidelines of The Society for Neuroscience, and were licensed under the *UK Animals (Scientific Procedures) Act 1986*.

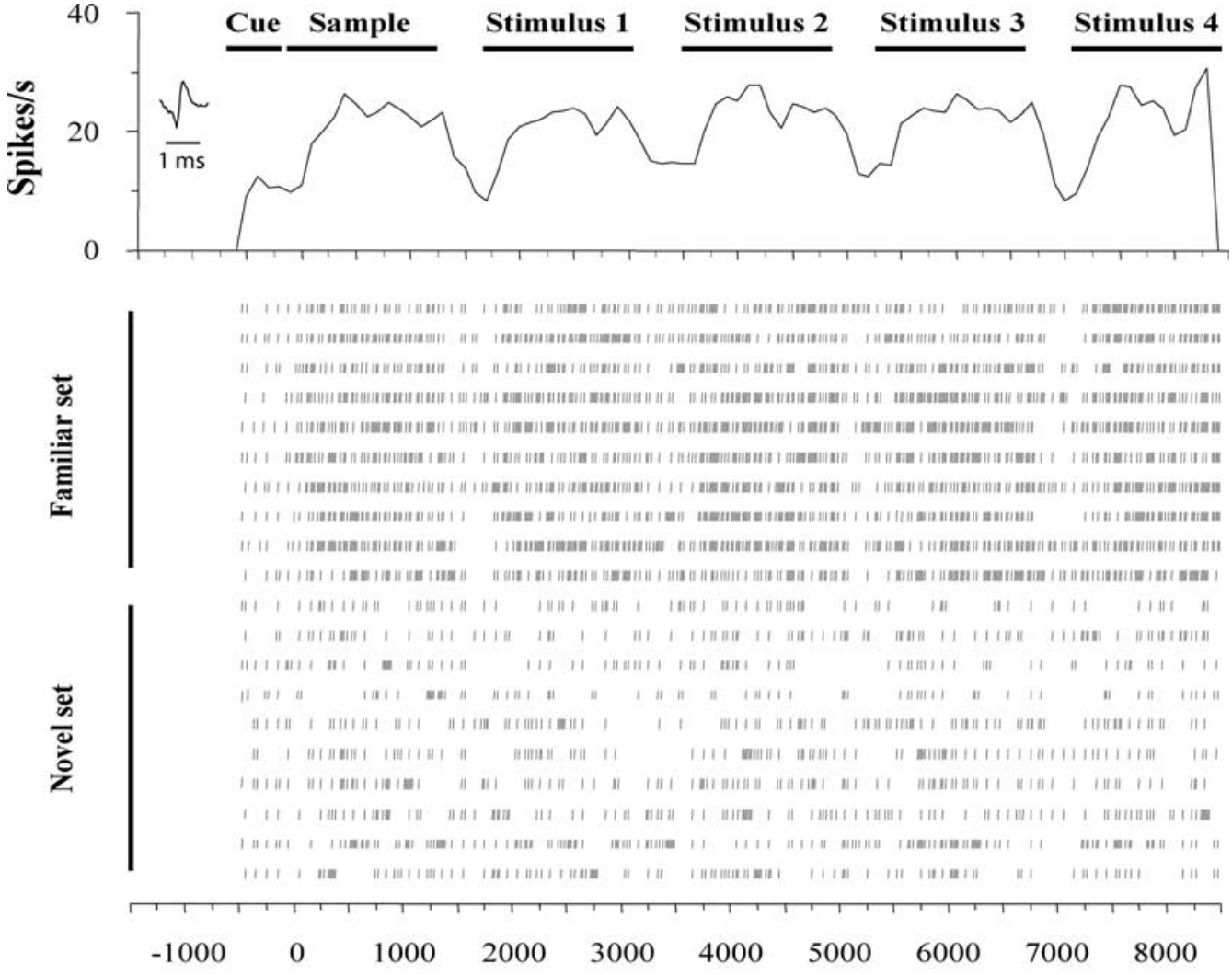
The delayed matching-to-sample task consisted of the presentation of an image (the 'sample' image) of an object on a 35-cm colour video monitor with a refresh rate of 100 Hz located at a distance of 78 cm (so that 1 cm on the monitor resulted in 0.75° of visual angle subtended on the retina), and the successive presentation of four images afterwards. The grayscale images were of real digitized objects and faces that differed in shape, and orientation, subtended approximately 11° at the retina, and were presented on a mid-level grey background. Examples of the images are shown in Fig. 1. One of the four images shown after the sample matched the sample image, and when the macaque licked during this 'match' image, it obtained a fruit juice reward. The monkey continued to look at the stimulus display during the licking and for the rest of the trial, as the lick tube was out of sight, and the monitor was the main item visible to the monkey. This resulted in a maximum of three intervening stimuli in the delayed matching-to-sample task. Licks at any other time resulted in (mildly aversive) saline delivery. Image presentation times were 1300 ms, with a delay between images of 400 ms (see Fig. 1). The intertrial interval was several seconds, and each trial was preceded by a 500-ms tone cue as shown in Fig. 1. A typical experiment on a perirhinal cortex neuron involved 80 trials. The first 10 trials were with the 'novel' set of images. The second set of 10 trials was with the familiar set of images, and so on up to the 80 trials. This alternation was used so that in every block of 20 trials, trials with both novel and familiar images were used, in order to exclude order effects. The actual order of non-match vs. match stimuli within a trial was randomized identically for the familiar and novel sets of images.

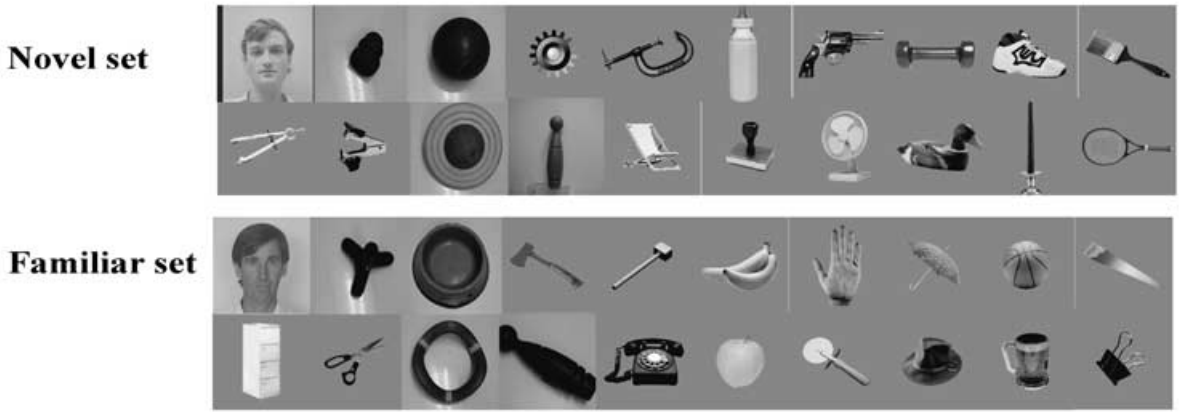
Each set of images consisted of 16 (or for some replications of the investigation, 20) images. A set of (16) images was designated as familiar if it had been used for more than approximately 15 previous testing days, involving hundreds of repetitions of each image in the familiar set. A 'novel' set of (16) images consisted of a set of images that had never been seen before by the monkey on day 1 of testing with that 'novel' set. The same set of images, still designated as the 'novel set', was used on 7–13 days of subsequent testing, allowing neuronal responses to be measured as a function of the number of presentations since this 'novel' set had been introduced. During that period of 7–13 days in different replications of the overall investigation, the same set of familiar stimuli was used. (Given that there were 16 different novel images in a set of novel images, five image presentations per trial and 40 trials in an experiment with a single neuron, each novel image was shown on average 12.5 times during the course of any one experiment. Each experiment was on a different neuron. Each stimulus presentation was for 1.3 s.) The images, examples of which are shown in Fig. 1, were randomly allocated to the novel and familiar sets.

The monkeys were trained to a criterion of 80% correct prior to recording, and maintained close to this level of performance for both novel and familiar sets of images throughout the recording sessions. It should be noted that the monkey was performing a short-term memory task, of within-trial delayed matching-to-sample, throughout the recording, and that whether the stimulus set being used with each set of 10 trials was 'novel' or 'familiar' made no difference to the performance. The neuronal responses were measured during the 1.3-s period in which each visual stimulus was being shown, delayed by 100 ms with respect to stimulus onset to allow the information to travel via the inferior temporal visual cortex (in which typical response latencies are 80–100 ms) to the perirhinal cortex. The monkeys maintained performance on the task equally well during the recording sessions for both familiar and novel stimulus sets, and this generally good level of performance, together with eye position recordings made with the scleral search coil technique (Judge *et al*., 1980), and described below, showed that the monkey fixated the stimuli during

FIG. 1. Rastergram and peristimulus time histogram showing the responses of a perirhinal cortex neuron to a set of familiar stimuli (trials 1–10) and to a set of novel stimuli (trials 11–20) in the delayed matching-to-sample task with up to three intervening stimuli between the sample stimulus (S) and the match stimulus. At the times labelled as Stimulus 1 – Stimulus 4 one of four stimuli was shown. In one case the stimulus matched the sample, and the monkey could lick on that trial to obtain fruit juice. In three other cases stimuli were shown that did not match the sample stimulus for that trial, and licks were not made, otherwise aversive saline was obtained. The times are with respect to the onset of the sample visual stimulus. A 500-ms tone cue preceded the onset of the sample stimulus, and spike data collection also started 500 ms before the onset of the sample stimulus. The peristimulus time histogram calculated over the 20 trials is shown at the top. It was smoothed with a Gaussian of width 5 bins in the 100-bin peristimulus time histogram. In the rastergram, each row is a different trial, and each vertical line represents an action potential from the neuron. On each trial, four randomly selected visual stimuli from a set of 16 were used, with one of the stimuli used as both the sample and the match stimulus. For the trials labelled 'Novel', four stimuli were chosen at random from the novel set. For the trials labelled 'Familiar set', four stimuli were chosen at random from the familiar set. For this neuron, it was the second experiment in which that novel set of stimuli had been used in an experiment. The inset near the top left shows the spike waveform; and the panels at the bottom show examples of the stimuli used, which had been randomly allocated to the different sets. (Cell BM017b01.)

each trial of the task. Detailed evidence on these points follows. The average percentage correct for the whole trial with four choices of image on each trial for monkey BI for the novel set was $83 \pm 1.5\%$ (mean $\pm$ SE calculated across the 29 recording sessions), and for the familiar set was $79 \pm 1.7\%$, $P = 0.3$. The corresponding figures for BL were 73 ± 1.1 and 75 ± 1.5, $P = 0.13$; and for BM were 76 ± 1.5 and $77 \pm 1.7\%$, $P = 0.25$. These good and similar levels of performance of the monkeys on the novel and familiar stimulus sets indicate that





Examples of the stimuli used

behavioural performance differences did not account for the differences in the neuronal firing found for the stimulus sets when they were novel. Recordings of eye position made for example on every session in monkey BI showed that the difference in the horizontal eye position for the novel and familiar stimuli measured during the 1300-ms stimulus presentation periods was $0.11 \pm 1.3^\circ$ (mean $\pm$ SD, $P = 0.44$), and for the vertical eye positions was $0.08 \pm 1.2^\circ$ ($P = 0.28$). This evidence shows that the fixation of the images in the novel and familiar sets was not different across recording sessions. Moreover, the accuracy with which the novel and familiar sets of stimuli were fixated within each session was not different, with a mean standard deviation of the horizontal eye positions during the familiar stimuli of 3.8°, and for the novel stimuli of 3.7° ($P = 0.4$). The corresponding data for the vertical eye positions were 4.4° and 4.3° ($P = 0.3$). (Thus for approximately 95% of the time the monkeys were fixating within 7.8° of the centre of the stimulus, which subtended 11° on the retina, so that for most of the time the fixation was within the stimulus or close to it.). These data, together with the evidence that the mean receptive field size of inferior temporal cortex (area TE) neurons, the major site of visual afferent input to the perirhinal cortex, in similar testing conditions is 78° (Rolls *et al*., 2003), and that the stimuli subtended 11° at the retina, shows that different viewing of the novel and familiar stimulus sets cannot account for the different neuronal responses to these sets found in this investigation.

Non-parametric (Mann–Whitney *U*) statistical tests were used to test whether the responses of a neuron were different to the stimuli in the novel and familiar sets of stimuli. Regression analyses were used to test whether the responses of neurons to the set of novel stimuli (relative to the familiar stimuli) became larger as a function of the number of testing sessions (each of which was an experiment on a single neuron involving 80 trials with on average 12.5 presentations of each novel stimulus) with a given set of novel stimuli. For these analyses, the mean firing rate of a neuron to all presentations of the stimuli within the novel stimulus set divided by the mean firing rate to all presentations of the stimuli within the familiar stimulus set (expressed as a percentage) provided one point for the regression line.

After the experiments were finished, 12 microlesions were made in the monkey's brain by passing current (100 μA for 100 s) through microelectrodes that were localized in the brain by X-ray. The monkey was anaesthetized and cardially perfused with saline and formalin. The brain was fixed in buffered formalin (10%), left in a 30% sucrose-formalin solution for 2 weeks and cut on a cryostat. Sections were stained with cresyl violet stain, the location of the lesions was identified, and the recording sites of all neurons were reconstructed using the histology, the corresponding X-rays and the X-rays on other tracks, as described elsewhere (Feigenbaum & Rolls, 1991). The accuracy of this reconstruction, which can be estimated from the regression analyses performed between the X-ray coordinates of each lesion and the corresponding location of each lesion in the histology, is approximately 1 mm. The recording sites are shown in Fig. 5.

Results

Recordings during the performance of the delayed matching-to-sample task were completed and analysed after initial training with a set of stimuli from 57 neurons (out of 154 recorded) in macaque BI, 137 in BL (out of 383 recorded) and 79 in BM (out of 163 recorded) in 285 daily recording sessions (134 in BM, 111 in BL and 40 in BI). (The remaining neurons either did not have visual responses in the task or were not held sufficiently long for 80 trials to be completed.) Throughout the results and discussion, the designation 'novel' refers to images in the 'novel' set, although of course after the 'novel' set had been shown a number of times, the stimuli were less novel than at the beginning. It is with the development of neuronal responses to images as they become gradually less novel and more familiar over hundreds of presentations of the initially 'novel' set of images that the main results presented in this paper are concerned.

Figure 1 shows the general experimental protocol, and some of the results obtained from one neuron during performance of the delayed matching-to-sample task. This neuron was recorded during the second experiment after that in which that novel set of images was introduced. The neuron responded more during the presentation of the very familiar than during the presentation of the 'novel' set of stimuli. (As described in the Methods section, on each trial four different images were shown from either the set of 16 images in the novel set or 16 images from the familiar set. Ten trials of data with the novel stimulus set, and 10 trials with the familiar stimulus set, are shown.) This neuron responded rather similarly to the different visual stimuli within a set of stimuli. Some other neurons had some stimulus selectivity to the different stimuli used in the task, as described and analysed below.

Figure 2A shows the mean responses of a neuron (BI19003) to the set of familiar and novel stimuli in the second experiment after a novel set of stimuli was introduced in BI. (In the first experiment with the novel set, performed with a different neuron, each image in the novel set had been shown approximately 12 times previously for 1.3 s each time.) The neuron responded significantly less to the novel than to the familiar stimulus set ($P < 2 \times 10^{-7}$). Figure 2B shows the mean responses of another neuron to the same set of familiar and novel stimuli 10 days after the set of novel stimuli had been introduced (and during which time each stimulus in the novel set had been shown approximately 250 times). The neuron did not respond significantly differently to the novel set and to the familiar set of stimuli ($P = 0.35$). Thus after many days of testing with the 'novel' stimulus set, the neuron showed in Fig. 2B responded similarly to the stimuli in the 'novel' and familiar sets. The results for all the neurons analysed are consistent with these two examples, as is shown in Fig. 3 the population values for the neurons recorded on the first ($n = 34$) and last ($n = 26$) days of all eight replications with the novel stimulus set, and

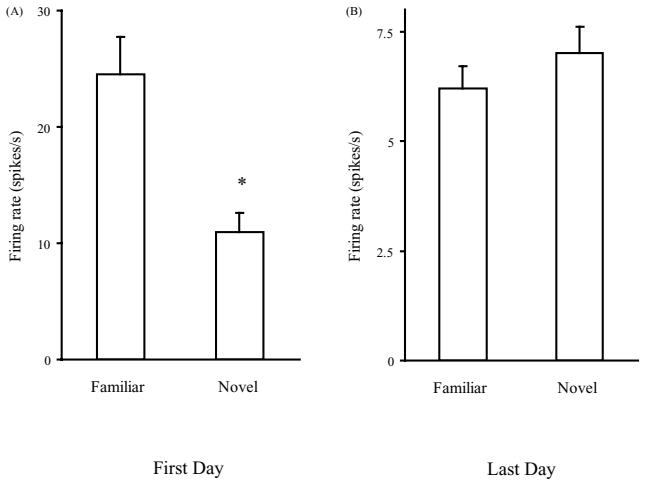


FIG. 2. (A) Response of neuron BI19003 to the set of novel or familiar images. This neuron was tested as the second experiment (which happened to be on the first day) after a novel set of stimuli was introduced. It responded more to the set of familiar than to the set of novel images. The mean ±SE off the mean firing rates are shown. (B) Neuron BI20101c was tested to the same stimulus sets, but on the 10th day after the set of novel stimuli was introduced.

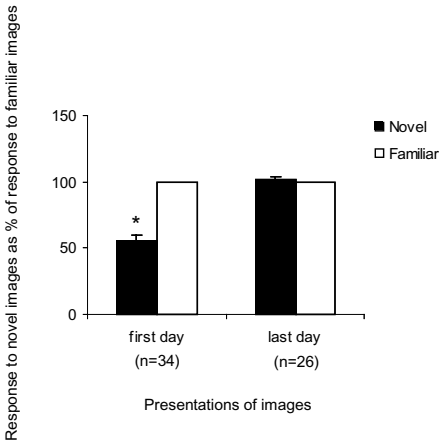


FIG. 3. Responses of the neurons recorded on the first day ($n = 34$ neurons) and the last day ($n = 26$ neurons) with an initially novel set of stimuli, shown for both the novel set of stimuli and the already familiar set of stimuli. The data were obtained across all eight replications of the investigation. For each neuron, the percentage of the response to the novel set relative to the familiar set was calculated, and the mean ± SE of the mean are shown.

in Fig. 4. The difference between the novel and familiar sets of stimuli on the first day was highly statistically significant ($P = 5 \times 10^{-18}$), and there was no difference on the last day of testing with the novel set ($P = 0.26$).

Figure 4 provides evidence that in every one of eight different replications of this investigation, the responses of perirhinal cortex neurons to a novel set of stimuli were initially smaller than to already familiar stimuli, until after hundreds of presentations the responses to the initially novel stimulus set became as large as those to the already familiar stimulus set. Figure 4A shows the results of three different replications of the whole investigation in macaque BL. Each replication consisted of starting with a completely new set of 'Novel' images, and using this set for 10 days of testing, in which experiments were performed on many different neurons. The ordinate shows the mean response of a neuron to the set of stimuli in the novel set expressed as a percentage of the response to the set of stimuli in the familiar set. In each replication of the overall investigation, for many neurons early after the novel set of stimuli were introduced, there were highly significant differences between the mean responses of the neurons to the set of familiar and novel stimuli, as shown by non-parametric (Mann–Whitney U) tests. Indeed, for many cells the difference between the responses to novel and familiar stimuli on the days soon after the novel stimuli were introduced were significant at $P < 10^{-5}$. [For example, in replication BI1, on day 1, two neurons had significant differences (s) at $P < 0.01$; day 2 = two s; day 3 = two s; day 4 = one s; day 5 = one s; day 6 = one s and two ns; day 7 = one ns; day 8 = two s; day 9 = two s and two ns; day 10 = one s, one ns; day 11 = two ns; day 12 = two ns; day 13 = one ns. This pattern of results was similar for the other replications.] For replication BL1, the degree of variation is indicated by the standard errors of the mean responses of each cell. The slope of the (linear) regression line for each replication (BL1 – BL3) was calculated and was highly significant, as indicated in Table 1. The intercept of the regression line, also shown in Table 1, indicates the average percentage of the neuronal response to novel stimuli compared with very familiar stimuli at the start of testing with novel stimuli. The regression lines show how long it takes neurons to respond to the novel set of images as well as to the highly familiar set, shown for hundreds of previous trials so that their maximal response level had been reached.

Figure 4B shows the results of three different replications of the whole investigation in macaque BI. Figure 4C shows the results of two different replications of the whole investigation in macaque BM. For many neurons early after the novel set of stimuli were introduced in all five of these replications, there were highly significant differences between the mean responses of the neurons to the set of familiar and novel stimuli, as shown by the non-parametric tests. The slope of the regression line for each replication was significant, as indicated in Table 1.

The set of results in each of the eight replications of the investigation, each involving substantial testing on a large number (13–51) of different neurons, are shown in Table 1. First, in all cases the regression lines were statistically significant, and indeed were typically highly statistically significant. This, together with the value of the intercept, shows that perirhinal cortex neurons respond less to novel than to familiar stimuli, and that over a long period, the responses to novel stimuli become as large as to familiar stimuli. Second, the mean value across replications of the intercept is 46.5%, indicating that on average the cells' response to novel stimuli is 46.5% of their response to familiar stimuli. This is a large change across a whole population of neurons. It reflects a change of the mean neuronal response of 5.3 spikes/s to the novel stimuli, to 11.4 spikes/s to the familiar stimuli. (The mean response of the neurons to the familiar stimuli was 11.4 spikes/s, and 5.3 spikes/s is 46.5% of this.) Third, from the values shown in Table 1, the mean number of experimental sessions for the response to novel stimuli to become as large as to familiar stimuli was 32.4 (as shown by the trial number at which the regression line intercepts with 100%). This corresponds to approximately 400 presentations of each novel image, for 1.3 s per presentation, before the neuron's response to that novel image became as large as its response to familiar images. (The number 400 arises from the fact that there were typically 16 different novel images in a set of images, and that each experiment involved 40 trials with the novel stimulus set and five images per trial.) Together, the data shown in Fig. 4 and in Table 1 provide very strong evidence that the response of perirhinal cortex neurons is initially smaller to novel than to familiar images, and that the time course of the increasing response to novel stimuli is slow, with approximately 400 1.3-s presentations of a novel stimulus being needed before the neuron responds to the image as strongly as to does to familiar visual stimuli.

Figure 5 shows the perirhinal cortex sites at which the neurons were recorded in the three macaques. Most of the neurons analysed were in the perirhinal cortex as defined by Suzuki & Amaral (1994a,b), Insausti *et al*. (1987) and Amaral *et al*. (1987), though some were in the border region between the perirhinal cortex and the entorhinal cortex. An extensive region of the perirhinal cortex was sampled, as shown, by moving the microelectrodes 1 mm between tracks. These electrode position changes were random with respect to the stage of each replication of the experiment, and in addition could not have influenced the results found, as neurons with responses of the type described here were found throughout the sites shown in Fig. 5.

Some of the neurons responded significantly differently to the different images used in the task, as shown by a one-way ANOVA performed on each neuron. In two monkeys in a sample of 221 of the perirhinal cortex neurons recorded, ANOVAs were computed to give an estimate of the proportion of stimulus-selective cells in the recordings. By this criterion, 9.5% of the cells had stimulus-selective visual responses ($P \leq 0.05$, though in some cases the values were much more significant, e.g. $P < 10^{-5}$). The measure a of the sparseness of the representation (Rolls & Treves, 1998; Rolls & Deco, 2002) was on average for the perirhinal cortex neurons analysed in this investigation 0.834 ± 0.125 (SD) for the familiar stimuli and 0.758 ± 0.145 for the

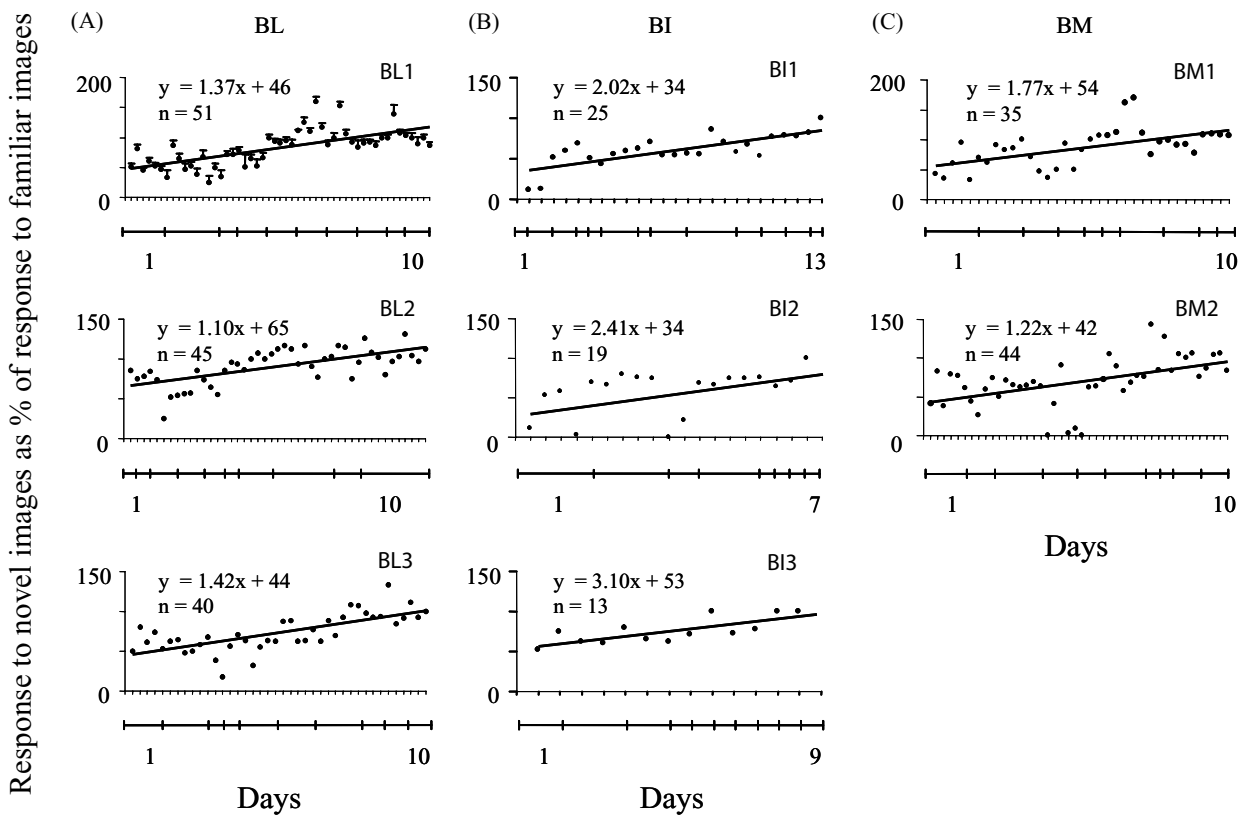


FIG. 4. (A) Regressions showing the relative response of each neuron to novel vs. familiar stimuli (expressed as a percentage) as a function of the number of experiments since the novel set of stimuli were investigated (abscissa), for three complete replications in BL. Each point on the graph shows the results of one experiment involving 80 trials of the delayed matching-to-sample task on one neuron. The 80 trials included 40 with the novel stimulus set, and 40 with the familiar stimulus set, with five stimuli on each trial. On some days more than one neuron was analysed in a separate experiment, and the number of days since introduction of the novel set of stimuli is also shown on the abscissa. Results for three separate replications of the whole investigation in one monkey (BL) are shown. Each replication involved starting with a completely novel set of images, and using that novel set on 10 days of testing in which on any day as many experiments as possible were performed, each experiment with a different neuron, and each experiment involving 40 trials with the novel set and 40 trials with the familiar set of images. The first replication (top) involved recordings in 51 experiments from 51 separate neurons over 10 testing days. The slope and intercept of the regression line are shown. The intercept indicates the magnitude of the response to novel stimuli expressed as a percentage of that to familiar stimuli at the start of the replication. During an experiment on each neuron, the set of novel stimuli was shown for approximately 12.5 1.3-s presentations of each novel stimulus during the delayed matching-to-sample task. Regression 1 for replication 1: slope $P < 4 \times 10^{-8}$. Regression 2 (middle) for replication 2 involving 45 experiments on 45 neurons over 10 testing days: slope $P < 1.5 \times 10^{-6}$. Regression 3 (bottom) for replication 3 involving 40 experiments on 40 neurons over 10 testing days: slope $P < 3.7 \times 10^{-7}$. The results for replication BL1 show the standard error of the mean response of the neuron to the novel relative to the familiar stimuli to give an indication of the degree of accuracy with which this could be estimated. The error bars are omitted from the other replications for clarity. (B) The regression analyses for three complete replications in macaque BI. Regression 1 (top) for replication BI1 involved 25 experiments on 25 neurons over 13 testing days. Regression 2 (middle) for replication BI2 involved 19 experiments on 19 neurons over seven testing days. Regression 3 (bottom) for replication BI3 involved 13 experiments on 13 neurons over nine testing days. The significance values for the regressions are shown in Table 1. (C) The regression analyses for two complete replications in macaque BM. Regression 1 (top) for replication BM1 involved 35 experiments on 35 neurons over 10 testing days. Regression 2 (bottom) for replication BM2 involved 44 experiments on 44 neurons over 10 testing days.

TABLE 1. Regression lines for *N*/*F* expressed as a percentage for different replications

Replication	Slope	Intercept	Number of experimental sessions until $N = F$	*F*-value of the slope	Significance
BL1	1.37	46	39.4	$F_{1,50} = 42.2$	$P < 4 \times 10^{-8}$
BL2	1.10	65	31.8	$F_{1,44} = 31.2$	$P < 5 \times 10^{-6}$
BL3	1.42	44	39.4	$F_{1,39} = 37.7$	$P < 4 \times 10^{-7}$
BI1	2.02	34	32.6	$F_{1,24} = 29.8$	$P < 2 \times 10^{-5}$
BI2	2.41	34	27.4	$F_{1,18} = 5.2$	$P < 0.04$
BI3	3.10	53	15.2	$F_{1,12} = 13.9$	$P < 0.003$
BM1	1.77	54	26.0	$F_{1,34} = 16.2$	$P < 3 \times 10^{-4}$
BM2	1.22	42	47.5	$F_{1,43} = 13.9$	$P < 6 \times 10^{-4}$

N, response to the novel set of stimuli; *F*, response to the familiar set of stimuli.

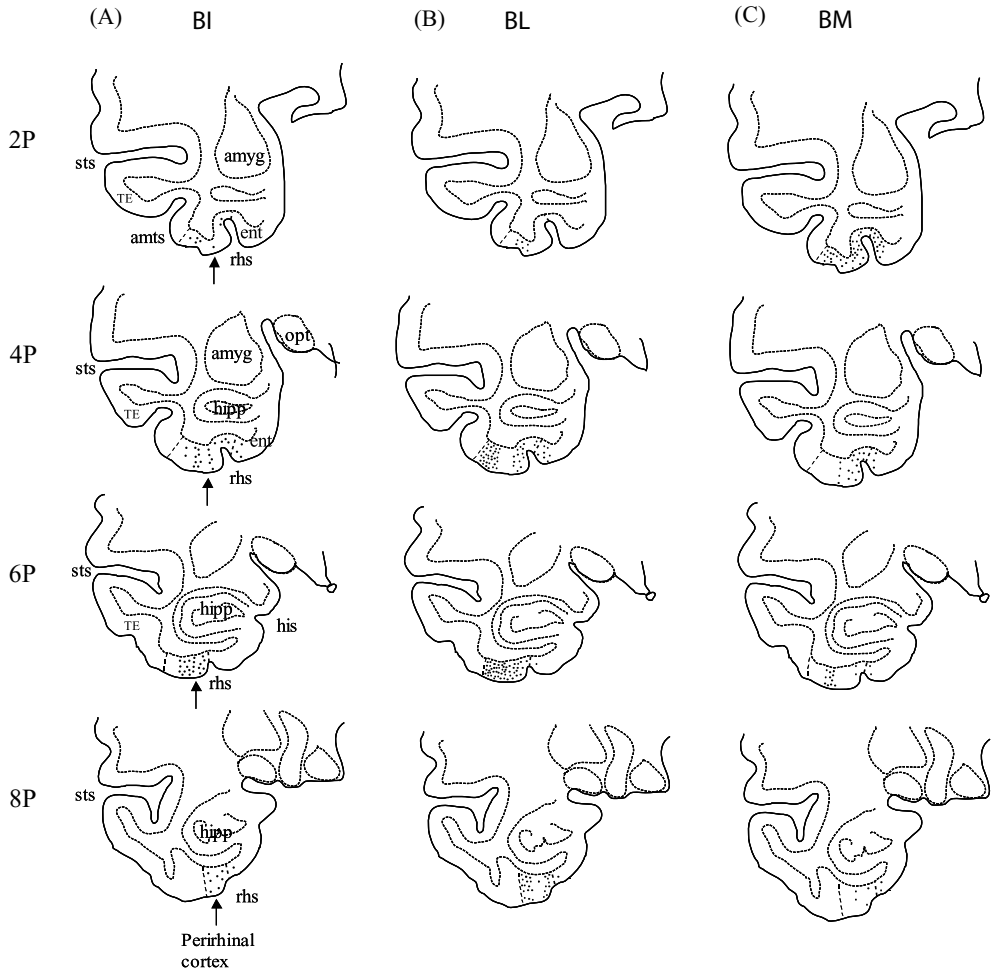


FIG. 5. Anatomical reconstruction of the sites in the perirhinal cortex (areas 35 and 36 in and near the banks of the rhinal sulcus) at which the neurons were recorded in investigations 1–3 in BI (A), in investigations 4–6 in BL (B) and in investigations 7–8 in BM (C). Coronal sections at different distances (in millimetres) posterior (P) to the sphenoid reference are shown. The sphenoid reference is at approximately the antero-posterior level of the optic chiasm and anterior commissure. The small dots show the sites of the neurons recorded in the perirhinal cortex, which is shown delimited by dashed lines. amts, anterior middle temporal sulcus; amyg, amygdala; ent, entorhinal cortex; hipp, hippocampus; his, hippocampal sulcus; opt, optic tract; rhs, rhinal sulcus; sts, superior temporal sulcus; TE, inferior temporal visual cortex.

novel stimuli ($P < 10^{-17}$). Thus the representation was more sparse for novel than for familiar stimuli, that is the neurons tended to respond a little more selectively to novel than to familiar stimuli. One of the changes with increasing familiarity was thus that the perirhinal cortex neurons tended to respond to more of the novel stimuli as they became familiar. However, for both novel and familiar stimuli the tuning is very broad, and the increasing breadth of the tuning of the neurons is not sufficient to account for the very large increase in the magnitude of the neuronal responses as stimuli become very familiar.

Overall, it was thus notable that stimulus selectivity was very much less than in the inferior temporal cortex (Rolls, 2000; Rolls & Deco, 2002). This was even confirmed by direct comparison in one of the macaques (BI) used in this study, in which while the macaque performed the same task, 15/22 (68%) of inferior temporal cortex (IT) neurons had selective responses to the same set of stimuli. Moreover, the selectivity of the inferior temporal cortex neurons was much greater than that of the neurons in the perirhinal cortex (that is, the sparseness of the representation for inferior temporal cortex neurons is lower, see Rolls, 2000; Rolls & Deco, 2002). Related perhaps partly to the specificity of the responses of many inferior temporal cortex neurons, in the experiments described here there was no difference apparent in the responses of IT neurons to the novel and the long-term familiar stimuli. This means at least that long-term familiarity is not made explicit in the responses of inferior temporal cortex neurons, whereas it is made explicit in the responses of neurons in the perirhinal cortex. By 'made explicit', we mean can easily be read off from the firing rates of one or a small number of neurons, by for example dot product decoding (Rolls *et al*., 1997a,b; Rolls & Treves, 1998; Rolls & Deco, 2002).

Some of the neurons analysed in this investigation responded more to the sample stimulus than to the same stimulus when it was shown later on the same trial as a match stimulus, as described by Hölscher & Rolls (2002). The results described here of neurons that respond to the long-term familiarity of stimuli were found to be the case overall

despite any short-term alterations of neuronal response related to working memory, which were counterbalanced in the design of the present study.

Discussion

The new finding in the present study is that many perirhinal cortex neurons responded more to familiar images than to novel images, with the familiarity building over hundreds of trials. Such a time-scale has not been investigated previously, because most studies did not record neuronal responses for longer than 24 h and did not allow a slow emergence of increased neuronal responses to images related to their long-term familiarity to be observed (Brown & Xiang, 1998; Xiang & Brown, 1998; Erickson & Desimone, 1999). Although some neurons responding more to familiar than to novel images, and others responding more to novel than to familiar images, have been found previously in the perirhinal cortex where novelty and familiarity refer to changes that occur over a few stimulus presentations (Sobotka & Ringo, 1993; Brown & Xiang, 1998; Hölscher & Rolls, 2002), we show in this study that the development of increased neuronal responses was related to a different, long-term, type of familiarity in which the increased neuronal responses to familiar images can take days or weeks to develop. We therefore propose that the perirhinal cortex builds a representation over large numbers of presentations of images that reflects long-term familiarity. Given the results shown in Table 1, the mean number of experimental sessions for the response to novel stimuli to become as large as to familiar stimuli was 32.4. This corresponds to approximately 400 presentations of each image in the novel set, for 1.3 s per presentation, before the neuron's response to that image in the novel set became as large as its response to images in the familiar set (as described in the Results section). Together, the data shown in Fig. 4 and in Table 1 show that the response of perirhinal cortex neurons is initially smaller to novel than to familiar images, and that the time course of the increasing response to novel stimuli is slow, with approximately 400 1.3-s presentations of a novel stimulus being needed before the neuron responds to the image as strongly as it does to familiar visual stimuli. It is useful to emphasize that the total viewing time corresponding to these 400 presentations of each stimulus is 8.66 min, and this is thus the time that it took for the familiar responses to develop fully to any one stimulus.

The findings of this neurophysiological investigation lead us to propose that the perirhinal cortex forms a representation of stimuli over large numbers of presentations of images, and that this representation is of importance for visual perception and the identification and discrimination of complex scenes or objects. Previous studies have shown that lesions of the perirhinal cortex impair the identification of complex stimuli or objects under visually difficult conditions (Buckley & Gaffan, 1997; Buckley *et al*., 1997; Bussey *et al*., 2002, 2003). Whereas monkeys were able to solve simple visual discrimination tasks in those studies, performance was impaired in the lesioned group when discrimination was made more difficult, e.g. by increasing the feature ambiguity of images (Bussey *et al*., 2003), or by increasing complexity by arranging objects in front of complex backgrounds (Buckley & Gaffan, 1998). We propose that the perirhinal cortex helps to develop representations of complex stimuli or scenes, and that these representations are needed to solve visual discrimination problems in difficult or ambiguous conditions. The stored representations, in that they reflect the familiarity of an object or scene, must contain information about the objects or scenes that enable the animals to recognize the scenes or items even when the visual details are partly obscured in the presentation. The perirhinal cortex is uniquely well placed to form such representations, because it receives stimulus-selective information about what object is being viewed from the inferior temporal visual cortex. Indeed, it has been shown in a tracer study that the anteroventral part of area TE (TEav) projects diffusely over a wide extent of perirhinal cortex (Saleem & Tanaka, 1996), making the perirhinal cortex anatomically suited for making associations between features in an object or the objects in a scene, or computing a general property of all inputs being received, such as how familiar they are. The perirhinal cortex can thus use the stimulus-selective input from potentially most parts of area TE of the inferior temporal visual cortex to form new associations between such selective inputs and thereby to form a unique representation of complex stimuli to identify familiar objects or scenes.

We note that to perform the delayed matching-to-sample task with up to three intervening stimuli correctly, the monkey had to perceive the stimuli. The monkeys were performing the task equally well for both the novel and the familiar set of stimuli (see Results section), and this allows for no other conclusion than that they looked at and processed the stimuli. The actual order of non-match vs. match stimuli within a trial was randomized identically for the familiar and novel sets of images. Furthermore, we note that even apart from the need to look at the images to perform the task correctly, the monkeys continued to look at the stimulus display for the whole trial, as the monitor was the main item visible to the monkey. Moreover, the detailed analyses of eye positions described in the Results section showed that there was no difference in the fixation of the stimuli in the novel and familiar sets during the performance of the delayed matching-to-sample task. This evidence shows that the gradually increasing responses to the stimuli as they became more familiar over repeated days of testing are not due to any possible differential looking at stimuli as a function of how familiar they are becoming.

The results obtained here are in agreement with previous studies on the perirhinal cortex in several respects: the peak firing rates of the neurons were relatively low (typically around 10 spikes/s on average, though for short periods they might be as high as 40 spikes/s); the stimulus-selectivity of the neurons was in some cases low; and instead of being tuned to particular stimuli, the neurons often reflected more general properties common to groups of stimuli, such as short-term novelty or familiarity, or their general relevance to the task being performed, or attention (Chelazzi *et al*., 1998; Xiang & Brown, 1998; Erickson & Desimone, 1999; Liu & Richmond, 2000). Indeed, we emphasize that, in agreement with previous studies (Riches *et al*., 1991; Li *et al*., 1993; Miller & Desimone, 1994; Xiang & Brown, 1998; Liu & Richmond, 2000), we do find in the short term, for example within a trial or across periods of up to 1 h, in general a larger response to novel than to familiar stimuli. In addition, we have extended earlier analyses of the short-term memory-related responses of perirhinal cortex neurons by showing that the responses of actual perirhinal cortex neurons (cf Li, Miller & Desimone, 1993) are reset at the start of each trial, and so do not reflect a passive decay of neuronal activity, but instead active recruitment into the short-term memory task (Hölscher & Rolls, 2002). In contrast to these short-term changes in perirhinal cortex neuron responsiveness that last for seconds or sometimes minutes, what is new about the present paper is that it reports on how the activity of perirhinal cortex neurons is related to the long-term familiarity of stimuli, where long-term means a gradual build-up of responsiveness to a set of stimuli over periods of many days and involving hundreds of repetitions of each stimulus, a time-scale not previously investigated (e.g. Fahy *et al*., 1993). We also found that some perirhinal cortex neurons (21/221) were tuned to respond with some degree of specificity to defined objects, although they were not as sharply tuned to specific objects as are neurons in the inferior temporal

visual cortex (Baylis & Rolls, 1987; Rolls *et al*., 1997a,b; Booth & Rolls, 1998; Rolls, 2000; Rolls & Deco, 2002). The finding that some neurons in the perirhinal cortex have relatively poor stimulus selectivity, and may be tuned to other aspects of tasks being performed, is in line with previous studies. For example, Liu & Richmond (2000) showed that a small stimulus above the main visual display, which indicated the number of trials of the task remaining before reward was given, influenced the firing of the perirhinal cortex neurons they studied more than did the particular visual stimulus being shown on the monitor. Furthermore, Xiang & Brown (1998) found that whereas there were some differences of the neuronal responses to novel and familiar stimuli in a recognition memory task, most of the neurons were not tuned to the identity of the particular visual stimuli used in the task. (In their task, they found that perirhinal cortex neurons tested with trial-unique visual stimuli tended to respond more to the first than to the second presentation of the stimuli. With stimuli that were already familiar, even this difference was not clear.) We note that some studies (e.g. Miller & Desimone, 1994) performed in the ventral temporal lobe have described the recordings as being in 'IT cortex', where this was taken to mean cortex between the rhinal sulcus and the anterior middle temporal sulci. This region contains what are probably very different areas functionally as well as architectonically, namely the perirhinal cortex and area TE, which is part of the temporal lobe visual association cortex (Suzuki & Amaral, 1994a,b; Rolls & Deco, 2002). In that the recordings in this study were separated into those in the perirhinal cortex and those in TE, the tuning of the neurons may be more accurately described than in the previous studies, which combined recordings in these two areas.

What advantages might the representation of the long-term familiarity of images, which can develop over very large numbers of presentations, and is reported for the first time in this paper, confer? The new concept we propose here, based on the finding that perirhinal cortex neurons build representations over hundreds of trials to enable them to respond more to very familiar stimuli than to novel images, and indeed to reflect the long-term familiarity of images, is as follows. First, the perirhinal cortex is well placed to form such representations, because it receives from the inferior temporal visual cortex (IT), and thus receives information about what is being seen (Rolls, 2000; Rolls & Deco, 2002). The perirhinal cortex neurons could develop their responses by increasing the synaptic strength from the IT inputs onto the perirhinal neurons by a small increment every time a particular object is being represented in the IT cortex. This would result in the perirhinal cortex neurons gradually becoming more responsive to any object that had produced object-related firing in IT neurons. It might also gradually produce the less sparse representation in the perirhinal cortex described above for familiar than for novel stimuli. A new set of IT neurons responding to a relatively novel stimulus would not as a set have the same strong synapses onto perirhinal cortex neurons as a set of IT neurons representing a familiar stimulus, so that with global inhibition in the perirhinal cortex related to the number of IT neurons that are firing, the perirhinal cortex neurons would respond much better to any very familiar object or image than to a novel object or image. Previous studies have shown evidence that such processes can occur in the cortex. In a recording study in area V1 of the selectivity of neuronal responses for stimulus orientation, it was found that after training, the tuning for the orientation of the training stimulus patterns had increased (Schoups *et al*., 2001). In addition, in a recording study of neurons in the perirhinal cortex, it was found that after training, pairs of neurons that are close together fire in a more correlated way after repeated presentation of rewarded visual stimuli (Erikson *et al.*, 2000). Our findings extend these results by showing that individual neurons can increase their firing responses over time when shown novel stimuli, and that the perirhinal cortex reflects, and probably builds, these familiarity-related representations of objects and scenes.

The potential functions of computing the long-term familiarity of objects or images in the brain are many-fold, and include recognition of complex object–environment configurations such as members of one's own social and family group, recognition of one's own possessions, recognition of one's own territory, etc. Furthermore, it is notable that the loss of the feeling of familiarity for objects and events introduced after medial temporal lobe damage is one of the important symptoms of medial temporal lobe amnesia, and this too may be related to these operations that we suggest are being performed by the perirhinal cortex. What we propose is that the identity of the object or face would be represented by area TE of the inferior temporal visual cortex (in the way reviewed by Rolls & Deco, 2002); and that the long-term familiarity of the object would be represented by how strongly the perirhinal cortex neurons described in this paper are firing. Together, the two types of neuronal activity encode both identity and long-term familiarity, but allow each type of information to be read out from the system (by other brain areas) independently of the other.

In conclusion, the findings described in this paper show that the long-term familiarity of visual stimuli is made explicit in the representation of information in the perirhinal cortex. The perirhinal cortex can, given its anatomical connections, use the stimulus-selective input from potentially most parts of the IT to identify for any object being seen how familiar it is. This capacity of the perirhinal cortex is not mutually exclusive with a function in short-term visual working/recognition memory, and also may facilitate as described above visual perception when it is performed under difficult conditions. But the finding described here does introduce an interesting new concept for one of the functions in memory of this brain region. The output of the perirhinal cortex to other brain regions would provide a large amount of information (in the information theoretical sense, see Rolls & Deco, 2002) about the degree of long-term familiarity of the stimulus being shown, of potential use in the types of function described above.

Finally, the data presented in this paper provide direct evidence for a form of slowly developing memory consolidation, in that the responses of the perirhinal cortex neurons gradually became stronger to images over hundreds of presentations. The concept of slowly developing memory traces has been in the memory literature for almost 100 years, and the evidence described here shows, that for this part of the brain, a memory trace that develops gradually over time and repeated experience can be shown to be reflected in neuronal activity. The new data described here suggest that synaptic strengths incrementing over a very large number of presentations may be important in some types of memory, such as the long-term familiarity memory described here.

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