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RECOGNITION MEMORY: NEURONAL SUBSTRATES OF THE JUDGEMENT OF PRIOR OCCURRENCE

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Abstract—Recognition memory relies on two processes: (i) identification and (ii) judgement concerning prior occurrence. A system centred on perirhinal cortex appears to be responsible for judgement of prior occurrence based on discrimination of the familiarity of stimuli or their recency of occurrence; in contrast, a hippocampal system probably supplies information concerning the episodic, contextual aspects of recognition memory.

This review chiefly concerns the perirhinal system and, in particular, neurones that signal the prior occurrence of stimuli by a decrease in response. Details concerning such decremental responses are given and it is argued that such responses in peririnal cortex are adequate for and central to discrimination of stimulus familiarity and recency in a wide range of situations.

Information is given of similar types of neuronal responses in anatomically related brain regions and what may be deduced about the operation of the recognition memory system. The possibility is discussed that the neuronal responses that signal information concerning the recent occurrence of stimuli may contribute to repetition priming as well as recognition memory.

Other described changes in the activity of individual neurones such as response enhancements, or sustained (delay) activity may allow solution of specialised forms of recognition memory tasks where relatively short-term working memory is adequate. Implications of the multi-faceted nature of recognition memory for the interpretation of results are emphasised.

Unsolved problems and avenues for future experimentation, including determining the nature of possible underlying synaptic plastic changes, are discussed. © 1998 Published by Elsevier Science Ltd. All rights reserved

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ABBREVIATIONS

fMRI	functional magnetic resonance imaging	PET	positron emission tomography

1. INTRODUCTION

1.1. Compass of Review

The ability to recognise the novelty or familiarity of sensory experiences, remembering individual items or events, is a normal part of everyday life. The ability is dependent on the operation of recognition memory. Recognition memory relies on two processes: (i) identification and (ii) judgement concerning prior occurrence (Mandler, 1980). This review will chiefly concern what is known of the neural processes that allow judgements about the prior occurrence of sensory experiences in mammals. Such judgements include information concerning how much time has elapsed since the item or event was last encountered (its recency of occurrence), whether it has been experienced much, little, or never previously (its relative familiarity), and the place, time and other associations of any previous experience (the context of the prior occurrence).

Recently there has been a rapid advance in uncovering of some of the possible brain mechanisms that may allow judgements concerning prior occurrence of items or events, though many important issues remain to be resolved. These advances have been made most notably through the study of visual recognition memory in animals. Thus selective lesion studies have clarified the regions necessary for such behaviour, while recording studies have revealed neuronal responses signalling information concerning the prior occurrence of stimuli. This review will primarily concern the changes in neuronal responses that occur when visual stimuli are seen more than once and which could provide a substrate for recognition memory. (Accordingly, it will not deal with peripheral sensory adaptation or general decrements in response to monotonously repeated stimuli—habituation.) It concerns such responses only as studied in mammals.

Recognition memory is not a unitary phenomenon as it is potentially dependent on any or all of a number of different types of information. There is evidence for the separation of processing of these different types of information at the neuronal level (Brown, 1996). Thus there is not a single neural mechanism underlying recognition memory, but a variety of processes adapted to provide solutions for specific problems. In particular, there is now much evidence that a separation can be made between a system centred on the hippocampus that deals with episodic, contextual aspects of recognition memory and a system centred on perirhinal cortex that is concerned with judgements of the familiarity or recency of occurrence of stimulus items (see for reviews: Delay and Brion, 1969; Aggleton and Brown, 1998), i.e. knowing that something has been experienced previously (perirhinal) rather than knowing where and under what circumstances it was

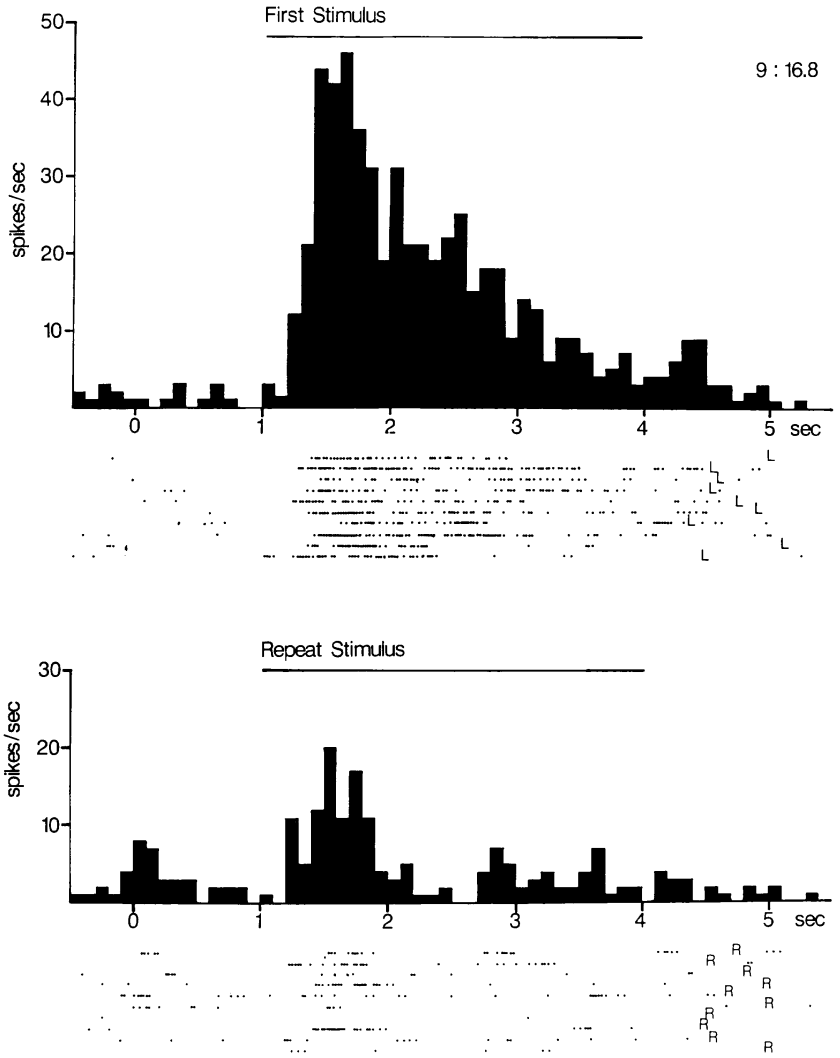

Fig. 1. Example decremental repetition-related neuronal response. Note the much stronger response of a perirhinal neurone to the *First* (upper histogram and raster) than to the *Repeat* (lower histogram and raster) presentations of 10 different pictures presented during a monkey's performance of a serial recognition memory task (Fahy *et al.*, 1993b). One picture was shown on each trial during the time indicated by the bar above the histogram. The occurrences of action potentials on each trial are indicated by separate rows of dots in the raster display under the histogram. A press after stimulus offset was rewarded if it was to the left side for a first presentation and to the right for a repeat presentation. Variable numbers of trials involving other pictures intervened between the first and repeat presentations of each stimulus. However, in the illustration the order of the ten stimuli in the second set of rasters is the same as that in the first. Unless otherwise indicated, neuronal responses in other Figures have also been obtained during performance of serial recognition memory tasks. Reproduced with permission from Brown (1990).

previously encountered (hippocampal). This review focuses on the perirhinal system. It is argued that the core mechanism of this perirhinal system is a decrease in the response of neurones when stimuli are repeated (see Fig. 1). There is mounting evidence that this decrease in response underlies the automatic, non-effortful recording in memory of the occurrence of encountered individual stimulus items. Such responses sensitive to the repetition of a stimulus carry information essential to recognition memory concerning the relative familiarity and recency of occurrence of particular stimuli (Fahy *et al.*, 1993b).

This review chiefly concerns neuronal responses and their relation to recognition memory: other recent reviews of this topic include Brown (1996), Desimone (1996) and Ringo (1996). Evoked potential studies fall outside its scope. The results of ablations and of human brain imaging—positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)—will receive only passing mention where of particular pertinence. There have been recent reviews with relevance to recognition memory of ablation studies (Mishkin and Murray, 1994; Aggleton and Shaw, 1996; Gaffan, 1996; Murray, 1996; Squire and Zola, 1996;

Suzuki, 1996a; Aggleton and Brown, 1998) and human imaging (Ungerleider and Haxby, 1994; Fletcher *et al*., 1995; Grafton, 1995; Buckner and Petersen, 1996; Nyberg *et al*., 1996; Tulving and Markowitsch, 1997). Similarly, this review will not deal in detail with processes underlying stimulus identification: there have been recent reviews of mechanisms for visual stimulus identification (Miyashita, 1993; Tanaka, 1996; Logothetis and Sheinberg, 1996; Nakamura and Kubota, 1996).

There have been radical re-assessments of the contributions to memory of medial temporal lobe structures in recent years. As background, a brief historical résumé of these advances in relation to recognition memory is given in Section 1.2. These advances have centred on an appreciation of the contribution of the perirhinal cortex. The location of this area in relation to neighbouring cortical regions is illustrated in Fig. 2. Brief anatomical details concerning this region are given in Section 1.3.

Neuronal responses in relation to recognition memory have been most studied in the anterior inferior temporal cortex, including perirhinal cortex. Correspondingly, the review will focus on what is known of these responses in this area and, in particular, responses that signal the prior occurrence of a stimulus by a reduction in response (Section 2). After consideration of the properties of such neuronal responses and the brain regions where such responses may be found (Sections 3 and 4), the possible mechanisms that may effect such changes (Section 5) and the adequacy of the response changes as a substrate for recognition memory (Section 7) will be discussed. It will be concluded that the decrease in response on stimulus repetition of neurones in perirhinal cortex is at the core of a system that enables judgements to be made about the familiarity and recency of occurrence of individual stimuli, though many issues remain to be investigated (Sections 7 and 8). In specialised circumstances, other processes including response enhancement and delay activity supplement or supplant this mechanism (Sections 6 and 7). Moreover, where the context or the spatial arrangement of items is important to remembrance of prior occurrence, the involvement of the hippocampal system is required (see Sections 3.1.6 and 4.1).

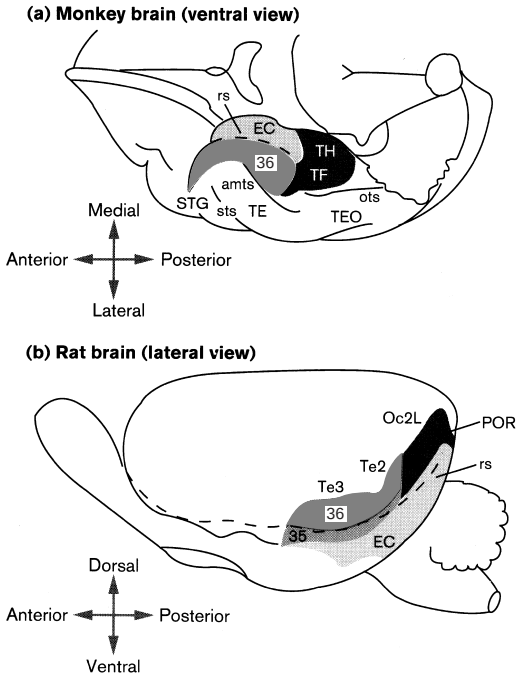

Fig. 2. The location of perirhinal cortex (35, 36; dark shading) in the monkey (a) and rat (b) brain. Also shown is the entorhinal cortex (EC) in light shading and, in black, areas TF and TH of the parahippocampal gyrus of the monkey and postrhinal cortex (POR) of the rat. Other abbreviations: (a) TE = area TE; TEO = area TEO; amts = anterior medial temporal sulcus; ots = occipitotemporal sulcus; STG = superior temporal gyrus; sts = superior temporal sulcus. (b) rs = rhinal sulcus; Te2, Te3 = temporal cortex; Oc2L = lateral occipital visual association cortex. Reproduced with permission from Suzuki (1996a).

1.2. A Brief Historical Background

Modern study of the neural basis of recognition memory, like that of many other memory functions, received major impetus from the memory deficits reported by Scoville and Milner (1957), and in particular the dense amnesia of one of their patients identified by the initials HM. In HM an operation removing parts of the medial temporal lobe bilaterally was performed for the relief of intractable epilepsy. The removal was believed to include the hippocampus, amygdala and surrounding cortex (though see Corkin *et al*. (1997) for the true extent of the removal). The resultant amnesia involved long-term but not short-term memory: items were remembered for only brief intervals or as long as the patient's attention was not distracted. Comparisons with other surgical removals led to the suggestion that damage to the hippocampus was the critical lesion responsible for the memory loss (Scoville and Milner, 1957).

It proved difficult to find an animal model for this human amnesia. However, a substantial advance was achieved by Mishkin (1978). Mishkin removed the hippocampus, amygdala and surrounding cortex bilaterally in monkeys, so replicating HM's lesion as originally described. Importantly, he also tested the animals' memory using a task, a variant of visual delayed non-matching to sample, that was closely equivalent to certain human recognition memory tasks. Trials in delayed non-matching to sample tasks comprise an acquisition phase separated from a test (choice) phase by a delay. During the acquisition phase the animal is presented with a sample stimulus. During the test phase the animal is presented with a choice of two stimuli, one of them being the original sample. In the matching variant of the task the correct (rewarded) choice is the previously presented sample stimulus; in the non-matching variant, the other stimulus must be chosen to gain reward. Crucially, Mishkin (1978) used a very large stimulus set, so that items to be recognised were repeated infrequently—thus mirroring typical human recognition tasks where stimuli are

infrequently rather than frequently encountered during a testing session. There was a major deficit in the performance of this task by the monkeys with the full lesion, but only a minor deficit was found when either the hippocampus or the amygdala was spared. These findings were interpreted as implying that either the hippocampus or the amygdala could be used to solve such recognition memory tasks and that therefore ablation of both was necessary to produce a major behavioural deficit (Mishkin, 1978, 1982).

In electrophysiological experiments using behaviourally trained monkeys, Brown *et al*. (1987) explored the medial temporal lobe looking for neuronal responses that differed for novel and familiar visual stimuli, i.e. responses that might provide a neural substrate for the solution of recognition memory tasks such as delayed non-matching to sample. Appropriate responses were found in cortex adjacent to the rhinal sulcus beneath the hippocampal formation, but not in the hippocampal formation itself. The distribution of such responses raised the possibility that the memory deficits observed after large medial temporal lesions might be due to damage to this non-hippocampal cortex or its connections, rather than to the hippocampus. That damage to regions adjacent to the hippocampus rather than the hippocampus itself might be responsible for amnesia had been suggested previously (McLardy, 1970; Horel, 1978).

Subsequent ablation studies in the monkey have indeed demonstrated the importance of the cortex adjacent to the rhinal sulcus for the performance of delayed matching and non-matching to sample tasks. In particular, cooling or ablation of cortex lateral to the fundus of the rhinal sulcus, the perirhinal cortex, has been shown to produce major impairment in the ability to perform such tasks (Horel *et al*., 1987; Gaffan and Murray, 1992; Meunier *et al*., 1993, 1996; Suzuki *et al*., 1993; Eacott *et al*., 1994), while excitotoxic lesions of the hippocampus that spare perirhinal cortex do not (O'Boyle *et al*., 1993; Mishkin and Murray, 1994; Murray, 1996; Murray and Mishkin, 1996; Aggleton and Brown, 1998)—though see Alvarez *et al*. (1995). Similarly, in the rat recognition memory shows major impairment following perirhinal lesions (Mumby and Pinel, 1994; Wiig and Bilkey, 1995; Ennaceur *et al*., 1996) and only minor impairment following hippocampal lesions (Aggleton *et al*., 1986; Steele and Rawlins, 1993; Mumby *et al*., 1995). The reason for Mishkin's (1978) findings turned out to be that surgical ablation of the amygdala damaged anterior parts of the cortex adjacent to the rhinal sulcus and its connections, while ablation of the hippocampus damaged posterior parts of this cortex. Thus removal of both the hippocampus and the amygdala damaged cortex adjacent to the whole length of the rhinal sulcus and its connections while ablation of either the hippocampus or the amygdala left part of this cortex intact (Murray, 1996).

Current evidence strongly suggests that a system centred on the perirhinal cortex is necessary for the performance of recognition memory tasks soluble by judgement of the relative familiarity or recency of occurrence of individual stimulus items, whereas a system centring on the hippocampus is necessary for tasks that are dependent on the remembrance of the spatial and possibly other interrelationships of items (O'Keefe and Nadel, 1978; Olton *et al*., 1979; Parkinson *et al*., 1989; Brown, 1990, 1996; Gaffan, 1991, 1994; O'Keefe, 1993; Eichenbaum *et al*., 1994; Eichenbaum, 1996; Wiener, 1996; Nadel and Moscovitch, 1997; Aggleton and Brown, 1998). In a given situation, the normal brain may be expected to use either or both of these systems depending on the particular strategy adopted by the subject.

It is now known from a recent MRI study (Corkin *et al*., 1997)—with some irony given the history of the subject—that HM's lesions are less extensive than originally supposed. The caudal hippocampus is spared, though the lesion probably includes the whole of entorhinal cortex and parts of the temporal pole in both hemispheres. It seems that removal of the human equivalent of perirhinal cortex may have been less than total. Nevertheless, any remaining perirhinal tissue may not be fully functional. Thus the lesion is likely to have disrupted perirhinal connections. Moreover, there is evidence that the effects of ablations can be indirect as well as direct: the removal of tissue may prevent the normal functioning of non-ablated regions. There is even evidence that partial hippocampal lesions may cause greater disruption than more complete lesions (Mumby *et al*., 1996). Additionally, HM's surgery was performed to relieve epilepsy: his epileptic attacks may also have had an enduring deleterious effect in other, related regions of the cortex; see for discussion Tulving and Markowitsch (1997).

More recent recording studies have established important properties of the responses of neurones whose activity could provide a basis for recognition memory founded on judgement of prior occurrence. Such responses have been most studied in anterior inferior temporal cortex, including perirhinal cortex, in unanesthetised, behaviourally trained monkeys. Section 2 will therefore cover the characteristics of such neuronal responses in that area.

1.3. A Brief Anatomical Résumé

There is not currently universal agreement as to the boundaries of perirhinal cortex (see for recent reviews: Burwell *et al*., 1995; Van Hoesen, 1995; Nakamura and Kubota, 1996; Suzuki, 1996a,b). A full discussion of this issue is beyond the scope of this review, but it should be noted that there has been considerable variation in the definition of perirhinal cortex used in different recording and ablation studies.

For simplicity, this review will follow the delineations of perirhinal cortex of Burwell *et al*. (1995) (see Fig. 2). Under this definition, monkey perirhinal cortex includes a larger area than earlier designations. Accordingly, the perirhinal cortex of the monkey extends immediately lateral to the full extent of the rhinal sulcus and includes cortex corresponding to areas 35 and 36 of Brodmann. It includes the medial half of the temporal pole (area TG; von Bonin and Bailey, 1947) and approximately half of the cortex of the inferior temporal gyrus

between the rhinal sulcus and the anterior medial temporal sulcus. Medially it abuts the entorhinal cortex. Laterally it is bounded by area TE (von Bonin and Bailey, 1947) of inferior temporal cortex. Caudally are found areas TF and TH of the parahippocampal gyrus (von Bonin and Bailey, 1947). In the rat, perirhinal cortex is located on either side of the caudal part of the rhinal sulcus. Immediately medial to it is entorhinal cortex. Posteriorly, caudal to the rhinal sulcus, postrhinal cortex continues from perirhinal cortex and may be the rat equivalent of monkey parahippocampal cortex (Burwell *et al.*, 1995). Gross markers for the precise location of perirhinal cortex in the human, where the rhinal sulcus is a weak and variable feature, remain to be established. It is commonly associated with the collateral sulcus, but this sulcus is a frequently interrupted and somewhat variable feature in the human brain (MWB, unpublished observations).

Perirhinal cortex is highly interconnected with many other brain regions (see for recent reviews: Burwell *et al.*, 1995; Suzuki, 1996a,b). A summary flow diagram of some important perirhinal connections is given in Fig. 3. It receives information from many areas of association cortex, including visual, auditory, olfactory, and somatosensory association areas, as well as from polymodal association areas including prefrontal cortex and the entorhinal cortex. It has return projections to these cortical regions, including a major projection to entorhinal cortex, and some input direct to the hippocampus (Liu and Bilkey, 1996). Entorhinal cortex provides the main input to the dentate gyrus and hippocampus. Perirhinal cortex also has reciprocal connections with the amygdala. Subcortical connections

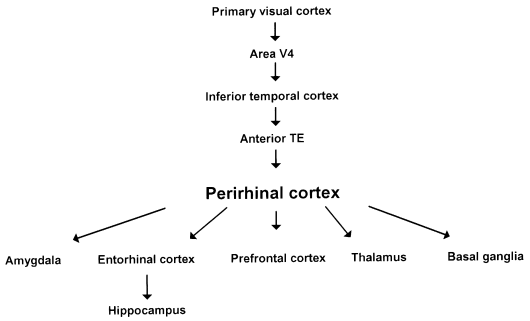

Fig. 3. A summary flow diagram of some important connections of perirhinal cortex. This diagram is designed to highlight major relationships between perirhinal cortex and other regions but does not present a complete picture of the connections of either perirhinal cortex or the other illustrated regions (see Section 1.3 for sources of further anatomical information). The diagram emphasises the main route followed by visual information to perirhinal cortex; other sensory systems have corresponding routes. However, spatial information from parietal cortex may largely bypass perirhinal cortex, reaching the hippocampus via the parahippocampal gyrus (or postrhinal cortex in the rat). Note that the diagram does not include return pathways such as those from the thalamus and prefrontal cortex to perirhinal cortex, nor pathways from perirhinal cortex to other parts of association cortex. Connections with the basal forebrain nucleus and the reticular formation have not been included.

are reciprocal with the thalamus (mediodorsal and midline nuclei). There are also projections to the caudate nucleus, putamen, and the nucleus accumbens septi. Although clearly anatomically distinct, perirhinal and entorhinal cortex are frequently grouped under the term *rhinal cortex*.

In this review *anterior inferior temporal cortex* will imply the anterior part of area TE and perirhinal cortex. Area TE is the major source of visual information to perirhinal cortex (Burwell *et al.*, 1995; Saleem and Tanaka, 1996). The term *hippocampus* will be used as a short-hand for subfields CA1 to CA4 of the hippocampus proper plus the dentate gyrus and subicular cortex.

2. NEURONAL RESPONSE CHARACTERISTICS IN ANTERIOR INFERIOR TEMPORAL, INCLUDING PERIRHINAL CORTEX

This section will detail what is known of neuronal responses that carry information of potential use for the solution of recognition memory tasks. Such responses have been termed *recognition-related*, though the designation implies merely that the information signalled is of potential use to recognition memory and not that it is necessarily used for such purpose (Brown, 1996). Thus it is arguably better to term such responses *repetition-sensitive*, in contradistinction to the more commonly encountered *repetition-invariant responses* which show no consistent change with stimulus repetition. However, the response changes to be discussed in this review are stronger and far more rapid than are those that accumulate over many repetitions in habituation (Thompson and Spencer, 1966; Horn, 1967; Kandel and Spencer, 1968; Brown, 1996) (see further Section 5.1): the major change for the responses to be discussed here is between the first and second appearance of a stimulus whose two appearances may be widely separated in time. Thus in this review the use of the term *repetition-sensitive response* will be in the context of the response's potential relation to a recognition memory process rather than any other, more generalised possible employment of the phrase, for example in the contexts of habituation or peripheral sensory adaptation.

The selectivity, rapidity, and long-lasting nature of the response changes to be discussed are what make them the foremost candidates for the neural substrates of certain aspects of recognition memory. Such response changes have been most studied using visual stimuli and for recordings made in the anterior temporal lobe, particularly in the anterior parts of inferior temporal cortex, i.e. anterior parts of area TE and perirhinal cortex. The characteristics of the responses of neurones in this region will therefore be described first. Importantly, the characteristics of these responses have been established using large stimulus sets containing stimuli which are unfamiliar or have been infrequently encountered by the animal and which are presented more than once.

2.1. Types of Tasks and Stimuli

The repetition-sensitive responses under review have been found using different types of stimuli and in the context of the performance of different behavioural tasks or none. Importantly, such changes occur for types of stimuli that have not been previously used in the training of an animal and, indeed, in animals that have not been trained in a recognition memory task (Riches *et al.*, 1991; Fahy *et al.*, 1993b; Zhu *et al.*, 1995a). The neuronal changes are therefore endogenous and are not induced (though their incidence may be influenced) by training of the animal in recognition memory tasks. Correspondingly, the response change is probably a result of an automatic rather than an effortful process (Riches *et al.*, 1991)—as has been suggested for hippocampal registration of experiences (Marr, 1971; Rawlins, 1985). Moreover, the natural direction of the change is a decrease in response to repeated stimuli (Brown *et al.*, 1987) (see e.g. Figure 1).

The recognition tasks employed have most commonly been variants of delayed matching or non-matching to sample in which on each trial single stimuli are presented successively in the choice phase, the stimuli either matching or not matching the previously presented sample stimulus (e.g. Miller *et al.*, 1993; Sobotka and Ringo, 1993) (see Fig. 4). Electrophysiological studies do not normally use the standard behavioural version of the task with simultaneous presentation of both a matching and non-matching stimulus at the test phase because this gives rise to difficulty in interpreting to which of the two stimuli a change (if any) in neuronal response should be ascribed. Where only one stimulus is presented at a time during the choice phase the animal must make one of two alternative responses dependent upon whether the stimulus is a match or a non-match; several stimuli may be successively presented during the choice phase, each being compared to the original sample (e.g. Miller *et al.*, 1993; Sobotka and Ringo, 1996). Other tasks have been variants of a running or serial recognition task (Gaffan, 1974) in which only one stimulus appears during each trial (Riches *et al.*, 1991; Otto and Eichenbaum, 1992a; Fahy *et al.*, 1993b) (see Fig. 4). Stimuli are eventually repeated in subsequent trials, but variable numbers of trials intervene between the first and second appearance of each individual stimulus. A different behavioural response is required depending on whether or not the stimulus has appeared on a previous trial. A critical difference between the serial recognition and delayed matching tasks that have been employed in recording studies is that the animal has to remember only one stimulus at a time in the delayed matching tasks, whereas the number of stimuli that must be retained in memory is indeterminate in the serial recognition task. For these types of experiments it is essential, whichever task is used, that the stimulus sets are large and contain many items that are infrequently encountered by the animal. They may additionally include stimuli that have been seen many times previously by the animal, so that the neuronal responses to such highly familiar stimuli may be compared to those to relatively unfamiliar stimuli. While response decrements on stimulus repetition are found in all these tasks, details of the type of task employed can have a major influence on the particular pattern of response changes that occur; in particular, whether there are found types of response changes—increments or sustained activity (see Section 6)—in addition to the standard response decrements. Further, it seems probable that response changes found in delayed matching tasks that use small stimulus sets of frequently repeating, highly familiar items are the result of a different learning mechanism (see Section 6.1).

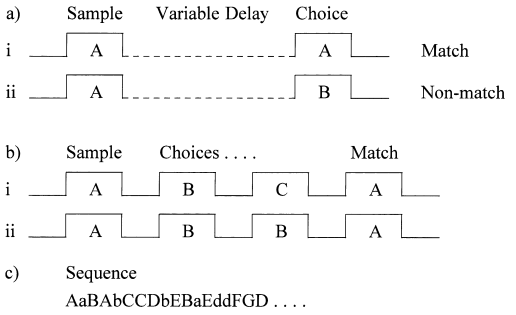

Fig. 4. Types of recognition memory tasks (as used in recording studies). (a) Delayed matching with variable delay: after presentation of the *sample* stimulus (A) there is a *variable delay* before either the sample is re-presented (*Match* trial) or another stimulus (B) is presented (*Non-match* trial); different responses are required on each type of trial. (b) Delayed matching with variable numbers of sequentially presented *choices* (stimuli B, C...) before the sample (A) is re-presented (*Match*); a response is required to the matching, but not to the non-matching stimuli. Versions with (ii) and without (i) repeats of the non-target stimuli have been used. (c) Serial recognition: a single stimulus is presented on each trial, the correct response depending on whether it has been seen previously. Unfamiliar stimuli (upper case letters) and, in some versions, familiar stimuli (lower case letters) are presented in a sequence trials with repeat presentations occurring pseudorandomly after varying numbers of intervening trials.

The types of stimuli that have been investigated have been very largely visual, varying between 2-D drawings of geometric shapes, through pictures of individual objects and faces, to pictures of scenes containing many individual items, and to the sight of 3-D objects (Riches *et al.*, 1991; Fahy *et al.*, 1993b). Response decrements have been found using all these types of stimuli. As yet there have been no essential differences reported between results using these different types of stimuli, though this does not mean that individual neurones always demonstrate precisely the same response change with different types of stimuli. Experiments have also been conducted in which the spatial relationships of stimuli as well as their relative familiarity are critical (Rolls *et al.*, 1989; Suzuki *et al.*, 1995; Rao *et al.*, 1997; Wan *et al.*, 1997a). Such experiments demonstrate that there are differences in the anatomical distribution of task-dependent responses where spatial information is crucial to task solution.

These types of experiment normally require very large numbers of clearly discriminable (and memorable) stimuli. In part because of this requirement,

little work has been done with modalities other than visual. However, odours have been used with rats (Otto and Eichenbaum, 1992a; Eichenbaum *et al.*, 1996; Young *et al.*, 1997). In these experiments odours are presented in a continuous delayed non-matching to sample (serial recognition) task: if the odour on the present trial differs from that on the previous trial, reward is available; if the odour on both trials is the same, no reward is available. However, this task has been used with a restricted stimulus set of 16 items. As mentioned above, there is evidence to suggest that the underlying neuronal mechanism used for task solution may differ if small, frequently repeating rather than large, infrequently repeating stimulus sets are used (see Section 6.1).

A different technique, immunohistochemical staining for the products of immediate early genes (IEGs) has recently been used in the rat to seek the locations of neurones with repetition-sensitive responses (Zhu *et al.*, 1995b, 1996; Wan *et al.*, 1997a). IEGs are expressed following neuronal activation and thus can be used (though not without circumspection) to locate activated neurones (Herrera and Robertson, 1997). Immunohistochemical staining for Fos, the protein products of the IEG c-*fos*, has been used to seek differences in the numbers of stained neurones (neuronal nuclei) produced by the passive viewing of novel and familiar stimuli (3-D objects or computer-displayed pictures). Recently, different novel and familiar spatial arrangements of sets of three familiar, computer-displayed, individual stimulus items have been used to explore regions activated by such spatial configurations of stimuli (Wan *et al.*, 1997a). For the rat, a paired-viewing procedure has been developed (Zhu *et al.*, 1996) (see Fig. 5). This exploits the rat's large monocular visual fields and allows a novel and a familiar stimulus to be presented simultaneously, one being viewed by each eye while the rat pokes its head through a hole. Information from each eye then passes via the largely crossed optic chiasma to the contralateral cerebral hemisphere. This within-animal design ensures that both sets of stimuli are presented under the same conditions of alertness and with similar eye movements.

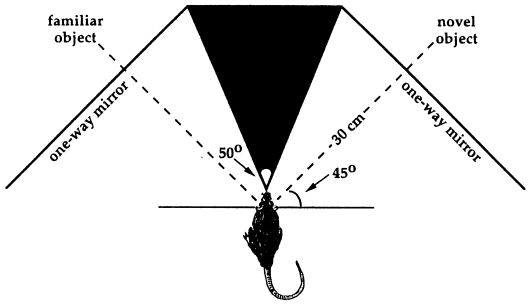

Fig. 5. Paired-viewing procedure (Zhu *et al.*, 1996). A rat holds its head in an observing hole in a perspex screen. After a computer-controlled variable delay and by means of an optical shutter, a novel and a familiar stimulus are made to appear simultaneously, one behind each of the one-way mirrors. At the end of the stimulus presentation the rat receives a drop of juice from a tube it can just reach with its tongue when its head is in the observing hole. The two objects are so placed that each is located in the monocular field of one eye; hence information initially passes to the opposite cerebral hemisphere. The cone prevents the rat from seeing both objects with a single eye. In recent experiments computer screens have replaced the one-way mirrors (Wan *et al.*, 1997b). Reproduced with permission from Zhu *et al.* (1996).

2.2. Stimulus Identification

Recognition memory requires discrimination between stimuli on the basis of their physical (sensory) attributes, in addition to information concerning their previous occurrence. Sensory information has passed through several stages of processing before it reaches the anterior temporal lobe (Jones and Powell, 1970; DeYoe *et al.*, 1994; Van Essen and Gallant, 1994; Burwell *et al.*, 1995). Such processing has been most studied in the case of the visual system. Indeed, the sensitivity to complex physical attributes of neuronal responses in the anterior temporal lobe has been widely documented (see for recent reviews: Tanaka, 1996; Logothetis and Sheinberg, 1996; Nakamura and Kubota, 1996) and thus will receive no more than brief mention here. Selectivity of response is found in perirhinal and entorhinal cortical neurones as well as those in area TE (Fahy *et al.*, 1993b; Brown *et al.*, 1996; Nakamura and Kubota, 1996). Thus, for example, some neurones respond only to stimuli of a certain colour, while others respond only to pictures of faces (see e.g. Figure 6). Such selectivity varies from neurones responsive to most of the stimuli tested, through those responsive to very few stimuli, to those that are not found to respond to any of the tested stimuli. Such neurones discriminate between stimuli and hence may contribute to stimulus identification. Such a suggestion is consistent with the findings of ablation studies in monkeys (Eacott *et al.*, 1994; Buckley and Gaffan, 1997) and with studies of human amnesia (Warrington, 1975; Hodges *et al.*, 1992; Graham and Hodges, 1997). Both neurones with repetition-sensitive and neurones with repetition-invariant responses show such stimulus selectivity. It is important to appreciate that neurones with repetition-sensitive responses are intermingled with those with repetition-invariant responses and, indeed, examples of both types of response may be simultaneously recorded through a single microelectrode (Xiang and Brown, 1997a, 1998) (see Fig. 21).

Once the physical identity of a stimulus has been established, it becomes appropriate for the nervous system to evaluate the behavioural importance of that stimulus. Such evaluation must include its past history, i.e. its previous occurrences and associations in the life of the subject.

2.3. Judgement of Prior Occurrence

The responses of a subset of neurones in perirhinal and neighbouring cortical areas change with stimulus repetition, i.e. are repetition-sensitive. In particular, the response of such neurones is typically maximal to the first presentations of stimuli and significantly reduced to their subsequent presentations

(see Fig. 1). Thus the fact that a stimulus has been encountered previously is signalled by a reduced response. Such reductions in response are found even if the time between presentations is very long (see further Section 2.3.3). The reduction does not signal general fatigue or inhibition of the cell as other stimuli that have not been encountered previously are still able to evoke strong responses. The reduction in response occurs after a single encounter with the stimulus: thus the change represents a correlate of single trial learning detectable in the activity of single neurones. The phenomenon has been variously described as *adaptive filtering* (Desimone, 1992), *stimulus specific adaptation* (Ringo, 1996), *response suppression* (Desimone, 1996), or merely descriptively as *declining* or *decremental responses* (Brown *et al*., 1987; Riches *et al*., 1991). Here the general term, *repetition-sensitive responses*, will be used because it does not prejudge putative processing mechanisms.

Such changes in anterior inferior temporal cortex have been reported from a number of different laboratories in the unanaesthetised monkey (Brown *et al*., 1987; Miller *et al*., 1991b; Riches *et al*., 1991; Desimone, 1992; Eskandar *et al*., 1992; Fahy *et al*., 1993b; Li *et al*., 1993; Miller and Desimone, 1993, 1994; Sobotka and Ringo, 1993, 1994, 1996; Lueschow *et al*., 1994; Nowicka *et al*., 1995; Xiang and Brown, 1997b, 1998). Similar responses have also been described in the unanaesthetised rat (Zhu *et al*., 1995a). There have also been reports of recognition-related responses, some of which appear to be repetition-sensitive, in human medial temporal cortex (Heit *et al*., 1988, 1990; Ojemann *et al*., 1988; Haglund *et al*., 1994; Fried *et al*., 1997), but as the recording and task conditions differ markedly from those used in animal work these will not be further discussed here.

2.3.1. *Selectivity and Generalisation of Responses*

If a change in response is to provide information of potential use to recognition memory, the change must signal the occurrence of a specific stimulus, i.e. the response must be stimulus selective. The critical repetition-sensitive responses demonstrate two types of stimulus selectivity. (i) The neurones typically respond to the first presentations of only a subset of the tested stimuli. In this respect these neurones are similar to the neighbouring cells with repetition-invariant responses. Some of the repetition-sensitive neurones are broadly tuned and respond to the great majority of visual stimuli tried, though not necessarily with the same strength of response to each different stimulus. Others of these neurones only respond to stimuli of a particular category, e.g. red stimuli, or stimuli with fine-grained patterns, or may respond to such a small proportion of the tested stimuli that their properties cannot be fully established. As a class, neurones with repetition-sensitive responses thus vary across a wide range of stimulus generalisation and stimulus selectivity in their responses to new stimuli (Riches *et al*., 1991; Fahy *et al*., 1993b; Li *et al*., 1993; Miller *et al*., 1993; Sobotka and Ringo, 1993). (ii) Within the subset of stimuli to which repetition-sensitive neurones respond on their first presentation, these neurones signal the subsequent occurrence of individual exemplars of this subset by a decreased response. Thus the decrement in response is specific to particular stimuli which have been encountered previously, but the cell will respond strongly to other stimuli of the subset that have not been seen before (Riches *et al*., 1991; Miller *et al*., 1993; Sobotka and Ringo, 1993). There is also evidence of generalisation, at least for stimulus size: for a majority of repetition-sensitive responses a similar decrement occurs even if a stimulus is shown at a different size on its second presentation (Lueschow *et al*., 1994). Again, this responsivity corresponds to that found for repetition-invariant neurones in inferior temporal cortex. There is as yet no published evidence as to whether repetition-sensitive responses show generalisation across different views of the same object, i.e. whether there is a decrement in response if a stimulus is presented in a different orientation the second time it is seen. Such studies might provide revealing evidence concerning the neuronal encoding of objects as integral items rather than as collections of views.

Thus neurones with repetition-sensitive as well as those with repetition-invariant responses encode information about the sensory attributes of stimuli. In combination these sets of neurones therefore encode knowledge about the identity of the stimulus and its history. This encoding is consistent with the loss of such knowledge found in patients with "semantic dementia" (Warrington, 1975; Graham and Hodges, 1997) who have damage to temporal lobe cortex, including perirhinal cortex, but sparing the hippocampus.

2.3.2. *Incidence of Repetition-Sensitive Responses*

The incidence of such repetition-sensitive responses varies with the conditions under which recordings are made, being maximal when the stimulus repetition frequency is high and the delay interval between repeats is short. Under these conditions half of the visually responsive cells show significant decrements in response with stimulus repetition, i.e. ~25% of the total of recorded neurones. In contrast, under normal conditions the incidence of neurones with response increments on stimulus repetition is less than might be expected by chance, i.e. $< 5\%$ (Fahy *et al*., 1993b; Miller *et al*., 1993; Xiang and Brown, 1998). The tendency to decrement is so marked that it is detectable in population measures of neuronal responses (Riches *et al*., 1991; Miller *et al*., 1993). Thus it has been possible to detect changes based on population imaging techniques including PET (Vandenberghe *et al*., 1995) and IEG expression (Zhu *et al*., 1995b, 1996). With the latter technique it has been shown in rat perirhinal cortex that the number of neurones stained for Fos following exposure to familiar visual stimuli is only 80% that for novel stimuli (Zhu *et al*., 1996); the corresponding figure for TE is 74%.

There is as yet no evidence that repetition-sensitive responses are produced by only one particular morphological type of neurone. Such responses have been recorded from both superficial and deep corti-

cal layers, without evidence that such cells are concentrated in particular layers (Fahy *et al.*, 1993b). Contrastingly, there is evidence that there is some clustering of such cells, though it is not yet known whether this means that they are organised in particular cortical columns (Fahy *et al.*, 1993b). In the rat neurones stained for Fos and so activated by visual stimuli are found in all cortical layers (Zhu *et al.*, 1995b) and include both pyramidal and stellate cells as well as gaba-ergic neurones (X.O. Zhu and M.W. Brown, unpublished observations). However, there is as yet no evidence from this material that particular cortical layers, or columns, or types of cell are responsible for a preponderance of the decremental responses. No evidence concerning the action potential shapes of repetition-sensitive neurones has yet been published. There is evidence that anterior inferior temporal neurones whose visual response is a reduction in activity (i.e. an inhibitory response) do not show recognition-sensitive changes in response in the monkey (Sobotka and Ringo, 1994), though neurones with inhibitory responses in corresponding regions of the rat cortex do (Zhu *et al.*, 1995a).

2.3.3. *Memory Spans*

If the change in response with stimulus repetition is to be useful to recognition memory, then the change must occur even if the second encounter with a stimulus is widely separated in time from its first occurrence (see e.g. Figure 7). It is useful to term the longest interval over which such a response change is found the *memory span* of the neurone. Note that this term implies merely that the neurone has access to information stored in memory for the particular period and not that the memory must be stored by that neurone itself. The length of memory span varies widely from one neurone to another but often response changes persist even when the interval is filled with many other presentations of stimuli (Brown *et al.*, 1987; Riches *et al.*, 1991; Fahy *et al.*, 1993b; Li *et al.*, 1993; Miller *et al.*, 1993; Sobotka and Ringo, 1993). Thus the responses of certain neurones can demonstrate evidence of information

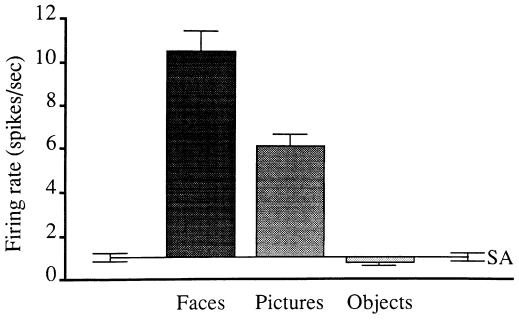

Fig. 6. Example of selective neuronal responsiveness. This neurone recorded in the anterior part of area TE of the monkey responded more strongly to pictures of human and monkey faces than to other pictures or to three-dimensional objects. In this and subsequent figures: error bars represent standard error of the mean; S.A. = spontaneous activity. Reproduced with permission from Brown *et al.* (1996).

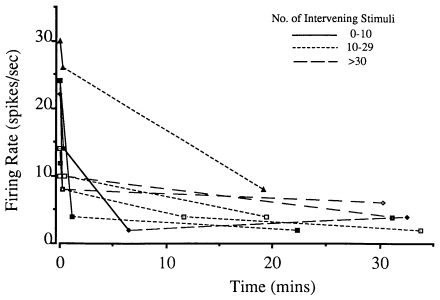

Fig. 7. Examples of a monkey perirhinal neurone's memory span. The responses to successive presentations of 7 different unfamiliar objects are plotted against time elapsed from the first presentation of each object. The response did not recover to its initial value for any of the subsequent presentations for any of the objects even though >30 min and >30 presentations of other objects intervened between two successive presentations of a given object. No behavioural response beyond viewing was required. Reproduced with permission from Fahy *et al.* (1993b).

concerning the prior occurrence of an item being maintained even when attention has been distracted and repeated rehearsal prevented. Accordingly, the information is of potential use to long-term and not only short-term memory.

The shortest memory spans are of only a few seconds duration and fail to survive even a single intervening stimulus presentation, though such short memory spans are typically encountered more posteriorly and laterally in inferior temporal cortex (Baylis and Rolls, 1987). The longest memory spans outlast the longest intervals tested (>24 h) and the presentation of hundreds of intervening stimuli (Fahy *et al.*, 1993b; Xiang and Brown, 1997b, 1998) (see e.g. Figure 8). Neurones have been found with responses to stimuli seen only twice on the previous day that are significantly reduced compared to responses for novel stimuli (Fahy *et al.*, 1993b; Brown *et al.*, 1996; Xiang and Brown, 1997b, 1998); indeed, such response decrements are significant even when measured across a population of neurones with rep-

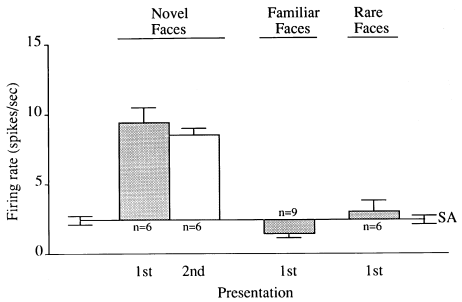

Fig. 8. Example of a neuronal memory span of more than 72 h. This monkey perirhinal neurone responded strongly to pictures of novel faces on either their first or second presentation within the recording session. It did not respond to pictures of faces that were familiar, having been seen during many previous recording sessions, but not during the last 3 days, nor to pictures of faces seen only two or three times previously over 72 h before. Memory spans of over 24 h have also been found using stimuli that are not pictures of faces. Reproduced with permission from Fahy *et al.* (1993b).

etition-sensitive responses (Xiang and Brown, 1997b) (see Fig. 9). Thus the memory spans so far demonstrated are sufficiently long to explain performance of all the common tests of monkey recognition memory (though not yet the full extent of that memory, which has been demonstrated to be at least six months (Ringo and Doty, 1985).

Memory spans have been far less extensively tested in the rat, but response decrements survive intervening presentations of other stimuli (Zhu and Brown, 1995). Moreover, in experiments using Fos staining as a marker for neuronal activity more neurones are activated by novel stimuli than by familiar stimuli last seen 3 h previously (Zhu *et al.*, 1996). Thus a population of rat neurones must have memory spans longer than 3 h.

The responses of neurones with long memory spans necessarily contain little precise information concerning small differences in the time that has elapsed since a stimulus was last encountered: they signal that a stimulus has been seen before, but not precisely when in the recent past (see e.g. Figure 9). Contrastingly, detailed information concerning how recently a stimulus last occurred is signalled by neurones with shorter memory spans, whose response decrement changes rapidly with the time elapsed since the last occurrence of a stimulus (see e.g. Figure 10). The occurrence of a range of memory spans is likely to be advantageous in determining how long ago a stimulus was last encountered, its recency of occurrence, and not merely that it has occurred previously. Such information can be determined from a population of neurones with differing memory spans. Moreover, neurones with short memory spans are useful for the solution of tasks where stimuli are frequently repeated but the correct response depends upon the last presentation of any particular stimulus, i.e. in situations where rapid forgetting pays.

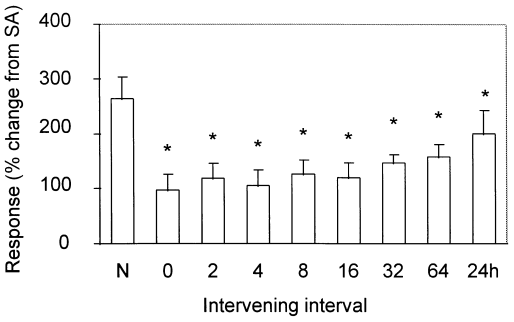

Fig. 9. Population 24 h memory span. The mean (+S.E.M.) responses of 23 recency neurones recorded in monkey anterior inferior temporal cortex to the first presentations of novel stimuli (*N*) and to the second presentations of such stimuli after varying *intervening intervals* either after the indicated numbers of intervening trials or after 24 h. Note the significantly reduced response even for stimuli seen twice on the preceding day. Note additionally, that for the shorter intervals this population response signals that a stimulus has been seen recently rather than precisely how recently it has been seen (the response decrements do not vary consistently with the size of the interval).

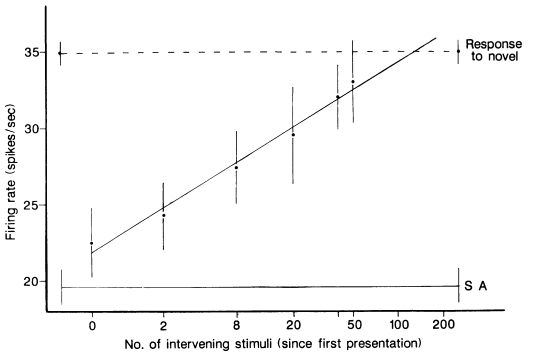

Fig. 10. Example of short memory span. The mean response to second presentations of stimuli is plotted against the number of intervening stimuli (logarithmic scale) since the stimuli first appeared. The mean response to the first presentations of the stimuli is also shown. The response decrement is significantly correlated with the number of intervening stimuli: the monkey area TE neurone's response signals how recently the stimuli were last seen (in terms of the number of intervening items). Reproduced with permission from Brown *et al.* (1996).

Although memory spans in posterior and lateral inferior temporal cortex are shorter than those in anterior inferior temporal cortex (Baylis and Rolls, 1987; Fahy *et al.*, 1993b), until recently no relationship had been found between the location of a neurone within anterior inferior temporal cortex and the likely length of its memory span. However, in a recent study (Xiang and Brown, 1998) the mean memory span for *recency neurones* (see Section 2.4) in perirhinal cortex was at least 24 h, whereas in area TE the mean memory span was in the region of 5–10 min. This finding suggests that the perirhinal responses may be more than passive reflections of those in area TE (though see also Section 4.2).

2.3.4. *Response Latencies*

The visual latency of neurones with repetition-sensitive responses is often as short as that for repetition-invariant neurones, i.e. 70–80 ms in monkey anterior inferior temporal cortex (Miller *et al.*, 1993). More significantly, for certain such neurones, the differential latency, i.e. the time when the activity produced by novel stimuli first differs from that produced by familiar stimuli, is the same as the visual latency (Fahy *et al.*, 1993b; Miller *et al.*, 1993). Evidence has been produced using population measures that the differential latency may reduce when stimuli are repeated more than once (Li *et al.*, 1993). However, in other experiments some individual neurones have approximately equal visual and differential response latencies even for the first repetition of stimuli (Fahy *et al.*, 1993b; Zhu and Brown, 1995), and in yet others population measures continue to show a delayed differential response latency even after numerous stimulus repetitions (Sobotka and Ringo, 1993; Ringo, 1996). Taken together these findings may mean that changes within the network result in an increase in the proportion of cells showing early differential latencies as the number of repetitions increase, but that only a proportion of the repetition-sensitive responses may ever show equal visual and differential

latencies. For neurones with equal visual and differential response latencies the differential responsiveness cannot be produced by any feedback or network processes that take much longer than ten milliseconds. Thus the difference in response must be fed forward or be generated by local synaptic or network processes that operate faster than this time. The necessary network operations therefore cannot involve long paths and hence are probably local.

Recent findings (Xiang and Brown, 1998) demonstrate that the mean differential latency of responses is significantly shorter for repetition-sensitive neurones located in anterior area TE than in perirhinal cortex. In turn, the perirhinal latencies are shorter than those in entorhinal cortex. This ordering of mean differential latencies is found for *recency*, for *novelty*, and for *familiarity neurones* (see Section 2.4). In area TE the mean differential latencies are all similar whereas in perirhinal cortex the mean differential latency for familiarity neurones is some 30 ms longer than those for recency and novelty neurones. These data strongly suggest that the repetition-sensitive responses in area TE are at least initiated in a way that is independent of perirhinal input, though the possibility of feedback effects from a small population of perirhinal neurones with very short differential latencies cannot be completely excluded. These data therefore allow the possibility that perirhinal responses are no more than passive reflections of those in area TE. However, as mentioned above (Section 2.3.3), for recency neurones there is evidence that mean perirhinal memory spans are longer than those in area TE. Accordingly, perirhinal responses must be more than mere reflections of those in area TE—unless the perirhinal responses are a result of inputs from a small population of neurones with very long memory spans in area TE.

2.3.5. *Control Considerations*

Although questions concerning the relationship of recognition-sensitive responses to recognition memory remain to be answered (see Section 7), it is quite clear that these response changes are not artefactual. Similar findings have been reported under closely controlled conditions from a number of different laboratories and using different stimuli and a variety of behavioural tasks (Riches *et al*., 1991; Fahy *et al*., 1993b; Miller *et al*., 1993; Sobotka and Ringo, 1993). Thus the neuronal response changes between first and subsequent presentations of the stimuli cannot be explained by the relation of the stimuli to reward, the particular response required of the animal, or eye movements. The neural response changes are found when visual stimuli are presented during a visual fixation task (Miller *et al*., 1993). When visual fixation is not required changes in neural responses are found to occur well before the onset of eye movement changes and, additionally, preceding any change in pupil diameter (Fahy *et al*., 1993b; Wilson and Goldman-Rakic, 1994). There is, however, evidence that the magnitude of the decrement is enhanced when a monkey saccades towards a repeated stimulus compared to when no saccade is necessary (Nowicka *et al*., 1995).

Further, neural response differences between first and subsequent presentations cannot be ascribed to generalised changes in alertness or attention to the first and repeat presentations of the stimuli: for example, during a serial recognition task first and subsequent presentations of stimuli are interleaved during the recording session and the occurrence of a repeated stimulus is not predictable by the animal. Moreover, repetition-sensitive and repetition-invariant neurones have been recorded simultaneously (Xiang and Brown, 1997a, 1998): such response differences between simultaneously recorded neurones cannot be produced by a non-specific, generalised change in arousal. However, it remains possible that once a stimulus has been identified as novel, attention to it may be more intense or sustained than to a stimulus identified as familiar (even though in the serial recognition task all correct trials are equally rewarded). There are two reasons for concluding that the response differences are not solely due to such selective attention to novel rather than familiar stimuli. Firstly, consider the situation when a recency neurone and a familiarity neurone (see Section 2.4) are simultaneously recorded (Xiang and Brown, 1997a). When an unfamiliar stimulus is repeated, the response of the recency neurone decrements while the familiarity neurone continues to respond strongly to the repeat presentation. Contrastingly, when a familiar stimulus is first presented, the recency neurone responds strongly while the familiarity neurone does not. This co-occurring dissociation of responsiveness to the sight of the same stimuli cannot be explained by a change in attention to the stimuli. Secondly, an attentive difference between novel and familiar stimuli can only be generated once the stimulus has been recognised as novel or familiar. This discrimination requires a difference in neuronal response between the first and subsequent presentations of the stimulus to be generated somewhere in the brain. The issue is then whether the difference is first generated in anterior inferior temporal cortex or at an earlier stage of visual processing. Given that the difference requires the discrimination of many highly complex stimuli, it is implausible that the difference can be generated before a high level of visual processing has been achieved. Accordingly, it may not be possible to judge the relative familiarity of large numbers of complex stimuli at an earlier stage of processing than inferior temporal cortex (or, at least, not in other areas before such discrimination has already been achieved in inferior temporal cortex). Neural memory spans are very restricted in posterior inferior temporal cortex (Section 3.1.1). Thus repetition-sensitive responses in anterior inferior temporal cortex are not passive reflections of those in posterior inferior temporal cortex. Moreover, visual information chiefly reaches anterior inferior temporal cortex via posterior inferior temporal cortex. Hence the absence of long memory spans in posterior inferior temporal cortex makes it unlikely that long memory spans exist in even more posterior visual cortical regions. Nevertheless, the conclusion needs experimental confirmation, i.e. there is a need to establish that changes in response between complex novel and familiar stimuli do not occur at an

earlier latency in another brain region, outside the medial temporal lobe.

As mentioned previously, because such decremental repetition-sensitive responses are found in situations for which animals have not experienced recognition training, such responses must be part of an endogenous process and cannot be solely a result of training on recognition memory tasks (Riches *et al*., 1991; Brown, 1996).

2.3.6. *Repetition-Sensitive Responses in Anaesthetised Animals*

Repetition-sensitive response decrements in inferior temporal cortex have also been reported in the anaesthetised monkey (Miller *et al*., 1991a) and in corresponding regions in the rat (Zhu and Brown, 1995) and rabbit (Chow *et al*., 1977). In the rat their incidence expressed as a proportion of visually responsive neurones was similar to that in the unanaesthetised animal, but their absolute incidence was only half that found in the unanaesthetised rat because the proportion of visually responsive neurones was lower (Zhu and Brown, 1995). The repetition-sensitive responses showed a number of similarities with those in the unanaesthetised rat. However, more work is required to establish whether the memory spans of the neurones are as long as those in the awake animal. These studies indicate that it may be possible to study repetition-sensitive response mechanisms in anaesthetised preparations. It is also of interest to note that there is some evidence of sparing of memory, particularly priming, during human anaesthesia; see Ghoneim and Block (1992) for review.

2.4. Discrimination of Recency, Novelty and Familiarity

It is possible to make a judgement about when an item was last encountered whether it is relatively familiar or unfamiliar (i.e. whether it has previously been encountered a great deal or very little). It is also possible to judge whether an item is relatively familiar or unfamiliar regardless of its last appearance having been a few moments or a long time ago. For example, if you look at a photograph you can judge both whether the picture is familiar and, if it is, whether you have seen it recently or not. Thus the recency of occurrence and relative familiarity (or novelty) of stimuli may be independently determined.

A similar separation of encoding has been demonstrated at the neuronal level. Thus the responses of certain neurones change in the same way when a stimulus is repeated whether the stimulus is very familiar or whether it has been seen infrequently or never before (Fahy *et al*., 1993b; Zhu *et al*., 1995b): for these neurones both the initial response and the decrement upon stimulus repetition are the same for familiar and unfamiliar stimuli (see e.g. Figure 11). Such *recency neurones* do not signal information concerning the relative familiarity of stimuli but do signal whether stimuli have been seen recently. Other neurones which do not decrement in response between the first and second presentations of a

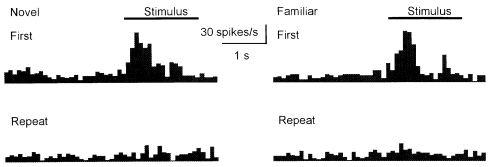

Fig. 11. Responses of a monkey recency neurone. Histograms are shown of the summated activity for trials on which 10 *Novel* and 10 *Familiar* stimuli are presented for the *First* and on a *Repeat* occasion. Note the strong response to the first but not the repeat presentations during the recording session for both novel (unfamiliar) and highly familiar stimuli.

stimulus respond significantly less to familiar than to unfamiliar stimuli even though it has been a long time since the familiar stimuli were last seen (see e.g. Figures 8 and 12). These *familiarity neurones* do not signal information about the recency of presentation of the stimuli but do convey information about the relative familiarity of the stimuli. Both recency and familiarity neurones have been found in both the rat and the monkey (Fahy *et al*., 1993b; Zhu *et al*., 1995b). In a recent experiment (Xiang and Brown, 1997b, 1998) a third class of response has been identified. The cells with these responses have been termed *novelty neurones* as they respond strongly to first presentations of novel or unfamiliar stimuli, weakly to repeat presentations of these stimuli, and but briefly to familiar stimuli (see e.g. Figure 13). Neurones that signal recency for unfamiliar but not for familiar stimuli, or recency for familiar but not for unfamiliar stimuli have also been described.(Fahy *et al*., 1993b; Brown *et al*., 1996). The remainder of the repetition-sensitive responses convey varying mixtures of recency and familiarity information. The proportions of these classes of neurones may be dependent on the training and testing situations. However, in a recent experiment when recordings were made during performance of a serial recognition task where both familiar and unfamiliar stimuli were repeated, the great majority (90%) of responses could be classified as either novelty, familiarity or recency responses: these classes were in the proportions of 40%, 40% and 20% respectively (Xiang and Brown, 1997b, 1998). In the rat the corresponding proportions were 25%, 45% and 30% (Zhu *et al*., 1995a). All these types of neurone can have memory spans of at least 24 h (Xiang and Brown, 1997b) (see e.g. Figure 14b). Again, there are no published data concerning the morphology of novelty, recency or familiarity neur-

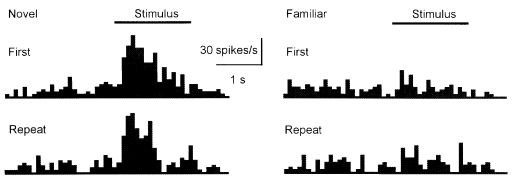

Fig. 12. Responses of a monkey familiarity neurone. Histograms are shown of the summated activity for trials on which 10 *Novel* and 10 *Familiar* stimuli are presented for the *First* and on a *Repeat* occasion. Note the strong response to the first and the repeat presentations during the recording session for novel but not for highly familiar stimuli.

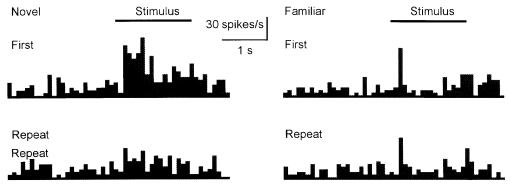

Fig. 13. Responses of a monkey novelty neurone. Histograms are shown of the summated activity for trials on which 10 *Novel* and 10 *Familiar* stimuli are presented for the *First* and on a *Repeat* occasion. Note the strong response to the first but not the repeat presentations of novel stimuli during the recording session, and the much briefer response to highly familiar stimuli.

ones. Such neurones are found throughout anterior inferior temporal cortex, including perirhinal cortex, and also in entorhinal cortex. As exemplars of more than one category may be recorded simultaneously through the same microelectrode, these neurones may be quite closely intermingled.

There are problems devising a consistent nomenclature in this area and it might be objected that the above nomenclature departs from convention. One problem is introduced by the decremental rather than incremental nature of the change in response; this is compounded by the occurrence of corresponding but incremental changes in certain other brain regions. The above names were chosen to emphasise the behaviourally useful type of information that might be extracted from the different types of repetition-sensitive responses, specifically, in comparison to the responses of neighbouring, repetition-invariant responses. The terminology becomes more confused if one attempts to emphasise the stimuli to which the neurones respond strongly rather than those to which they respond weakly. Thus both recency and familiarity neurones respond strongly to unfamiliar stimuli, but their response to unfamiliar stimuli is not what distinguishes between them: to call both "unfamiliarity neurones" would obscure the different types of information they signal about stimuli that have been seen before. Moreover, use of the term "unrecency neurone" would be an obfuscation: what is "unrecency"? The same principle of potential behavioural usefulness leads to the term "novelty neurone", although here it is the positive rather than negative aspect of the cell's responsiveness that is being emphasised. Rather less satisfactory is the use here of "novelty" rather than "unfamiliarity": it is not clear that these neurones signal absolute novelty (that a stimulus has never been seen before). However, the designation "novelty neurone" was again chosen to distinguish such responses from those of recency and familiarity neurones, the term "unfamiliarity neurone" being precluded by the potential confusion with "familiarity neurone". In the usage of each of these terms it is important to appreciate that the neuronal responses themselves are stimulus-selective (stimulus-bound) rather than being generalised detectors of some abstract, stimulus-independent novelty, familiarity or recency.

It remains possible that there is a continuum in the variation of the different types of responses across the whole population of cells, rather than individual subsets forming clearly separated classes. Even if there should be such a continuum, the essential point is that separation of these differing types of information may be achieved by sampling differing subsets of the population of cells with repetition-sensitive responses. Hence the encoding of recency and familiarity information can be doubly dissociated both in the activity of single neurones and across the population of cells. These findings demonstrate fractionation of processing at the single neuronal level even within a single type of memory. They also indicate that there are either two qualitatively different mechanisms responsible for the response decrements (one for recency- and one for familiarity-related changes) or that a single process can have widely differing temporal characteristics at different synapses. There is no simple means of generating the two types of response using a single plastic synaptic process with an invariant time course.

There is evidence that elapsed time rather than the number of stimulus repetitions is important to generation of the response decrement in familiarity neurones. Thus there are neurones that show little

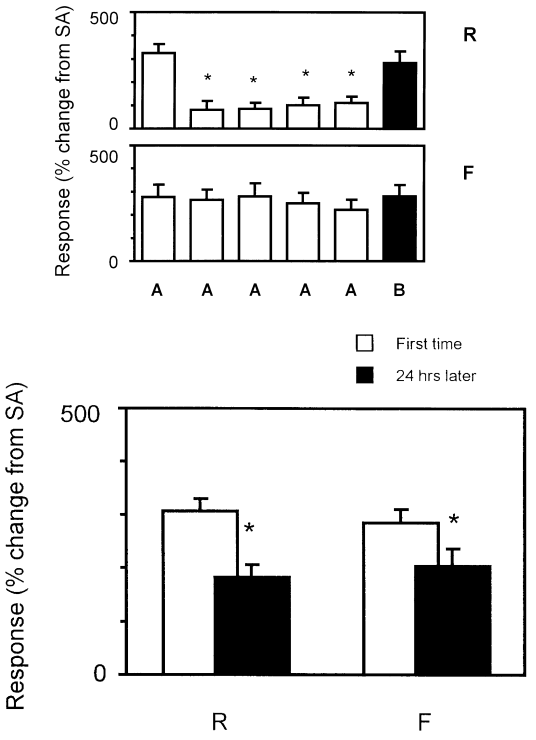

Fig. 14. Different time course of development of decremental response change for recency and for familiarity neurones. (a) Repeating a novel stimulus five times on successive trials produces a significant (*) reduction in response for recency neurones (*R*) but not for familiarity (*F*) neurones. *A* and *B* represent different novel stimuli. The responses have been averaged across 35 recency and 35 familiarity neurones recorded in monkey anterior inferior temporal cortex. (b) The response to unfamiliar stimuli seen only twice 24 h previously is significantly (*) reduced for familiarity as well as recency neurones. The responses have been averaged for the same anterior inferior temporal cortex neurones as in (a). Thus elapsed time rather than the number of stimulus repetitions is important for the development of a reduced response in familiarity neurones.

evidence of response decrement when unfamiliar stimuli are repeated within a short time but which fail to respond to stimuli that have been seen only a few times a long time previously (Fahy *et al*., 1993b) (see e.g. Figures 8 and 14). In a recent experiment this finding has been further substantiated (Xiang and Brown, 1998). Repeating an unfamiliar stimulus five times within a period of about a minute did not produce a significant response decrement in a population of familiarity neurones that demonstrated a significantly reduced response to unfamiliar stimuli seen twice 24 h previously (see Fig. 14). The existence of such neurones further supports the idea that familiarity neurones are not produced from recency neurones simply by giving multiple repetitions of stimuli, but that recency and familiarity neurones are separate classes of neurone. This conclusion is greatly strengthened by the findings from experiments in which simultaneous recordings have been made from neurones with repetition-sensitive responses (Xiang and Brown, 1997a) (see e.g. Figure 15). Such recordings have established that physiological coupling (one cell driving another at short latency) is common between pairs of recency, or pairs of familiarity, or pairs of novelty neurones, but occurs no more than rarely between familiarity and recency neurones (Fig. 16). Moreover, the short latency, short duration functional coupling that occurs during stimulus presentation in the serial recognition task is not found between neurones responsive in other visual discrimination tasks (Xiang and Brown, 1997a). This selective functional coupling further suggests that neurones with repetition-sensitive responses in anterior inferior temporal cortex are actively involved in information processing during performance of the recognition memory task.

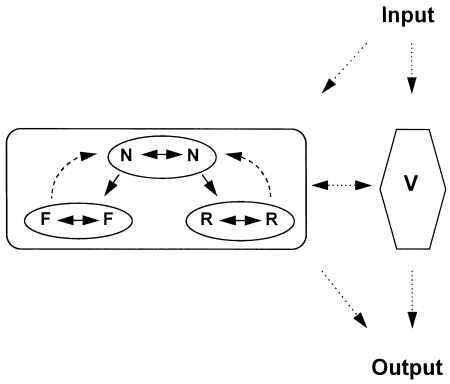

Fig. 16. Physiological coupling between different types of repetition-sensitive neurones in monkey anterior inferior temporal cortex. Simultaneous neuronal recordings reveal that the action potentials of novelty neurones are commonly followed at short latency by action potentials of other novelty (*N*) neurones, familiarity (*F*) neurones, and recency (*R*) neurones (*arrows with continuous lines*). Action potentials of novelty neurones follow those of familiarity and recency neurones only at relatively long (> 10 ms) latency (*arrows with interrupted lines*). Recency neurones are physiologically coupled to other recency neurones at short latency, as are familiarity neurones to other familiarity neurones; however, recency and familiarity neurones are rarely coupled. V, Visual invariant neurone.

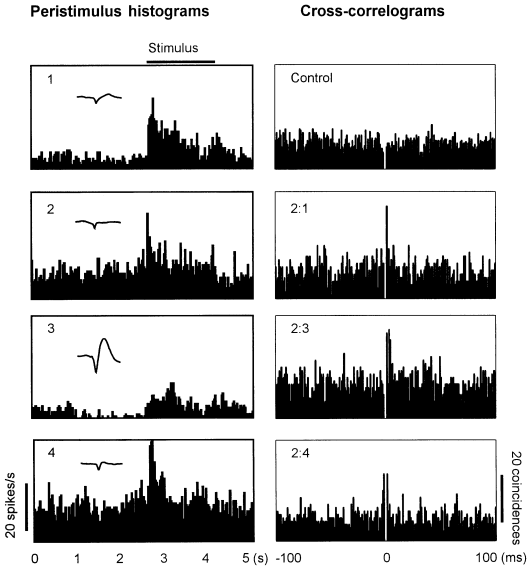

Fig. 15. Example monkey anterior inferior temporal cortex neuronal interactions. In the first column are shown the *peristimulus histograms* (40 ms bins) for four neurones (inserts give spike shapes) recorded simultaneously through the same microelectrode. In the second column are *cross-correlograms* (2 ms bins) relating the times of occurrence of the action potentials of one neurone to those of another simultaneously recorded neurone. The top correlogram is for activity in the absence of stimulus presentation: it shows no evidence of correlated firing. The next two correlograms indicate that action potentials of neurone 2 are followed at short latency (2–4 ms) by action potentials of neurone 1 during stimulus presentations. The bottom correlogram illustrates synchronous firing of neurones 2 and 4, both being driven by some unrecorded neurone. Thus the neuronal interactions are conditional on the presence of a stimulus.

The existence of novelty neurones could imply a third type of plastic synaptic mechanism. If so, it is not obvious how invoking this third plastic mechanism used in isolation could lead to a simple explanation of the form of the observed response: novelty neurones respond to second as well as to first presentations of familiar stimuli, but only briefly (see Fig. 17). Alternatively, it might be possible to generate novelty responses by appropriately combining the other two mechanisms. However, novelty responses are not a simple summation of recency and familiarity responses (nor are recency or familiarity responses simple functions of the other two types) see (Fig. 17). Further, simultaneous recordings of neuronal interactions between novelty and familiarity or recency neurones indicate that novelty neurones are upstream rather than downstream of familiarity and recency neurones. Thus novelty neurones drive familiarity and recency neurones at short latency, but are themselves driven only at a longer latency (> 10 ms, i.e. by multisynaptic paths) by recency and familiarity neurones (see Fig. 16) (Xiang and Brown, 1997a). Given present limited knowledge, it seems more parsimonious to assume that generation of the responses of novelty, recency and familiarity neurones occurs using complex circuitry and two rather than three synaptic plastic

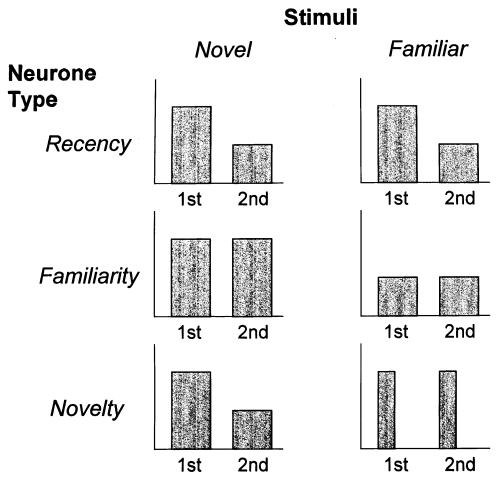

Fig. 17. Patterns of responsiveness for idealised *recency*, *familiarity* and *novelty* neurones (bars representing the magnitude and duration of responses to 1st and 2nd presentations of *novel* and *familiar* stimuli). Note that for none of these categories can the pattern be produced by simply adding the other two patterns, though more complex interactions might achieve this.

mechanisms. However, the issue remains to be resolved by future experiments.

It seems probable that the number of times a stimulus has been encountered previously is also encoded, i.e. the previous *frequency* of occurrence. For novelty and recency neurones when stimuli are repeated more than once, the largest decrement in response is usually between the first and the second presentation of the stimulus. Indeed, typically this decrement is about 50% of the response to the first presentation (see e.g. Figure 9). For certain neurones further repetitions produce further reductions in response (Li *et al.*, 1993), while for others there is little further reduction in response after the stimulus has been seen the second time (Riches *et al.*, 1991; Xiang and Brown, 1997b, 1998) (see e.g. Figure 14a). Across a population of neurones that have differing rates of response decrement with different numbers of repetitions of the stimulus it would be possible to calculate how many times a stimulus has been encountered previously, i.e. its previous frequency of occurrence. These findings again indicate that if there is a single mechanism underlying the response changes, its characteristics are capable of considerable variation.

3. RECOGNITION-RELATED NEURONAL RESPONSIVENESS IN OTHER AREAS

Although the results of lesion studies, in consistency with those of recording studies, point to a central role for perirhinal cortex in the judgement of prior occurrence, this role requires the operation of a complete system for its implementation (see Fig. 3). The components of this recognition memory system, their interrelationships and their individual contributions are far from fully understood (see further Section 4). Repetition-sensitive responses that provide information of potential use for the judgement of prior occurrence have been described in several brain regions in addition to perirhinal cortex. As for perirhinal cortex, control conditions have enabled the response changes to be dissociated from alterations in alertness, reinforcement or behavioural responses for many of these regions. The incidence of such responses in certain regions that have been investigated using a serial recognition memory task are given in Table 1. This Section gives further details concerning such responses in areas surrounding perirhinal cortex and in more distant areas which ablation and/or recording studies suggest might be components of the recognition memory system. For comments on where delay activity has been found see Section 6.3.

3.1. Temporal Lobe

It is important to emphasise that repetition-sensitive responses are not confined to perirhinal cortex

Table 1. Topographical incidence of repetition-related neuronal responses

Brain regions	Differential (D)		Visual (V)		Total (T)
	D(n)	D/V(%)	V(n)	V/T(%)	No.
Rhinal cortex and area TE	423	38	1122	64	1744
Hippocampus	2	4	50	14	350
Orbitofrontal cortex	150	38	392	59	659
Dorsal lateral prefrontal cortex	13	7	188	25	741
Anterior cingulate gyrus	139	31	451	49	928
Ventral putamen	143	32	452	69	658
Dorsal putamen	9	9	96	42	226
Tail of caudate nucleus	101	26	391	68	574
Lateral geniculate nucleus	26	4	663	92	720
Pregeniculate nucleus	343	25	1347	84	1608
Total	1349		5152		8208

The number (n) of neurones with repetition-related responses (*Differential D*) is given as a proportion of the visually responsive (V) and of the total recorded (T) neuronal populations in various brain regions of the monkey. These data have been obtained under comparable conditions during performance of a serial recognition memory task (Brown and Xiang, 1997; Xiang and Brown, 1997a; Xiang and Brown, 1998; and J.-Z. Xiang and M.W. Brown unpublished observations). Such responses can also be found in other areas (see Section 3), notably the medial thalamus and basal forebrain; these data are not included as different recording conditions mean that the proportions of neurones with repetition-related responses are not directly comparable. Chance predicts D/V = 5%.

but are found in widespread regions of inferior temporal cortex, and possibly in more posterior visual cortical areas.

3.1.1. *Area TE and More Posterior Visual Cortex*

All studies of repetition-sensitive responses that have included recordings in perirhinal cortex have also made recordings in area TE, though the converse is not true (see Section 2.3). Until recently no clear division in the properties or incidence of repetition-sensitive responses had been established between area TE of anterior inferior temporal cortex and perirhinal cortex—though establishing such differences has been hindered by uncertainties concerning the boundaries of perirhinal cortex (see Section 1.3). Further, evidence from simultaneous recordings has indicated no difference in the parameters of coupling between repetition-sensitive neurones in TE and perirhinal cortex (Xiang and Brown, 1997a). Recent evidence (Xiang and Brown, 1998) has indicated differences in the mean latencies of differential responses and in the mean length of memory spans between perirhinal cortex and area TE (Sections 2.3.3 and 2.3.4.). Thus there are many more neurones with short latencies in area TE than in perirhnial cortex and there are many more neurones with long memory spans in perirhinal cortex than in area TE: accordingly, the contributions of the two regions to recognition memory are unlikely to be the same. However, this evidence does not establish with certainty that only perirhinal cortex or only TE are responsible for the generation of repetition-sensitive responses (see Section 4.2), it remains a possibility that both regions may be involved.

Further studies of differential latencies and memory spans, or of stimulus specificity and generalisation exhibited by the neuronal responses might provide conclusive evidence concerning the relationship between processing in these two areas. Such evidence may also come from future work employing multiple neuronal recording and seeking physiological coupling of cells in perirhinal cortex with cells in TE. Anatomically, perirhinal cortex differs from TE in receiving multimodal sensory information, whereas area TE is predominantly visual in function. A recent ablation study suggests that functional differences will be found between these areas (Buckley *et al*., 1997).

Repetition-sensitive responses have also been reported more posteriorly in monkey inferior temporal cortex (Gross *et al*., 1972; Pollen *et al*., 1984; Baylis and Rolls, 1987; Richmond and Sato, 1987; Miller *et al*., 1991a; Colombo and Gross, 1994; Vogels *et al*., 1995). Most of these studies did not investigate the response changes in detail and, crucially, did not explore their ability to maintain information across extended periods. However, the impression is given that at the more posterior levels of inferior temporal cortex the memory spans of the neurones are very restricted. When memory spans have been measured they have been found rarely to exceed one intervening stimulus (Baylis and Rolls, 1987). Such responses would be useful only to short-term memory. This finding also suggests that the repetition-sensitive responses found more anteriorly are not merely passive reflections of those found posteriorly.

There have also been reports of response changes with stimulus repetition in more posterior monkey visual cortical areas (Hubel and Wiesel, 1965; Haenny and Schiller, 1988), but no details or memory spans are given. In the rat a few repetition-sensitive responses were noted in occipital visual association cortex, but again the extent of their memory spans was not established (Zhu *et al*., 1995a).

3.1.2. *Parahippocampal Gyrus*

Although this area (TF and TH; von Bonin and Bailey, 1947) has not been very extensively studied in the monkey, no evidence of repetition-sensitive responses has been found using individual stimuli (Riches *et al*., 1988, 1991). Given the inputs of spatial information to this area (Burwell *et al*., 1995), and the findings in rat postrhinal cortex (see Section 3.1.3), studies of neuronal responses in relation to recognition memory performance dependent on spatial information may prove fruitful.

3.1.3. *Postrhinal Cortex*

This area lies immediately caudal to perirhinal cortex in the rat and may be homologous to the parahippocampal gyrus of primates (Burwell *et al*., 1995). This area has not been explored electrophysiologically. In Fos studies it does not demonstrate a greater number of neurones activated by novel than familiar individual stimuli (Wan *et al*., 1997a). This result is in contrast to that for perirhinal cortex, but is consistent with the electrophysiological results for the primate. However, the region reveals a greater number of neurones activated by novel than by familiar arrangements of familiar stimulus items shown on a computer screen, whereas perirhinal cortex does not (Wan *et al*., 1997a). Thus neurones of postrhinal cortex convey information about the relative familiarity of spatial arrangements of items whereas perirhinal neurones convey information about the familiarity of individual items. Again this result has parallels with PET studies of human spatial processing (Maguire *et al*., 1996). It should be noted, though, that the lack of difference in a population measure for postrhinal or perirhinal cortex does not necessarily exclude differences in the responses of their individual neurones.

3.1.4. *Amygdala*

Repetition-sensitive responses have also been found in the amygdala (Nishijo *et al*., 1988; Riches *et al*., 1991; Wilson and Rolls, 1993). The memory spans of such amygdala responses are relatively restricted (< 10 intervening items, i.e. < 2 min) and the sensory specificity of the neuronal responses also is less than those in anterior inferior temporal cortex (Wilson and Rolls, 1993). Differential latencies appear to be longer (> 150 ms) than those in anterior inferior temporal cortex, though the measurements in the two regions were not made in the same experiments and hence not for precisely equivalent

stimulus materials (Wilson and Rolls, 1993; Xiang and Brown, 1998).

3.1.5. *Entorhinal Cortex*

In the study by (Fahy *et al.*, 1993b), repetition-sensitive responses were found in lateral but not medial or posterior entorhinal cortex in the monkey. However, more recent experiments (Xiang and Brown, 1997b, 1998) indicate that such responses are present more widely in entorhinal cortex. The mean differential latencies of recency, novelty, and familiarity neurones are all longer than the corresponding latencies in perirhinal cortex and area TE. Repetition-sensitive responses have also been found in this area in the rat (Zhu *et al.*, 1995a). Moreover, in the monkey responses that are sensitive to the position as well as the repetition of stimuli have been recorded in this region (Suzuki *et al.*, 1995). These findings add strength to the view that entorhinal cortex forms a part of, and therefore a link between, both the perirhinal and the hippocampal systems (Aggleton and Brown, 1998).

3.1.6. *Hippocampal Formation*

Some repetition-sensitive responses have been reported in the hippocampus (here used as a shorthand for the hippocampus proper together with the dentate gyrus and subicular cortex) of the monkey (Rolls *et al.*, 1989, 1993), though not in all studies (Brown *et al.*, 1987; Riches *et al.*, 1991; Xiang and Brown, 1997b). Response changes on repetition of relatively simple stimuli have been reported in the hippocampus of the unanaesthetised rabbit and cat (Vinogradova, 1975; Brown and Horn, 1977), but without investigation of possible memory spans. Response changes in the rat hippocampus have also been found using odours (Otto and Eichenbaum, 1992b), but the changes are abstract or generalised rather than conveying stimulus-specific information, in contrast to results for rhinal cortex (Young *et al.*, 1997) (see also Section 6.1). Using complex, unfamiliar stimuli a few repetition-sensitive responses have been found in the rat hippocampus (Zhu *et al.*, 1995a), though the incidence of Fos stained cells in the hippocampus and dentate gyrus when the stimuli are individual visual objects is very low (Zhu *et al.*, 1995b, 1996; Wan *et al.*, 1997a). Overall, it is clear that the incidence of repetition-sensitive responses is very much lower in the hippocampus than in anterior inferior temporal cortex when the repeated stimuli are individual objects whose spatial location is not important to task solution. Further, to date the memory spans of hippocampal repetition-sensitive responses have not been demonstrated to be as long as those described in anterior inferior temporal cortex and their differential latencies appear to be longer (Fahy *et al.*, 1993b; Miller *et al.*, 1993; Rolls *et al.*, 1993; Zhu and Brown, 1995).

When the spatial location of repeated stimuli is made relevant, a higher proportion of hippocampal cells show responses that are related both to position and to prior occurrence (Rolls *et al.*, 1989; Feigenbaum and Rolls, 1991; Rolls and O'Mara, 1995; Wiener, 1996). In the rat, the proportion of hippocampal cells compared to that of perirhinal cortical cells staining for Fos is markedly increased when a rat enters a novel as opposed to a familiar environment and when pictures that contain arrangements of multiple individual items in a spatial relationship to each other (visual scenes) are used rather than individual items (Wan *et al.*, 1997a; Zhu *et al.*, 1997) (see Fig. 18). Moreover, familiar arrangements of familiar items result in greater numbers of Fos stained cells than do novel arrangements of these familiar items in the dentate gyrus and subiculum, while the opposite direction of change is found in subfield CA1 (Wan *et al.*, 1997a). It is important to note that such opposing changes could result in a net change of zero in an imaging study with insufficient spatial resolution. Overall, the results are consistent with the large body of evidence demonstrating the importance of the hippocampus in spatial information processing (see for reviews: O'Keefe and Nadel, 1978; Gaffan, 1991; O'Keefe, 1993; Eichenbaum *et al.*, 1994; Wiener, 1996; Nadel and Moscovitch, 1997).

3.2. Prefrontal Cortex

Repetition-sensitive responses are common in the inferior convexity of prefrontal cortex (Miller *et al.*, 1996; J.-Z. Xiang and M.W. Brown unpublished observations) and the anterior cingulate gyrus (J.-Z. Xiang and M.W. Brown unpublished observations). Repetition-sensitive responses have not been found in dorsolateral prefrontal cortex (Wilson *et al.*, 1994). There are both similarities to and differences from the corresponding responses in the medial temporal lobe: (i) a greater number of neurones have repetition-sensitive responses (Miller *et al.*, 1996);

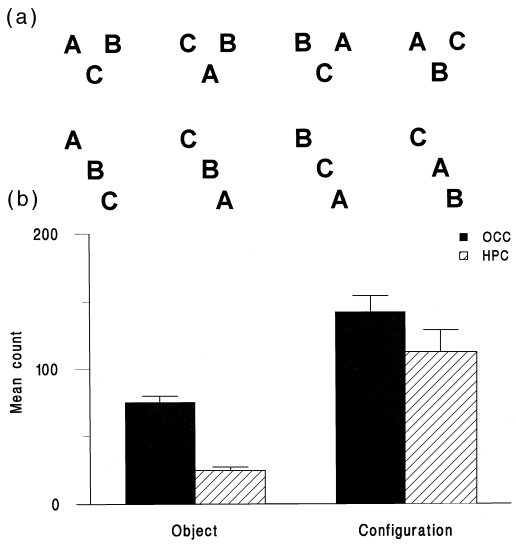

Fig. 18. (a) Examples of different spatial arrangements of three stimulus items (*A, B, C*). (b) Greater numbers of rat hippocampal neurones (*HPC*) stain for the products of the immediate early gene c-fos when spatial arrangements of familiar stimuli (*Configuration*) are viewed than when individual items (*Object*) are viewed (Wan *et al.*, 1997b). This effect is regionally specific as the increase (ratio of counts) is significantly greater than that for occipital visual association cortex (OCC).

(ii) the neuronal responses carry somewhat less specific sensory information (Miller *et al.*, 1996); (iii) incremental as well as decremental responses are found commonly (Miller *et al.*, 1996; J.-Z. Xiang and M.W. Brown unpublished observations), and (iv) both recency and familiarity information is signalled (J.-Z. Xiang and M.W. Brown unpublished observations). Responses that combine spatial and mnemonic information are also found (Rao *et al.*, 1997).

3.3. Subcortical Structures

3.3.1. *Thalamus*

A few repetition-sensitive responses have been described in the medial thalamus, in either the mediodorsal or paraventricular midline thalamic nuclei (Fahy *et al.*, 1993a). The statistical significance of the response changes was high, although the incidence of such changes was low. An interesting feature of the response of one mediodorsal neurone was that the activity at the time of the monkey's behavioural response as well as that at the stimulus onset was repetition-sensitive (see Fig. 19). The task required that the behavioural response was delayed until after the end of the stimulus presentation. The activity change at the time of the behavioural response could be dissociated from the movement *per se*, as no such activity was found in a visual discrimination task requiring the same behavioural response. Thus the activity might represent either recall or re-activation of the memory for the sample stimulus at the time of the behavioural response, or be related to the behavioural output required, i.e. to the organisation or selection of a behavioural response rather than the categorisation and processing of sensory information (Fahy *et al.*, 1993a). In the paraventricular nucleus one neurone raised the overall level of its level of activity when the task to be performed was serial recognition, though not if it was an equally accurately performed visual discrimination task. During the serial recognition memory task the neurone responded to first but not second presentations of unfamiliar visual stimuli, but did not respond to the first presentations of unfamiliar

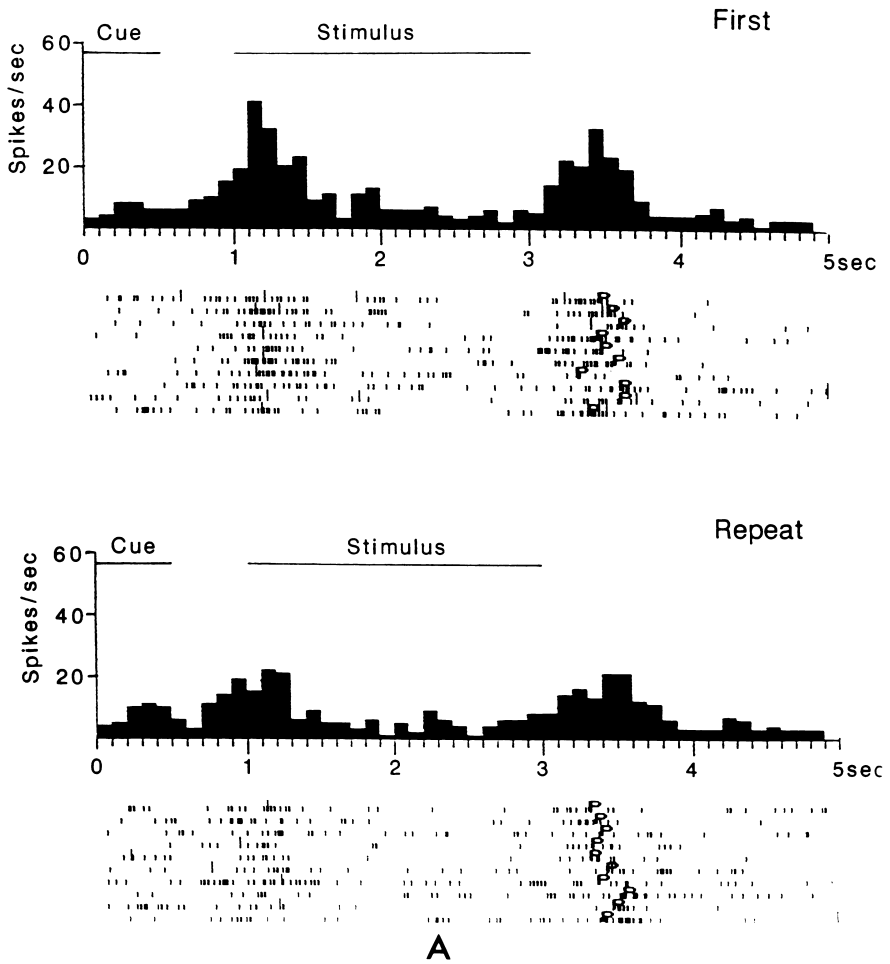

Fig. 19. Double response decrement for a monkey mediodorsal thalamic neurone. There was a significant reduction in activity both following stimulus onset and preceding the behavioural response (*P*) when stimuli were repeated. Activity during a control task (not shown) allowed the latter reduction to be dissociated from the movement required for the behavioural response. Reproduced with permission from Fahy *et al.* (1993a).

stimuli when made outside the context of the task. Such activity changes are appropriate to neurones forming part of a gating or enabling system, and could play a role in selective attention (Fahy *et al*., 1993a).

An unexpected finding in the rat was differential activation of neurones of the ventral lateral geniculate nucleus, with novel stimuli producing higher counts of Fos stained neurones than familiar stimuli (Zhu *et al*., 1996). The ventral lateral geniculate nucleus's main inputs are from the retina, the pretectal area, the superior colliculus, and visual association cortex. Its main outputs are to the superior colliculus and the pretectal area (Jones, 1985). Although repetition-sensitive responses have been reported in the superior colliculus of the anaesthetised rabbit (Horn and Hill, 1964), the colliculus showed no differential staining for Fos (Zhu *et al*., 1996). Thus the staining difference in the ventral lateral geniculate nucleus is more probably due to inputs from area TE (Burwell *et al*., 1995; and R.D. Burwell, personal communication). This result is consistent with the subsequent finding of repetition-sensitive neuronal responses in the monkey pregeniculate nucleus (Brown and Xiang, 1997). These responses convey both familiarity and recency information. It is possible that these response differences are concerned with eye movement control and/or form part of an attentive mechanism (Crick, 1984). Such differences were not found in the dorsal lateral geniculate nucleus of the monkey in the same experiment (Brown and Xiang, 1997). Dorsal lateral geniculate neurones do not stain for Fos (Zhu *et al*., 1996); however, no consistent difference in staining for novel or familiar visual stimuli has been found in primary visual cortex in the rat (Wan *et al*., 1997a).

3.3.2. *Basal Ganglia*

Repetition-sensitive responses have been described in the tail of the caudate nucleus and the ventral putamen (Caan *et al*., 1984; Johnstone and Rolls, 1990; Riches *et al*., 1991; Brown *et al*., 1995; J.-Z. Xiang and M.W. Brown unpublished observations). The proportions of such responses and their properties have differed markedly between these studies, possibly because of the different tasks employed. Both of these regions receive inputs from anterior inferior temporal cortex and thereby provide a possible pathway by means of which repetition-sensitive responses may influence the motor system and hence behavioural output. The repetition-sensitive responses are typically of later onset than those in anterior inferior temporal cortex, thereby starting to span the time between the appearance of the stimulus and the time of the behavioural response (J.-Z. Xiang and M.W. Brown unpublished observations). The responses can encode both recency and familiarity information (J.-Z. Xiang and M.W. Brown unpublished observations).

3.3.3. *Basal Forebrain*

Repetition-sensitive responses during performance of a recognition memory task were first described in a periventricular region of the diencephalon near but ventral to the anterior thalamus (Rolls *et al*., 1982). Such responses are found, albeit infrequently, in a band that stretches anteriorly through the basal forebrain (substantia innominata) and into the diagonal band (Wilson and Rolls, 1990; Fukuda *et al*., 1993). This region contains cortically projecting neurones, including cholinergic cells. It is not known whether such responses are also to be found in the medial septal nucleus that projects to the hippocampus. Some of the repetition-sensitive responses were inhibitory (i.e. the activity decreased on presentation of a visual stimulus), the responses then decrementing, i.e. showing reduced inhibition on stimulus repetition. Other neurones had responses which incremented on stimulus repetition, i.e. were maximal to the second rather than the first presentations of stimuli (Rolls *et al*., 1982; Wilson and Rolls, 1990). This increment occurred without the animal having been trained to distinguish between the repetition of rewarded and unrewarded stimuli (see Section 6.2). The memory spans exceeded the maximum interval tested, although this interval was relatively restricted (16 intervening stimuli or a few minutes). In general it seems that such neurones are less stimulus selective than those in anterior inferior temporal cortex (Wilson and Rolls, 1990). It is not known whether such neurones signal recency or familiarity information.

3.3.4. *Locus Coeruleus*

Neurones recorded in the locus coeruleus of the brain stem respond to the first but not the second presentations of novel objects that are not associated with any reinforcement contingency (Foote *et al*., 1980; Vankov *et al*., 1995). The response latencies of these neurones have not been precisely determined, but appear to be greater than those of repetition-sensitive responses in anterior inferior temporal cortex. Accordingly, the responses of locus coeruleus neurones may be dependent on input from anterior inferior temporal cortex, though this has not been investigated. Further, there are relatively few cells in the locus coeruleus, so that such responses will probably convey general rather than stimulus specific information. Moreover, the conduction velocity of locus coeruleus neurones is slow, so that such signals cannot be expected to be important for fast, detailed processing of the prior occurrence of specific stimuli. However, their widespread axonal distribution will ensure that the generalised information concerning prior occurrence of stimuli reaches many brain regions.

3.4. Other Areas Requiring Investigation

Although many different brain regions have been appropriately investigated for the presence of repetition-sensitive responses, information is still lacking for a number of areas of interest, including the medial and lateral septal nuclei, the mamillary bodies and anterior thalamus, the nucleus accumbens septi, parts of the reticular formation, retrosplenial cortex, and more posterior visual cortical regions. In addition, information is incomplete for

basal forebrain regions, and sensory systems other than the visual have received little study.

4. THE RECOGNITION MEMORY SYSTEM

4.1. Comments on the Organisation of the System

The findings summarised in the previous section indicate that many regions are likely to be involved in the perirhinal recognition memory system. All the sensory cortices feed information to perirhinal cortex. From perirhinal cortex there are a variety of output paths: to the hippocampal formation and amygdala, to prefrontal cortex, to other cortical regions, and to subcortical structures (caudate nucleus, putamen, nucleus accumbens, thalamus, and basal forebrain nucleus) (see Section 1.3 and Fig. 3). However, information flow through these structures is unlikely to follow a simple serial circuit. The regions receiving perirhinal outputs often give rise to perirhinal inputs, and the sensory association cortices can also receive perirhinal outputs (Burwell *et al*., 1995; Suzuki, 1996a,b). Neuronal responses typically last hundreds of milliseconds, providing ample time for interactive feedback and returning feedforward processes to operate, and for decisions concerning further processing and behavioural reactions to be made.

Ablation studies, in consistency with the findings of recording work, have established the essential role of the perirhinal cortex in the judgement of prior occurrence (Brown, 1996; Murray, 1996). The crucial nature of this role could be because of perirhinal cortex's central anatomical location within the system and/or because this is where the synaptic plastic changes necessary for the memory occur. In further exploring the system, it may be anticipated that appropriate lesions of sensory inputs to perirhinal cortex will produce recognition memory impairments by cutting off essential sensory information—see for example the recognition memory impairment produced by lesions of area TE (Mishkin, 1982). However, as there are several potential routes by means of which information may pass from the perirhinal cortex to regions responsible for effecting behaviour, it may be more difficult to produce impairment by lesions directed at the output targets of perirhinal cortex. Other components of the system may provide alternative types of information, further processing, information storage, or allow other interactions (including motivational, attentional and alertness).

Connections of perirhinal cortex with the amygdala and nucleus accumbens potentially allow links to be made with emotional and motivational factors. Additionally, attentional and motivational factors may interact with the system through the involvement of the basal forebrain nucleus, non-specific thalamic nuclei and reticular formation, these structures presumably being concerned with enabling/gating functions rather than detailed information handling.

The hippocampus and fornix system may be expected to participate when the judgement of prior occurrence involves spatial and probably other, contextual information. Thus both lesion and recording data suggest that the hippocampus is centrally concerned in processing information related to the allocentric spatial relationships of items (see for reviews: O'Keefe and Nadel, 1978; O'Keefe, 1993; Eichenbaum *et al*., 1994; Wiener, 1996; Nadel and Moscovitch, 1997; Aggleton and Brown, 1998). Such information is important to recognition memory when whole scenes or events need to be remembered, particularly if the prior occurrence of one event must be differentiated from that of other events on the basis of differences in the spatial arrangement of frequently encountered items (Gaffan, 1994). Spatial information is a major component of contextual information in normal recognition memory. Whether the hippocampus is important for non-spatial types of contextual information, and if so which types, is still keenly disputed (O'Keefe and Nadel, 1978; Olton *et al*., 1979; Brown, 1982, 1990; Eichenbaum *et al*., 1994; Eichenbaum, 1996; Nadel and Moscovitch, 1997; Aggleton and Brown, 1998).

The role of prefrontal cortex is unknown, and potentially complex. Under normal circumstances (i.e. in the absence of disconnection or ablation) it may be expected to interact with perirhinal cortex via the uncinate fasciculus and mediodorsal thalamic nucleus, though information may also potentially travel by longer, transcortical routes. Its involvement in the generation of decremental repetition-sensitive responses is unknown, though it influences other repetition-sensitive activity, i.e. delay activity (Fuster *et al*., 1985). The prefrontal cortex may be expected to be important in decisions relating to the behavioural use made of information provided by perirhinal cortex, to its further processing, to retrieval mechanisms, and probably also to discrimination of the serial order of presentation of stimuli rather than their recency alone, (e.g. Eslinger and Grattan, 1994). Results from patients with frontal damage suggest that it might additionally be important to the conscious appreciation or veridical judgement of the previous occurrence of stimuli (e.g. Curran *et al*., 1997; Moscovitch and Melo, 1997), though other structures including the hippocampal formation have also been proposed to be involved in such functions (see for review: Verfaellie and Keane, 1997). However, it is important to appreciate that a route via prefrontal cortex is not the only way by means of which perirhinal cortex can influence behaviour; outputs to the putamen and caudate nucleus or transcortical routes could also satisfy this requirement.

4.2. Locating the Site of Critical Synaptic Changes

One of the most important questions that remain to be answered if the mechanism underlying judgement of prior occurrence is to be understood is where the neurones with appropriately plastic synapses are located, i.e. which region is critical for originating the plastic change. Such a region must show appropriate recognition-related neuronal activity changes and its ablation must result in major impairment in the judgement of prior occurrence. The presence of appropriate neuronal activity

changes is necessary but not sufficient for such an area: such changes could be passive reflections or non-essential concomitants of the critical changes. Similarly, behavioural impairment may follow ablation of regions that do not contain the critical synapses: impairment may follow removal of essential input to or output from the critical region, including modifying inputs that do not carry the critical information but whose normal operation is nonetheless necessary for plastic changes to occur.

Large numbers of repetition-sensitive responses are found in entorhinal cortex, perirhinal cortex, and the anterior part of area TE (Fahy *et al*., 1993b; Xiang and Brown, 1997b) (see Fig. 2 for the locations of these areas). Lesions of the entorhinal cortex produce only a transitory deficit (Meunier *et al*., 1993; Leonard *et al*., 1995). Thus even if there are such synapses in entorhinal cortex, they are not necessary for the maintenance of the behaviour. Accordingly, entorhinal cortex is not the region containing the critical plastic synapses nor is its influence necessary for the essential plastic changes. In contrast, lesions of perirhinal cortex produce a major and lasting deficit in recognition memory tasks (Gaffan and Murray, 1992; Meunier *et al*., 1993, 1996; Suzuki *et al*., 1993). Thus the critical plastic synapses could be located in perirhinal cortex, or regions providing afferents to it, including area TE. The possible involvement of regions other than area TE that provide afferents to perirhinal cortex will be considered first. There are a number of such regions, both subcortical and cortical (Burwell *et al*., 1995).

Although the contributions of subcortical regions (amygdala, basal forebrain nucleus/substantia innominata, reticular formation and thalamus) to plastic changes have yet to be established, most such subcortical regions do not have sufficient processing capacity to contain the critical, stimulus-specific information-storing synapses. Even the mediodorsal nucleus of the thalamus has only a very low incidence of repetition-sensitive responses (Fahy *et al*., 1993a). Moreover, amygdalar lesions that spare perirhinal connections do not impair delayed non-matching to sample (Murray, 1991, 1996). Medial thalamic lesions may produce impairment through the effects of damage to the mediodorsal nucleus on processing in prefrontal cortex rather than by disconnection of perirhinal and prefrontal cortex; additionally, processing in temporal cortex may be impeded because of damage to the midline nuclei with which it is interconnected (Burwell *et al*., 1995).

Amongst the cortical regions, both the hippocampal formation and the prefrontal cortex possess sufficient information processing capacity potentially to provide adequately detailed signals to perirhinal cortex. Lesions of medial and orbitofrontal cortex impair delayed non-matching to sample tasks and repetition-sensitive neuronal responses are found in these regions (Bachevalier and Mishkin, 1986; Miller *et al*., 1996; Meunier *et al*., 1997; J.-Z. Xiang and M.W. Brown unpublished observations), so that the critical synapses might be in prefrontal cortex. However, there are several grounds for concluding that prefrontal cortex does not contain the critical synapses. Firstly, the deficit after prefrontal lesions is not as great as that after perirhinal lesions (Meunier *et al*., 1997). Secondly, prefrontal neuronal responses carry less information concerning the stimuli that are repeated than do those in perirhinal cortex (Miller *et al*., 1996). Thirdly, it is not obvious that feedback signals from prefrontal cortex could be sufficiently fast to satisfy the requirement that perirhinal responses' differential latencies can be as short as their visual latencies. Fourthly, cutting the uncinate fasciculus, the main connection between perirhinal cortex and prefrontal cortex, produces no noticeable impairment in delayed matching to sample (Gaffan and Eacott, 1995). This latter finding does not exclude prefrontal involvement in the production of behaviour based on judgement of prior occurrence, as information may pass from perirhinal cortex to prefrontal cortex via the mediodorsal nucleus of the thalamus or via multisynaptic transcortical relays (Burwell *et al*., 1995). However, a thalamic route could not provide the detailed feedback necessary to produce the stimulus-specific neuronal response changes in perirhinal cortex (see Section 3.3.1). Thus detailed feedback signals from prefrontal cortex are not necessary to the behaviour and the critical synapses cannot be in prefrontal cortex (given that the strategy of task solution is not altered by the lesion).

That the critical synapses are located in the hippocampus may be discounted for three reasons: (i) selective lesions of the hippocampus produce no major deficit in delayed matching tasks (O'Boyle *et al*., 1993; Murray and Mishkin, 1996; though see Alvarez *et al*., 1995), (ii) repetition-sensitive responses are infrequently encountered and the memory spans of the neurones have yet to be shown to be sufficiently long to explain those found in perirhinal cortex (Fahy *et al*., 1993b; Rolls *et al*., 1993; Xiang and Brown, 1998), and (iii) similarly, the latencies of the responses that have been found are insufficiently short (Miller *et al*., 1993; Rolls *et al*., 1993; Zhu and Brown, 1995). Thus it is implausible that the repetition-sensitive responses of perirhinal cortex are dependent on hippocampal influences. However, this deduction needs experimental confirmation.

As visual input reaches perirhinal cortex from area TE, lesions of area TE could produce a recognition memory deficit either by ablating the critical plastic synapses or by preventing essential sensory information reaching such synapses in perirhinal cortex. Thus the impairment following complete ablation of area TE may not prove conclusive in determining whether area TE contains the critical synapses (Mishkin, 1982). Partial lesions of area TE do not produce a major impairment in delayed non-matching to sample (Buckley *et al*., 1997), but neither do partial lesions of perirhinal cortex (Murray, 1996). Infusing scopolamine into perirhinal cortex impairs delayed non-matching to sample (Tang and Aigner, 1996), but infusions into area TE do not. Although suggestive that perirhinal cortex is therefore the site of the critical synapses, these results are not yet conclusive. For example, whether the infusions pervaded the whole of each area remains to be published. Further, it needs to be demonstrated that scopolamine's effects on beha-

viour are due to actions involving the plastic synapses: for instance, plastic synaptic changes in area TE might be unaffected by scopolamine infusions while such infusions disrupt the further transmission of this information through perirhinal cortex.

In parallel to the arguments concerning lesion studies, the changes in neuronal responses in perirhinal cortex could be no more than passive reflections of changes first generated in area TE. Alternatively, changes in area TE may merely reflect the feedback of changes first generated in perirhinal cortex. Evidence for the dependency of neuronal response changes in area TE upon the integrity of perirhinal cortex has been found in paired associate learning (Higuchi and Miyashita, 1996; Miyashita *et al*., 1996). However, for repetition-sensitive responses the feedback path would need to be sufficiently fast for no observable difference to be generated between the visual latency and the differential latency.

The cortical regions immediately afferent to perirhinal cortex, from which sensory information may be fed forward, such as area TE, are in general unimodal. Thus if stimuli whose prior occurrence and familiarity can only be established on the basis of a conjunction of information from more than one sensory modality (e.g. recognition of a person based on that person's voice), it would seem necessary for there to be such synapses in a region that receives information from more than one modality, i.e. in perirhinal cortex. However, the existence of multimodal repetition-sensitive responses has not been established experimentally—though lesions of perirhinal and parahippocampal cortices impair delayed non-matching to haptic as well as visual stimuli (Suzuki *et al*., 1993). It accordingly remains possible that the critical synapses are found solely in perirhinal cortex, with the changes in area TE being dependent on feedback from perirhinal cortex.

Nevertheless, although perirhinal cortex is the most probable site of critical plastic synapses, there are as yet no conclusive arguments to exclude area TE as the site of such synapses for visual stimuli, with corresponding high order sensory processing regions acting in a similar way for other modalities. There are many similarities between area TE and perirhinal cortex in the types of responses and the interactions between neighbouring neurones (Section 3.1.1). The differential latencies of repetition-sensitive neurones within area TE are on average shorter than those in perirhinal cortex, consistent with perirhinal responses being passive reflections of those in area TE (Xiang and Brown, 1998). However, the memory spans of perirhinal neurones are on average longer than those in area TE, at least for recency neurones (Xiang and Brown, 1998), suggesting that perirhinal responses may more than solely passive reflections of those in area TE. These data may indicate that neurones in both perirhinal cortex and area TE show independent plastic changes, but the argument is not yet conclusive. Thus there is overlap in the distributions of differential latencies and of memory spans for neurones of perirhinal cortex and of area TE. Hence the possibility cannot yet be excluded that a small population of neurones with very early differential latencies in perirhinal cortex could be responsible for feeding back these changes to area TE, or that a small population of area TE neurones with very long memory spans are responsible for such spans in perirhinal cortex. In spite of these possibilties it should be noted that there are many more neurones with short latencies in area TE than in perirhnial cortex and there are many more neurones with long memory spans in perirhinal cortex than in area TE: accordingly, the contributions of the two regions to recognition memory are unlikely to be the same.

As discussed above (Section 2.3.5), the necessary discrimination of many complex stimuli makes it unlikely that the critical synapses are at earlier stages of the sensory pathways. Thus for visual information such plastic synapses could be solely in TE, or perirhinal cortex, or in both TE and perirhinal cortex. Combined imaging and selective lesion studies provide one potential means of determining whether the changes in one or other of these regions are dependent on the integrity of the other. Determining neuronal responses after a selective lesion of each of these structures provides a second possible means. Others include looking for regions in which there are biochemical or anatomical changes associated with synaptic plasticity.

It is possible that many regions rather than one contain potentially plastic synapses that may contribute to the judgement of prior occurrence under varying circumstances. Thus, for instance, there may normally be synaptic modifications in entorhinal cortex on stimulus repetition, but should entorhinal cortex be rendered dysfunctional (e.g. by ablation), changes in perirhinal cortex can themselves be capable of supporting the discrimination. Moreover, there may be synaptic changes that contribute to the registration of prior occurrence at earlier cortical stages of the visual pathway (e.g. V4), but these changes by themselves may be insufficient to discriminate between the prior occurrence of many complex visual stimuli with overlapping individual features. Detailed recordings in such posterior visual areas during the performance of recognition memory tasks would establish whether there is an absence of response changes and hence of such synaptic changes in these regions. However, if there were to be such response changes, these could be due to feedback. In such a case, detailed and extensive latency studies or recordings after selective anterior ablations would be necessary to settle the issue.

5. POTENTIAL UNDERLYING MECHANISMS RELATED TO REPETITION-SENSITIVE RESPONSE DECREMENTS

The synaptic mechanisms underlying repetition-sensitive response decrements are not known. The response reduction does not signal general fatigue or non-specific inhibition of the cell as other stimuli that have not been encountered previously are still able to evoke strong responses. The existence of both familiarity and recency neurones indicates that there are either at least two underlying mechanisms, or a single mechanism with widely differing tem-

poral characteristics in different cells. It is not yet clear to what extent the observed response decrements are due to network properties of neuronal assemblies in addition to the properties of individual synapses on individual neurones (Brown, 1996; Ringo, 1996). It is necessary for the change on repetition to be initiated by a change at individual synapses, but the observed effects must also be due to amplification or expression of this change by a network (see Section 5.3).

5.1. Synaptic Plastic Mechanisms

Any mechanism of synaptic plasticity invoked to explain the response change has to be long lasting, fast in implementation, capable of registering specific, detailed information, and occur as a result of a single previous exposure. At least three synaptic mechanisms may be proposed: (i) build-up of inhibition, (ii) use-dependent self-generated synaptic depression (e.g. habituation), and (iii) synapse-specific depression (e.g. as underlying homosynaptic long-term depression; LTD) (see Fig. 20).

Currently, the absence of positive evidence in its support makes it unlikely that the sole mechanism responsible for response decrements is a build-up of inhibition. Thus a build-up of inhibition could be produced by an increase in the firing of inhibitory neurones. Achieving stimulus specificity implies the availability of a large number of synapses: there therefore have to be either many small inhibitory

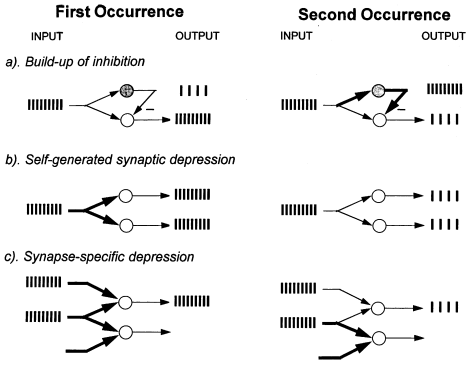

Fig. 20. Different mechanisms that might underlie repetition-sensitive response decrements. (a) A build-up of inhibition on stimulus repetition results in a reduced response (*output:* short bars represent notional action potentials) of a principal cell (*unshaded*) on the *second* compared to the *first occurrence* of a stimulus through enhancement of the efficacy of the synapses (*shown by thicker arrows*) received and/or given by the inhibitory neurone (*shaded*). If the synapses on to the inhibitory neurone are strengthened by repetition of the stimulus, then the firing (*output*) of the inhibitory neurone will increment from the first to the second occurrence. (b) If self-generated synaptic depression relies solely on a presynaptic mechanism, then all the synapses of the presynaptic cell will be weakened (*thinner arrows*) on stimulus repetition, resulting in non-selectively reduced responses (*output*) in many cells on the second occurrence of a stimulus. (c) In contrast, if plasticity is dependent on both a pre- and a post-synaptic condition, depression can be synapse specific as shown by the reduced response (*output*) and synapses (*thin arrows*) of only the active cell when the stimulus occurs a second time.

cells or somewhat fewer large inhibitory cells. In either case, examples of cells with incremental responses should have been reported more often than expected by chance, but they have not been—at least in the monkey, where most studies have been made (see Section 2.3.2). Alternatively, a build-up in inhibition could be produced by a long-term increase in the efficacy of inhibitory synapses: such a mechanism would not necessitate a change in the firing of inhibitory neurones. However, inhibitory neuronal responses in the monkey do not change with repetition, so that at least the inhibitory connections responsible for *these* responses do not demonstrate a build-up of efficacy with stimulus repetition (Sobotka and Ringo, 1994). Moreover, whatever the underlying means of increasing inhibition, there might be expected to be evidence of a build-up of inhibitory interactions between pairs of simultaneously recorded cells: none has been found (Xiang and Brown, 1997a). Nevertheless, a build-up of inhibition cannot yet be firmly excluded as it remains possible that the absence of evidence is due to sampling biases: (i) of the microelectrode technique against recording potentially small or rare inhibitory neurones, and (ii) of the cross-correlational technique against detecting inhibitory coupling, which is temporally more variable and graded than excitatory coupling.

The second mechanism, self-generated synaptic depression, would rely on a process similar to that underlying habituation (Thompson and Spencer, 1966; Horn, 1967; Kandel and Spencer, 1968). In this mechanism each individual plastic synapse is less efficient if it has been used previously. In classical habituation as studied in Aplysia and elsewhere this reduction in efficacy is due to reduced release of transmitter (Horn, 1967; Kandel, 1981). The mechanism is presynaptic and dependent on reduced calcium influx to the terminal. If habituation is invoked as the mechanism, it must be realised that the situation here differs from that in which classical habituation has typically been studied. Firstly, the effect is seen although the stimulus repetitions do not form a monotonous series. Thus a large decrement in response occurs even when the second presentation of a stimulus does not occur until after a long interval during which there have been many, distracting presentations of other stimuli. Secondly, the occurrence of other alerting stimuli produces no evidence of dishabituation. Thirdly, the decrement occurs for stimuli which the animal is using to obtain reward rather than for neutral sensory stimuli. Fourthly, the decrement is larger (typically 50%) and faster (after a single repetition of a novel stimulus) than commonly observed in classical habituation. Nevertheless, a similar, though more powerful mechanism might be invoked to explain the observed reduction in responses. However, a major problem with habituation as a mechanism is that the change is dependent solely on the activity of the afferent neurone; there is no necessary dependency of the change on the postsynaptic contacts of the synapses. Accordingly, if a synapse at one of the presynaptic cell's terminals changes, then synapses at all its other active terminals must also change. The change than becomes specific to a whole cell

(the presynaptic cell) rather than to an individual synapse or group of synapses, with catastrophic loss of potential information processing and storage capacity.

The third mechanism, requiring synapse-specific depression such as underlies homosynaptic LTD (Ito, 1989), remains plausible, though also without convincing experimental support. Whereas associative learning requires in logic the underlying plastic process to be dependent on the conjunction of some type of activity in two or more neurones, there is no necessity for the mechanism underlying signalling of prior occurrence of a stimulus to be associative (as long as association of the stimulus with other concurrently present items is not required). Nevertheless, although the plastic change is not required by logic to be dependent on a conjunction of pre- and post-synaptic conditions, such a requirement results in any change being specific to synapses between individual pre- and post-synaptic cells: such synaptic specificity is likely to be essential to achieve adequate information storage capacity. It has been possible to produce depression of evoked field potentials in perirhinal cortical slices using patterns of stimulation that produce long-term depression in hippocampal slices (Ziakopoulos *et al.*, 1996, 1998). However, as yet such depression, produced in the superficial cortical layers, has not been found to last longer than 1 h. The deeper cortical layers remain to be investigated. This depression is partially, but not completely blocked by the NMDA glutamate receptor antagonist AP5 (Ziakopoulos *et al.*, 1996, 1998).

5.2. Generation of New Representations

A discussion of the generation of new neuronal representations of stimuli in general is outside the scope of the present article (for a recent review see Rolls, 1995). Here only the relationship between repetition-sensitive responses and the formation of such representations will be discussed.

It is improbable that the repetition-sensitive responses themselves could form the representation of a new stimulus because the stimulus would generate different activity when it was subsequently encountered, even though it remained the same stimulus. It is difficult to imagine how perceptual stimulus constancy could be achieved on such a basis. (Indeed, if activity in repetition-sensitive neurones were the essential basis of the representation, one might be tempted to predict that the percept would fade on repetition.) It is not *necessary* for the observed decremental responses to be part of a mechanism that enables a representation of a novel stimulus to be established across an assembly of neurones, though they may in fact do so. The response decrement (perhaps in comparison to repetition-invariant responses) allows judgement of the prior occurrence of a stimulus; it does not require the representation of that stimulus to be held in the activity of neurones with repetition-sensitive responses. However, the increased activity of neurones with repetition-sensitive responses to the first presentations of stimuli is likely to lead to additional processing of these stimuli when they are novel compared to when they are familiar. Such additional processing could assist in the setting up of new associations or even representations of unfamiliar stimuli. However, the additional processing need not necessarily lead to such changes. It is quite plausible that most novel stimuli can be classified (''identified'') by their production of a unique pattern of activity across some subset of neurones with repetition-invariant responses, without requiring adjustment of the synaptic strengths between the elements of the neuronal assembly. Altered synaptic connections would only be needed if the stimulus had to be learnt in the sense that its individual components needed to be associated together in ways for which there was no pre-existing coding or, more commonly, to allow formation of particular associations of that stimulus with other stored or perceived stimuli. It seems unnecessary to believe that each new face one encounters results in a new representation formed by alterations in synaptic connections. However, there does need to be a mechanism to determine whether a particular pattern of activity has been encountered previously, i.e. whether a particular exemplar of a class (a particular face) has been encountered before: this is precisely what the assembly of neurones with repetition-sensitive responses makes possible. The existence of such a mechanism may greatly reduce the necessity for repeatedly changing synaptic weights in assemblies of neurones responsible for the categorisation of stimuli.

Setting up a new representation is commonly assumed to result in an enhanced responsiveness to that stimulus of at least some members of a neuronal assembly, though if information storage capacity is to be maximised, the proportion of synapses (and hence, probably, neurones) undergoing modification should be small (Marr, 1971; Amari, 1989; Rolls, 1995). Nevertheless, even with such sparse encoding, it might be expected that incremental responses would be encountered at least occasionally in recordings made during the performance of recognition memory tasks employing large sets of unfamiliar stimuli. Theoretically, it would be convenient for the mean activity of a neuronal assembly to remain approximately constant over many learning experiences. Suppose the response decrements with stimulus repetition are an adjunct of the setting up of a new representation. When a stimulus is repeated, 30–40% of the visually responsive neurones in perirhinal cortex and anterior TE reduce their responses by an average of about 50%. It would therefore be necessary for the counterbalancing increments to be very large. However, if responses averaged across all presented stimuli are considered, then the observed proportions of neurones with net incremental responses on stimulus repetition are less than might be expected by chance (Riches *et al.*, 1991; Fahy *et al.*, 1993b; Miller *et al.*, 1993; Sobotka and Ringo, 1993; Xiang and Brown, 1997b). Thus in a recent study there were only 9 (1%) incremental responses in a recorded population of 1122 visually responsive neurones in anterior inferior temporal cortex: none of these response changes was significant at the 0.01 level (Xiang and Brown, 1998). Moreover, there have been no reports of neurones that increment markedly their responses to a small proportion of

repeated stimuli, while their responses to the majority of stimuli decrement (e.g. Miller *et al.*, 1993). Furthermore, there is as yet no good evidence that there is even a proportion of neurones that respond strongly and constantly to one or more stimuli while having decremental responses to the rest of the stimuli. Nevertheless, the existence of neurones with such responsiveness in these areas and under these conditions cannot yet be totally excluded—although it seems unlikely that they would have gone unnoticed among the very large number of neurones recorded in these regions, unless their incidence was extremely low or their response increments were small. A further possibility, though computationally inconvenient, is that incremental responses occur in regions outside the anterior inferior temporal cortex. It is important that further, specific tests for the presence of such incremental responses are made in future work. The chance of finding such responses would seem likely to be increased if the great majority of the tested stimuli were genuinely novel (i.e. having never been seen before by the animal) and as far as possible also represented novel classes of stimuli.

5.3. Network Involvement

The necessity for the involvement of the network comes from consideration of the observed physiological coupling between pairs of neurones with repetition-invariant and repetition-sensitive responses (see e.g. Figure 21). Consider three possibilities when a neurone with repetition-sensitive responses is driven at short latency by a neurone with repetition-invariant responses (see also Fig. 22): (i) the coupling does not change on stimulus repetition, i.e. the synaptic connections between the cells are not plastic; (ii) the coupling diminishes once a stimulus has been repeated and does not recover, i.e. the synapses between the cells undergo long-lasting change; (iii) the coupling is strong each time a new stimulus is first presented but weak when each new stimulus is repeated, i.e. the coupling is conditional on the type of (the history of) the presented stimulus.

Given the constant responding of the presynaptic repetition-invariant cell, type (i) coupling cannot be responsible for the diminished responding on stimulus repetition of the postsynaptic repetition-sensitive cell. Initially, type (ii) coupling may seem to be the most plausible way of explaining the change in response of the postsynaptic cell on stimulus repetition. Indeed, apart from the possibility of a build-up in inhibition (which condition would still be subject to the logic of the following argument), the *synaptic* change underlying type (ii) coupling would seem to be the only possible way of accounting for the observed response reduction: the repetition-sensitive responses must arise from the existence somewhere of long-term changes in synaptic connections between repetition-invariant and repetition-sensitive cells. However, type (ii) coupling implies that once the synapses between such a pair of cells have become weakened, the given presynaptic cell cannot subsequently strongly drive the particular postsynaptic cell. This conclusion contradicts observation (see e.g. Figure 21): type (iii) coupling has been found for 31/177 (18%) of such neuronal pairs in anterior temporal cortex (Xiang and Brown, 1997a). This type of coupling implies that the synapses between the two cells are apparently less efficacious once a stimulus is repeated, yet are seemingly restored to full efficacy if a subsequent novel stimu-

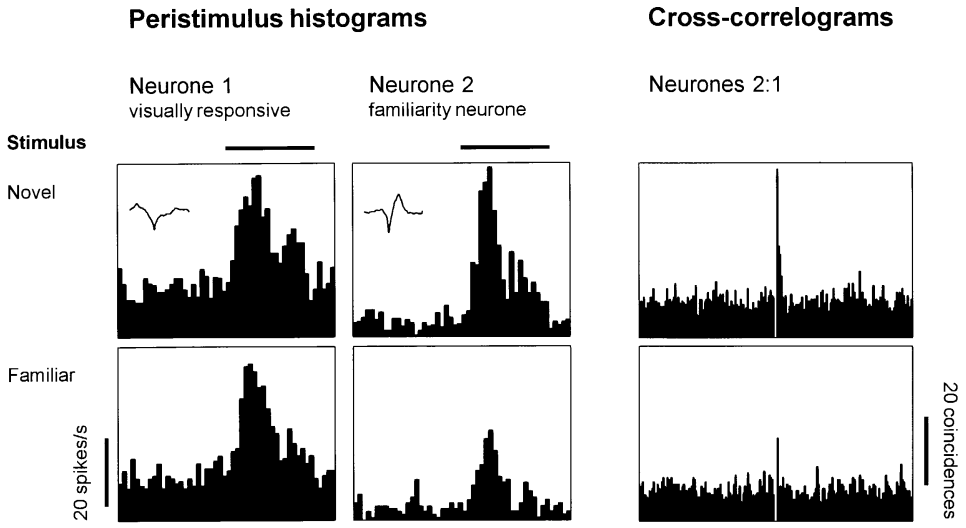

Fig. 21. Conditional physiological interaction between a repetition-invariant (visually responsive) and a repetition-sensitive (familiarity) neurone recorded simultaneously in monkey anterior inferior temporal cortex. *Peristimulus histograms* for presentations of *Novel* (upper) and *Familiar* (lower) stimuli are shown in the first column for the repetition-invariant neurone and in the middle column for the repetition-sensitive neurone. *Cross-correlograms* of the relative times of occurrence of the action potentials of the two neurones are shown in the last column for time periods during the presentation of *Novel* (upper) and *Familiar* (lower) stimuli. The action potentials of the repetition-sensitive neurone follow those of the repetition-invariant neurone significantly more frequently for novel than for familiar stimuli, i.e. the synaptic interaction is conditional. Time bins for histograms 40 ms, for correlograms 2 ms.

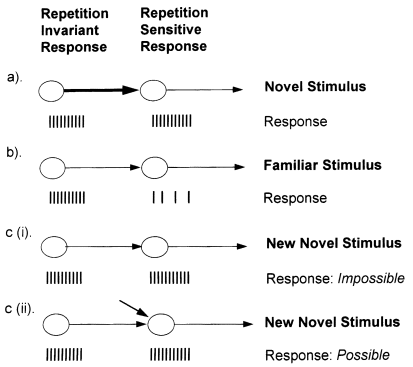

Fig. 22. Implications of conditional coupling between a repetition-invariant neurone and a repetition-sensitive neurone. In (a) a novel stimulus evokes a strong response in both the repetition-invariant and the repetition-sensitive neurone (the short bars represent notional action potentials): the connection between the two is strong (shown by the thick line between the cells). In (b) the stimulus, now familiar, evokes a strong response in the repetition-invariant neurone but only a weak response in the repetition-sensitive neurone: this could be taken to imply that the connections between the two cells have been weakened by the prior occurrence of the stimulus (shown by the thin line between the cells). Such weakening of synaptic connections is consistent with the reduced response of the repetition-sensitive neurone and the reduced coupling observed between such a pair of cells for familiar stimuli compared to that for novel stimuli. However, when a subsequent novel stimulus arrives (c) the repetition-sensitive neurone will again respond strongly. This response cannot be explained if only the connections between the two cells are considered as their connections have been weakened (c)(i). There must be an additional influence upon the postsynaptic cell (c)(ii) for the coupling to be conditional. This influence would probably be provided by a very large rather than a small number of other inputs (see text for further comments).

lus is presented, being immediately weak again when a repeated stimulus is presented, etc. There is no plausible mechanism by means of which the strength of the individual synapses between the two cells could be repeatedly decremented and incremented in this way, if there are no influences additional to the synapses between the two cells. Explanation of type (iii) coupling requires that physiological connectivity between the two cells has some additional condition that is not determined solely by the synapses between those two cells (otherwise only type (i) or (ii) coupling could be found). This additional condition must arise from other synaptic inputs to the postsynaptic cell (or on to the connections between the cells, such as for presynaptic inhibition) (Perkel *et al*., 1967). Thus the observed response changes can only be explained by considering the operation of a neuronal network and cannot be deduced by considering only isolated pairs of neurones (see Fig. 22).

Given that the differential latency of repetition-sensitive responses often cannot be distinguished from their visual latency, these other inputs are likely to arise from local rather than distant neurones, i.e. the neuronal network is likely to be chiefly local. The required conditionality of the coupling can be achieved by either a generalised or, more probably, a more specific increase in the postsynaptic cell's excitability when a stimulus appears for the first time (or, equivalently, a relative decrease in excitability or increase in inhibition when a stimulus is repeated). The generalised increase in postsynaptic excitability could be produced by a non-specific input that summates the increased level of excitation produced by such a novel stimulus compared to that produced when the stimulus appears again. The more specific increase could be produced by the combined action of afferents from many different neurones, the synapses of some of these would reduce somewhat in efficacy when a particular stimulus was repeated, the synapses of other afferents when a different stimulus was repeated. A novel stimulus would excite sufficient synapses of sufficient strength to drive the postsynaptic cell strongly and lead to coupling being observed. A repeat presentation of a stimulus would provide overall less net afferent excitation to the postsynaptic cell, hence fewer postsynaptic spikes, and therefore apparently weaker coupling. This mechanism avoids the strengths of individual synapses having to change erratically from the presentation of one stimulus to another, i.e. only the mechanism of synaptic change underlying type (ii) coupling is required to explain type (iii) conditional coupling as long as network connections are considered.

The above mechanism requires that synaptic changes are specific to connections between individual pairs of neurones, i.e. all the synapses of a given pre- or post-synaptic cell do not change at the same time. Arguments concerning increases in inhibition can be made similarly, and there is no reason why a combination of generalised and specific mechanisms concerning both excitation and inhibition should not operate in conjunction with each other. However, whichever of these mechanisms is used, the observed responsiveness cannot be explained by consideration solely of connections between pairs of cells, understanding the network connections is also essential.

The above argument raises a further issue concerning the continuing overall excitability of neurones with repetition-sensitive responses. For many neurones, diminished responding to previously encountered stimuli is a long-lasting phenomenon. Given human psychological performance, for some such neurones the change would have to last for years. Accordingly, synaptic strength within neuronal assemblies with repetition-sensitive responses would be being continually diminished as a result of on-going experience of new stimuli. There would correspondingly be the possibility that the system would become progressively less able to operate efficiently in judging the prior occurrence of stimuli, unless there is some compensatory mechanism controlling the mean excitability of the neuronal assembly. There is currently no evidence concerning such a compensatory mechanism for such neurones (see Stewart *et al*., 1996). However, the continuing efficient operation of such a system would seem to require some mechanism effecting the counterbalancing of the overall level of excitability of either the individual cell (see Stewart *et al*., 1996) or the network. Such a compensatory system would neverthe-

less need to maintain signalling of the prior occurrence of stimuli by differential neuronal responsiveness across the network.

6. OTHER NEURONAL ACTIVITY CHANGES PUTATIVELY RELATED TO RECOGNITION MEMORY

Several types of plastic changes putatively related to memory processes have been described in monkey inferior temporal cortex (see Fig. 23). In some cases, these changes develop as the result of many stimulus presentations and do not appear to be appropriate to the judgement of the prior occurrence of stimuli *per se* (though see below Section 6.1). However, besides response decrements on stimulus repetition, there are two other types of change that do seem to be related to the prior occurrence of unfamiliar stimuli. One type of change is an incremental response to the repetition of a target stimulus. The second type of change is a sustained alteration, typically an increase, in the firing of a neurone during the delay interval of a delayed matching task ("delay activity"). Both these types of change provide information of potential use to the solution of certain types of memory tasks, namely those in which a single target stimulus recurs within a circumscribed time. Accordingly, both these types of change may be neuronal counterparts of psychological processes related to attention, active working memory or "holding in mind" (Brown, 1996; Desimone, 1996).

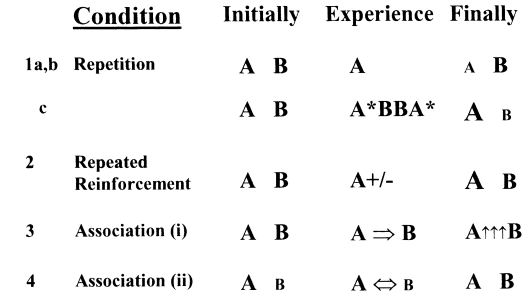

Fig. 23. Types of neuronal activity changes found in anterior inferior temporal cortex. In four different *Conditions* activity produced in response to stimuli (A, B) changes from an *initial* to a *final* state as a result of intervening *experience*. The relative size of the letters represents the change in response to the stimuli. Thus in *Condition 1* repetition of A results in a reduced response to A. This change may be produced by at least two mechanisms (a, b; see Section 2.4). Additionally, repetition may result in response enhancement for the target stimulus (A*) rather than reduction as for the non-target stimulus (B) (c; see Section 6.2). In *Condition 2* the ± represents association of A with positive or negative reinforcement, though it is possible that merely sufficiently repeated exposure or lack of exposure may also produce change (Merzenich *et al*., 1996). Although the results of many studies suggest an enhanced number of responsive cells or size of response to A (see e.g. Section 6.1), it might additionally be that the response to B (a non-experienced stimulus) is reduced relative to A, i.e. that there is tuning rather than solely enhancement of responsiveness (Jagadeesh *et al*., 1996; Ringo and Nowicka, 1996). The *vertical arrows* in *Condition 3* represent sustained or delay activity occurring after presentation of stimulus A and before stimulus B where the occurrence of A predicts the occurrence of B (see Section 6.3). In *Condition 4* repeated temporal pairing (A predicts B, B predicts A) of two stimuli results increased numbers of neurones that respond strongly to both of the stimuli (Sakai and Miyashita, 1991).

6.1. Response Differences in Delayed Matching Tasks with Small Stimulus Sets

Response differences in highly practised delayed matching or non-matching tasks that use small sets of frequently recurring, highly familiar stimuli need to be clearly distinguished from the repetition-sensitive response changes that occur in recognition memory tasks with large stimulus sets chiefly composed of infrequently encountered stimuli. It remains to be established that the differences in response for a stimulus presented as the sample, or the matching, or non-matching stimulus in the former case where stimuli are being frequently repeated (see for example: Gross *et al*., 1972; Mikami and Kubota, 1980; Brown, 1982; Riches *et al*., 1991; Otto and Eichenbaum, 1992b; Nakamura and Kubota, 1995, 1996; Young *et al*., 1997) are produced by the same underlying mechanism as the response changes over the first few presentations of infrequently encountered stimuli in the latter situation (Riches *et al*., 1991; Fahy *et al*., 1993b; Miller *et al*., 1993). The large numbers of times specific stimuli and particular trials are experienced with small stimulus sets makes possible the implementation of more gradual experience-dependent learning mechanisms (e.g. Merzenich *et al*., 1996): such mechanisms are excluded by the single exposure learning required for accurate performance with large stimulus sets, particularly in serial recognition tasks. A potential analogy is with the distinction between the single exposure registration of episodic memory and the multi-exposure learning of semantic memory.

Against the learning mechanism being the same with small as with large stimulus sets is that: (i) for a given stimulus response decrements asymptote after a few exposures to the stimulus (though there are few data for familiarity neurones on the dependency of the change on the number of previous repetitions of a stimulus) (Riches *et al*., 1991; Li *et al*., 1993); (ii) that tasks using small stimulus sets are more difficult to train than those with large sets (e.g. Mishkin and Delacour, 1975); and (iii) that lesions of perirhinal cortex impair performance with large but not small stimulus sets (Eacott *et al*., 1994). The last point indicates that even should the mechanisms prove to be related, the brain regions concerned are likely to differ. Notwithstanding these arguments, neurones with repetition-sensitive responses that have short memory spans could contribute to the solution of tasks with small stimulus sets. Indeed, in the primate such neurones are found outside perirhinal cortex (Baylis and Rolls, 1987). The critical experiment to determine whether the same mechanism is employed requires the recording of the responses of neurones in animals that have been taught to perform delayed matching with small

stimulus sets while a new small set of stimuli is introduced and repeatedly used.

6.2. Incremental Responses

In the monkey's anterior inferior temporal cortex neurones that *increase* their response upon stimulus repetition are rare under normal circumstances; indeed, their incidence is less than might be expected by chance (Riches *et al*., 1991; Miller *et al*., 1993; Xiang and Brown, 1998). These ''normal circumstances'' include passive observation of stimuli without any behavioural contingency and performance of standard recognition memory tasks. However, incremental responses are found in anterior inferior temporal cortex when a monkey is required to distinguish between repeats of stimuli that lead to reward and repeats of stimuli that are unrewarded (Miller and Desimone, 1994; Desimone, 1996). The discrimination is presented in the following way (see also Fig. 4). Monkeys are trained on a variant of delayed matching to sample in which a number of stimuli (A, B...) are presented successively for choice (e.g. in the sequence ABCDA), the animal making a press to gain reward when the sample stimulus A eventually re-appears. In such a design it is possible to present sequences of the form ABBA, A being the sample stimulus and B a different, repeated, distractor stimulus. In this situation (the *ABBA* variant of delayed matching), all repetition-sensitive neurones in anterior inferior temporal cortex show a reduced response to the second presentation of B, but certain (~30%) of these neurones show an increased response to the re-appearance of the sample stimulus A—for the remaining 70% the response is reduced (Miller and Desimone, 1994). Such incremental responses are also found, but with increased incidence and magnitude, in the inferior convexity of prefrontal cortex (Miller *et al*., 1996). The existence of such incremental repetition-sensitive responses in other regions—such as the hippocampus, the medial thalamus or basal forebrain—has not been investigated.

It is not known whether such incremental responses are first generated in perirhinal cortex, area TE, or prefrontal cortex, or by an interaction between the regions. Additionally, it has not been demonstrated that such response increments occur when more than one stimulus has to be held in mind at one time and when it cannot be predicted that the target stimulus will re-occur within a circumscribed time window. When a single stimulus has to be remembered for a limited period, it seems plausible that an attentive or working memory (Baddeley, 1996) mechanism might be engaged to solve the task, the target stimulus being ''held in mind'' until it recurs (Brown, 1996; Desimone, 1996). These incremental responses might also be related to an active retrieval mechanism (Desimone, 1996).

Solving tasks requiring discrimination of repeated distractors from target items could, however, involve mechanisms in addition to those of working memory. Human subjects can perform with high accuracy a repeated recognition task in which interspersed sets of both target and distractor items have been seen recently, the sets being too large to be held in short-term or working memory (Brown and Brown, 1990). In this *repeated recognition task* subjects are asked to discriminate targets from distractors in a sequential list of items (Test 1); the same discrimination has then to be made during the presentation of a second list of the same targets and distractors (Test 2). This task satisfies both the required conditions of multiple targets and non-predictable re-occurrence of specific targets. Accordingly, there must be a brain mechanism that allows discrimination of repeated targets from repeated distractors under general circumstances. It was hypothesised that the human subjects made the discrimination on the basis of the context of presentation of the target list (Brown and Brown, 1990), but the underlying brain mechanism is not known. Evidence that the mechanism is dissociable from that used to solve the recognition memory task for the first presentation of the list (Test 1) is provided by subjects given lorazepam and by Alzheimer patients: both groups, unlike control subjects, show differential impairment for the repeated test (Test 2) (Brown and Brown, 1990; Tollworthy *et al*., 1991). The impairment takes the form of intrusion errors (false positives), i.e. the subjects falsely categorise distractors as targets. Such errors would be expected if the subjects were making judgements based on recency rather than the original context of occurrence. Thus it might be speculated that the hippocampal system would be involved in the discriminations necessary to solve the task during the second (repeated) presentation of the list. There is as yet no experimental evidence for the neural substrates of such distinctions.

6.3. Sustained or Delay Activity

Sustained increases in firing during the delay period of delayed matching to sample tasks have been found in several laboratories, for example, in inferior temporal cortex (Fuster and Jervey, 1981; Miyashita and Chang, 1988; Riches *et al*., 1991; Sakai and Miyashita, 1991; Miller *et al*., 1993; Nakamura and Kubota, 1995), prefrontal cortex (Fuster and Alexander, 1971; Kojima and Goldman-Rakic, 1982; Funahashi *et al*., 1989, 1997; Di Pellegrino and Wise, 1993; Wilson *et al*., 1993; Funahashi and Kubota, 1994; Miller *et al*., 1996) and parietal cortex (Koch and Fuster, 1989; Constantinidis and Steinmetz, 1996; Zhou and Fuster, 1996; see for reviews Fuster, 1995; Desimone, 1996). Such delay activity can carry specific information relating to auditory (Bodner *et al*., 1996) as well as visual stimuli, to position as well as objects (e.g. Wilson *et al*., 1993), and to the position of specific objects (Rao *et al*., 1997). During the ABBA variant of delayed matching, such delay activity does not last beyond the first distractor item in anterior inferior temporal cortex, but does do so in prefrontal cortex (Miller and Desimone, 1994; Miller *et al*., 1996). Cooling of prefrontal cortex reduces but does not abolish such activity in inferior temporal cortex (Fuster *et al*., 1985). Thus both inferior temporal cortex and prefrontal cortex must have important roles in the generation of such activity: in neither region is delay

activity merely a passive reflection of activity in the other.

Delay activity provides a valuable potential mechanism for the solution of recognition memory tasks when the need to make decision concerning the subsequent re-occurrence of the sample stimulus is predictable within a restricted time period after the sample presentation, and when only one sample stimulus needs to be remembered at any one time. It has not been demonstrated that such activity provides a possible solution to recognition memory tasks in which more than one stimulus must be remembered at a time. It is possible that the activity is related to an attentive or rehearsal mechanism (Fuster, 1995; Brown, 1996; Desimone, 1996; Naya *et al.*, 1996).

7. RELATION TO MEMORY OF NEURONAL RESPONSE CHANGES

Repetition-sensitive neuronal responses may potentially be of value to more than one type of memory. The response changes in automatically registering previously encountered stimuli provide a trace that can potentially be utilised in the service of attentive mechanisms (Desimone, 1996), operant conditioning (Brown, 1990), human or animal working memory (Olton *et al.*, 1979; Baddeley, 1996), priming (Wilson *et al.*, 1988; Riches *et al.*, 1991) and recognition memory (Brown *et al.*, 1987; Brown, 1996). The adequacy of these responses, particularly perirhinal decremental responses, as potential substrates for recognition memory and priming will now be considered. Their other potential uses will not be discussed in this review.

7.1. Relationship to Recognition Memory

As previously indicated (Section 1.1), recognition memory is not a unitary phenomenon, but a collection of processes allowing judgement of the prior occurrence of particular stimuli and events. As there are a number of different types of judgement based on differing types of information that can underlie recognition memory, so it is to be anticipated that there will be more than one underlying neuronal substrate of recognition memory. Progress in establishing the relationships between neuronal activity and recognition memory require that this diversity is understood and acceded to in the design of experiments and in the interpretation of their results. Progress in this area also requires careful definition of terms. This care is required at all levels, anatomical, physiological and behavioural. For example, there is not yet universal agreement over precisely which area of cortex is perirhinal. ''Familiarity'' is used in differing ways. It is not obvious that all human subjects will use the same judgement when asked whether they ''know'' that a stimulus has been previously encountered rather than ''remembering/recollecting'' its prior occurrence. More generally, there may be more than one strategy employed to solve recognition memory tasks, and the strategy employed may depend subtly on the precise experimental conditions, including previous instruction and practice. The strategy for solution may therefore vary between species even when a task superficially appears to be the same in each situation.

There is good evidence that there is a division of function between on the one hand the hippocampal formation and its associated structures and on the other the perirhinal cortex and areas associated with it; see Aggleton and Brown (1998) and also Sections 3.1.6 and 4.1. Review of the human literature (Aggleton and Shaw, 1996), in consistency with animal studies, indicates that the system centred on the hippocampal formation is essential to recognition memory based on recollection of stimulus occurrence by context, whereas the system centred on the perirhinal cortex is essential to judgements of prior occurrence based on stimulus familiarity and recency (Aggleton and Brown, 1998). This review chiefly concerns the latter system and it is arguments concerning the relationship to recognition memory of repetition-sensitive, particularly decrementally changing, neuronal responses within that system which will now be considered.

7.1.1. *Response Decrements and Recognition Memory*

There are good grounds for believing that the repetition-sensitive response decrements described in the perirhinal system are central to the neural counterpart of recognition memory concerning the judgement of stimulus familiarity and recency (necessary for feelings of knowing that something has been encountered previously). Nevertheless, such a correspondence remains to be established with certainty. In favour of such a correspondence is that, as far as these have been explored, the properties of the neuronal response changes in monkeys are sufficient to account for the capabilities of these animals in recognition memory tasks. The response changes reflect single trial learning, are stimulus selective, appear to have a very large storage capacity, and are long lasting (though neither ablation nor recording experiments have explored memory lasting many days). The changes occur in a variety of different experimental situations including the performance of explicit memory tasks. Nevertheless, they are automatic and endogenous, being neither induced by training nor dependent upon a particular behavioural contingency. Control procedures have demonstrated that the changes are not a result of artefactual or trivial concomitants of the learning. Simultaneous recording of the activity of individual perirhinal neurones indicates that they are actively engaged in information processing during performance of recognition memory tasks (Xiang and Brown, 1997a). Furthermore, no other type of activity has been discovered that is capable of providing a satisfactory basis for the solution of a wide range of recognition memory tasks, in spite of the now large number of recordings made during the performance of memory tasks. Thus neither delay activity nor response enhancement has yet been shown to be a possible basis for the solution of recognition memory tasks where remembrance of more than one stimulus at a time is required. Moreover,

neither have these changes been shown to occur outside a training paradigm, while decremental responses do so occur. It has been established that repetition-sensitive decremental responses can be found in corresponding regions in rats as well as monkeys (Fahy *et al.*, 1993b; Zhu *et al.*, 1995a; Xiang and Brown, 1997b), and that the response changes are consistent with PET changes seen in humans where instructions ask for familiarity judgement rather than recollection (Vandenberghe *et al.*, 1995). (In contrast, increases may be found in PET and fMRI studies requiring retrieval i.e. recollection (Nyberg *et al.*, 1996). The retrieval of many contextual items could provide a reason for such increases). Moreover, it has been suggested that human recognition memory performance is consistent with such an underlying mechanism (Doty and Savakis, 1997). Critically, the responses are found in regions, notably perirhinal cortex, where lesions produce devastating impairments in recognition memory tasks (Gaffan and Murray, 1992; Suzuki *et al.*, 1993; Meunier *et al.*, 1996; Murray, 1996). Again, there is general consistency between the findings in monkeys, rats and humans (Brown, 1996; Aggleton and Brown, 1998). Additionally, lorazepam and diazepam, drugs that cause recognition memory impairments in humans (Brown *et al.*, 1982; Brown and Brown, 1990), prevent the differential expression of c-fos produced by viewing novel and familiar stimuli in perirhinal cortex and area TE of the rat (Wan *et al.*, 1996). Furthermore, the reduction in response on stimulus repetition is such a major change, readily detectable in population measures of neuronal responsiveness in perirhinal cortex and area TE, that it would be surprising if the only use the brain made of the neurones with such responses was in relation to processing novel stimuli: the response changes clearly provide detailed additional information concerning the prior occurrence of stimuli. Accordingly, it seems implausible that the repetition-sensitive response decrements of perirhinal neurones will prove to be an epiphenomenon.

Nevertheless, other means of encoding prior occurrence may be imagined, for instance, using the precise timing or synchronisation of action potential trains (Abeles, 1982; Singer and Gray, 1995; Konig *et al.*, 1996). Evidence from the simultaneous recording of the activity of individual neurones has indicated that such interneuronal correlations in action potential production are indeed likely to be important to generation of repetition-sensitive responses (Xiang and Brown, 1997a). The specificity of these interactions suggest that anterior inferior temporal neurones are actively engaged in information processing during presentation of stimuli in a serial recognition memory task (in contradistinction to their role in conditional visual discrimination) (Xiang and Brown, 1997a). However, there are arguments against alterations in the time but not the rate of production of action potentials being the only underlying mechanism. Firstly, the repetition-sensitive effects observed by recording neuronal responses or by Fos immunohistochemistry or PET imaging do indicate the existence of changes in the rate of production of action potentials and such changes can be related to recognition memory performance: accordingly, to invoke a further mechanism lacks parsimony. Secondly, should synchronisation of action potentials, or reduction of such synchronisation, provide the mechanism underlying the judgement of prior occurrence, then such synchronisation (or its absence) will necessarily produce firing rate changes at the next stage in the neural pathway: accordingly, such changes might be part of the process, but are unlikely to be its sole means of expression.

It might be wondered whether it is sensible to suppose that judgement of prior occurrence should depend upon a relative reduction rather than an increase in neuronal activity. In fact, greater responsiveness to novel than to familiar stimuli has particular advantages. Thus, the difference implies that novel stimuli are receiving more processing than familiar stimuli. Enhanced processing is appropriate to establish the nature of novel stimuli and to evoke greater attention to such stimuli: attention to novelty is behaviourally advantageous. Correspondingly, familiar stimuli receive faster, more nearly optimised processing, potentially allowing faster behavioural responses while not unnecessarily occupying attention. Additionally, most stimuli encountered in everyday life are familiar. Thus processing capacity is maximised and energy usage minimised if activity reduces rather than increases each time a familiar object is encountered.

Although the hypothesis that response decrements on stimulus repetition provide a central part of the mechanism by means of which prior occurrence is judged is currently the best available, such changes are not all there is to the neural basis of recognition memory. Firstly, within anterior inferior temporal cortex there is already known to be more than one type of change in neuronal activity that can potentially provide solution for a recognition memory task. Indeed, even within the population of decremental responses there are at least three categories of change (represented by novelty, familiarity, and recency neurones). Additionally, for specific types of task, delay activity and response enhancement provide alternative potential means of solution. Secondly, the hippocampal system is likely to prove essential for recognition memory tasks where solution depends on judgements concerning the context of prior presentation. Thirdly, recognition memory requires the operation of a system, not merely of perirhinal cortex. Information has to be exported from perirhinal cortex as well as imported into it (see Section 4 and Fig. 3). Prefrontal cortex is likely to have important roles relating to the use that is made of the information being signalled by anterior inferior temporal neurones. It is not known by which routes (cortical and/or subcortical) the available sensory data is able to lead to appropriate behavioural responses. Neither is it known which parts of the system are necessary for the conscious and veridical remembrance of the prior occurrence of a stimulus as opposed to its automatic, subconscious registration, though certain patients with prefrontal damage appear to have particular problems with confabulation, including falsely identifying distractors as having been previously seen (Curran *et*

al., 1997; Moscovitch and Melo, 1997; Verfaellie and Keane, 1997).

A further, currently unresolved issue is whether neurones in perirhinal cortex are concerned solely with the prior occurrence of individual stimulus items or whether they are similarly involved with encoding the prior occurrence of scenes and events. Perirhinal neurones certainly signal the prior occurrence of complex scenes (Fahy *et al.*, 1993b), but it is not known whether the response is determined by individual items within the scene rather than by the composition as a whole. This issue is likely to be resolved by investigations using tasks that depend for their solution on the prior occurrence of particular combinations of foregrounds (objects) and backgrounds, e.g. object-in-place tasks (Gaffan, 1994). Bilateral fornix lesions or a unilateral fornix lesion with a contralateral perirhinal lesion lead to behavioural impairment of such a task, indicating roles for both the hippocampal and the perirhinal systems in memory for the location of particular objects within a background (Gaffan, 1994; Gaffan and Parker, 1996).

7.1.2. *Experimental Challenges to the Relationship*

There has to date been no finding that is fatal to the hypothesis that response decrements in perirhinal cortex are a central part of the normal mechanism for making judgements of the prior occurrence of stimuli based on their familiarity or recency. Nevertheless, three apparently adverse findings need explanation.

Firstly, Sobotka and Ringo (1996) reported a dissociation between decremental responses and behaviour in a recognition memory task. Stimuli were presented monocularly to either the left or right eye of a monkey with a divided optic chiasma so that visual information could initially reach only the ipsilateral hemisphere. Neuronal responses were recorded in anterior inferior temporal cortex while the animal performed a delayed matching to sample task. Neurones were found for which successive presentations of the same stimulus to the same eye resulted in the expected response decrement with repetition; however, when the second presentation of a stimulus was to the opposite eye, no response decrement was seen (see Fig. 24). The animal's performance under the latter conditions was impaired, but remained well above chance. Thus there was a dissociation between behaviour and decremental responses. If further substantiated, such a dissociation could prove fatal to the hypothesis. However, for such disproof it is necessary to establish that there is no alternative strategy allowing solution of the task available to the animals, and that decremental responses are not still being used for task solution but with these response changes occurring elsewhere. There is a possible alternative strategy for task solution; it is provided by delay activity, as the monkey needed to hold only one target stimulus in mind at a time. Moreover, possible alternative regions where decremental responses might still be occurring include perirhinal cortex—for the majority of the recordings were in area TE rather than perirhinal cortex—and prefrontal cortex.

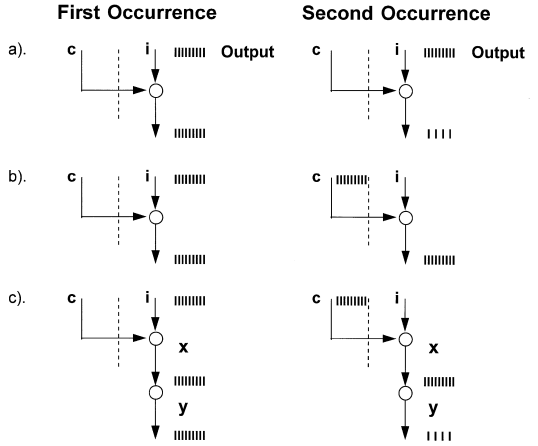

Fig. 24. Diagrammatic representation of observed (a and b) and hypothesised (c) responses of repetition-sensitive neurones when stimuli are presented to the left or right eye so that information reaches the neurone from the contralateral (**c**) or ipsilateral (**i**) hemisphere. The dotted line represents the midline, the short bars notional neuronal responses. (a) When the stimulus-evoked activity reaches the repetition-sensitive neurone over the same pathway (**i**), the neuronal response is reduced for the second presentation (*output*). (b) When the stimulus-evoked activity reaches the repetition-sensitive neurone over a different pathway (first presentation **i**; second presentation **c**), the neuronal response is not reduced for the second presen-

There are grounds for expecting that decremental responses may still be found in perirhinal and prefrontal cortex under these stimulus presentation conditions. Information from successive presentations of the same stimulus to different eyes will arrive by different sets of afferents (see Fig. 24). Any synapse-specific loss of synaptic efficacy would not therefore produce a reduced response when a different set of afferents is activated by the second presentation (as observed). However, unless neurones with repetition-sensitive responses never project to other neurones with repetition-sensitive synapses (i.e. unless neurones with such synapses form a 'monolayer'), the next such neurone in the chain will receive information concerning both presentations of the stimulus over the same set of synapses; correspondingly, it should show a response decrement with repetition (though no such cells were observed).

Secondly, Eacott *et al.* (1994) found evidence that monkeys with perirhinal lesions had a perceptual deficit: their performance of a delayed matching to sample task was impaired at zero delay if the stimulus set used was very large. Moreover, in the same animals there was no deficit if the stimulus set was very small (2 items). The deficit with large numbers of items is explicable by the role perirhinal cortex is likely to have in stimulus identification. Indeed, a perceptual role for perirhinal cortex is consistent with the existence of stimulus specific repetition-invariant neuronal responses in this cortex and with human findings of 'semantic amnesia' following lesions including this region (Warrington, 1975; Hodges *et al.*, 1992; Graham and Hodges, 1997). In fact, the observed deficit with the large set became

still larger with increasing delays, consistent with a mnemonic in addition to a perceptual role for perirhinal cortex. The variant of the task using a small stimulus set might be solved by the animals using a different strategy for task solution (see Section 6.1); such a strategy would be likely to have a different neural basis, possibly involving changes that could develop over the multiple trials on which the two stimuli are experienced. Alternatively, the task might be solved by using neurones with repetition-sensitive responses but short memory spans, as found outside perirhinal cortex in inferior temporal cortex (Baylis and Rolls, 1987; Fahy *et al*., 1993b).

Thirdly, Miller and Desimone (1993) found that administration of scopolamine produced a dissociation between behaviour and repetition-sensitive neuronal responses in anterior inferior temporal cortex. Responses were recorded in monkey anterior inferior temporal cortex during performance of a delayed matching task before and after the animals were given systemic scopolamine. The animal's behaviour was impaired by the drug, but the neuronal responses and their decrements were unimpaired. To disprove the hypothesis in this case requires that the drug acts to produce its impairment of behaviour in the region within which the recordings were made. Otherwise, for example, the drug may produce impairment of behaviour by actions in prefrontal cortex or anywhere else on the output side of anterior temporal cortex. In this context it should be noted that behaviour was impaired even at a delay of < 1 s. and the impairment was not shown to be delay dependent; accordingly, the impairment is not necessarily of memory *per se*. Again, the delayed matching task used in this experiment could have been solved by a strategy dependent on delay activity rather than decremental responses: hence disruption of delay activity by scopolamine could have produced the behavioural impairment (Brown, 1996). Recently, Tang and Aigner (1996) have demonstrated impairments in delayed non-matching to sample when scopolamine is infused unilaterally directly into perirhinal cortex. No impairment was found with inferior temporal cortex or dentate gyrus infusions. In this case, the impairment with perirhinal infusion has been tested for lists of 20 items so that it is unlikely that a strategy based on delay activity could have been used. Unfortunately, neuronal responses under scopolamine have not been tested at long delays and when more than one target item has to be remembered at a time. It should be noted that it is neurones recorded in perirhinal cortex for which an effect might be expected and not those recorded in area TE. Moreover, the effects of local infusion of scopolamine into perirhinal cortex have not been tested at short delays. Thus a critical test of the hypothesis requires determination of the effects of local infusions of the drug on neuronal response decrements for multiple stimuli over long delays.

7.2. Relationship to Priming

Although the possibility has been appreciated for some time (Wilson *et al*., 1988; Riches *et al*., 1991), it is not yet clear whether there is any relationship between the described repetition-sensitive responses and priming, the modification of performance by prior experience. It is possible to dissociate priming and recognition memory in a variety of ways (Tulving and Schacter, 1990; Schacter *et al*., 1993). Indeed, it is possible to doubly dissociate word-stem completion priming from recognition memory (Brown *et al*., 1989; Brindle *et al*., 1991; Schacter *et al*., 1993; Sharp *et al*., 1993). Most notably, recognition memory is an essentially conscious form of memory whereas priming is not (Jacoby and Witherspoon, 1982; Graf and Schacter, 1985; Schacter *et al*., 1993). However, although these findings indicate that there are differences between the neural substrates of priming and recognition memory, they do not preclude there being some overlap in the underlying mechanisms. Moreover, it is important to remember that there are many different types of priming, more than one type of judgement leading to recognition memory, and more than one type of repetition-sensitive response. Thus global parallels between all these different measures could not be expected.

The most obvious potential parallel would seem to be between repetition priming (most easily measured by a decreased latency of behavioural response to repeated stimuli) and the responses of recency or novelty neurones (which encode the prior occurrence of stimulus items). The responses of familiarity neurones would not seem to provide a satisfactory basis for such priming, at least over short time intervals. There is no logical difficulty in a decreased response resulting in enhanced performance. Thus a single inhibitory link could be used to reverse the sign of the response change. Alternatively, the decreased neuronal activity could represent more streamlined processing with repetition, leading straightforwardly to a reduced latency of behavioural response (Zhu and Brown, 1995; Brown, 1996; Erickson and Desimone, 1996). Both human PET and fMRI studies have indicated decreased activation for repeated (primed) stimuli, including in anterior temporal cortex (Squire *et al*., 1992; Vandenberghe *et al*., 1995; see for review: Verfaellie and Keane, 1997). Parsimony, or the consequence of evolutionary pressure to reduce unnecessary duplication, would suggest that one mechanism that records the prior occurrence of stimuli should be sufficient for both repetition priming and recognition memory based upon recency judgements. Necessarily, the use made of the information concerning prior occurrence would differ for the two types of memory, one of which is essentially unconscious, the other essentially conscious. Potentially against such a conclusion is the finding of intact visual word identification priming in a patient with a temporal lobe lesion that includes all of perirhinal cortex (Hamann and Squire, 1997); However, this case does not exclude the priming being supported by repetition-sensitive responses in anterior visual association cortex (i.e. the human equivalent to monkey anterior TE). It does imply that such responses in perirhinal cortex are not necessary for such priming, though they may accordingly underlie recognition memory (recency discrimination).

8. DIRECTIONS FOR FUTURE RESEARCH

Work to date has established that within anterior inferior temporal, including perirhinal cortex, there are powerful neuronal mechanisms for providing information concerning the prior occurrence of stimuli (their recency and relative familiarity). Arguments have been presented (Section 7.1.1) that these mechanisms are not artefactual nor an epiphenomenon. Ablation experiments have demonstrated the importance of perirhinal cortex, though not of the neuronal mechanisms themselves, for recognition memory tasks that can be solved using these types of information. The evidence to date establishes the potential importance of these mechanisms, but much further work is required before their use and properties are properly understood. There are several different directions in which such future research is needed. These requirements for further research may be grouped into experiments concerned with increasing knowledge of the underlying neural mechanisms and experiments attempting to link these mechanisms with recognition memory.

8.1. Further Investigations of Putative Neural Mechanisms

8.1.1. *Investigating Neurones with Repetition-Sensitive Responses*

Such studies need to include further exploration of the properties of repetition-sensitive responses. What are the limits on processing capacity in terms of stimulus specificity and generalisation? What are the limits on mnemonic capacity—the types of information signalled and the maximum memory spans (thus the existence of memory spans lasting many days is unexplored)? How and where is the prior occurrence of particular spatial arrangements of familiar items encoded? How is the relationship between objects and their backgrounds (contexts) encoded? Does the size of stimuli influence the type of encoding?

Additionally, it will be important to discover the particular neurones involved. Which morphological types of neurones have which types of response? What are the local network connections and how do these contribute to the responses?

8.1.2. *Investigating the Operation of the Recognition Memory System*

It is essential to establish which regions are responsible for which parts of the processing necessary to recognition memory performance. In particular, which regions contain the plastic synapses? (see Section 4.2). Do such changes occur on the afferent side of perirhinal cortex? What is the importance of feedforward and feedback influences on response changes? Which are the critical inputs to perirhinal cortex and which are the critical outputs? What are the roles of other critical regions (e.g. prefrontal cortex, basal forebrain, medial thalamus)? What are the precise information processing functions of each of these regions?

Notably, it will be important to explore the interrelationship of the perirhinal and hippocampal systems in recognition memory. When is the hippocampal system and when is the perirhinal system used in recognition memory and precisely what are their individual functions? What is the relationship between processes underlying judgements of prior occurrence for individual items and those used for scenes and events? (i.e. more generalised episodic memory). When are stimuli processed as objects as opposed to scenes or environments? Thus hippocampal lesions in rats affect performance of a recognition memory task differentially according to the size of the stimuli (Cassaday and Rawlins, 1995). An additional complication here is how stimuli displayed on computer monitors may be processed compared to three dimensional reality: are computer-displayed scenes objects, patterns, or environments and does the task or discrimination required influence this?

The involvement of the neurones of perirhinal cortex and associated structures in the acquisition and retrieval of information, and in its permanent or temporary storage also need investigation. These issues may be explored by extending the time between initial exposure to stimuli and their subsequent re-appearance so as to allow the application of drugs or lesions at the time of either acquisition or retrieval, and possibly additionally seeking evidence of retrograde amnesia.

8.1.3. *Locating the Plastic Synapses*

The plastic synaptic changes need to be localised both regionally and neuronally, i.e. determining which brain area(s) contain the essential plastic synapses and which synapses on which neurones are involved. Critical regional changes may be further localised by employing selective lesions, localised drug injections, including reversible inactivation (e.g. Tang and Aigner, 1996; Kim and Thompson, 1997), microstimulation (e.g. Ringo, 1995), or cooling (e.g. Horel *et al.*, 1987), particularly if combined with a technique for monitoring changes in neural activity as well as behaviour. Seeking Fos changes (Zhu *et al.*, 1996) after selective lesions provides an example employing ablation combined with imaging. Drugs and lesions can prevent learning in ways other than by directly blocking a plastic process (for example by preventing necessary information reaching the critical synapses or by non-specifically disrupting neuronal processing). Hence it will also be necessary to employ other techniques to localise these synapses such as seeking selective biochemical and anatomical changes localised to critical areas or neuronal contacts, or measuring changes in neuronal connectivity through simultaneous recording.

8.1.4. *Uncovering the Underlying Synaptic Plastic Mechanisms*

Is there more than one underlying synaptic plastic mechanism, or only one but with widely varying temporal properties? Initial work on this problem may be facilitated by *in vitro* studies, but these must eventually be validated *in vivo*. If these neuronal response changes are specifically generated in perirhinal cortex, then any potentially corresponding

changes found in perirhinal cortical slices could be expected to have characteristics that are particular to this region. However, it has to be remembered that such properties might rely on extra-perirhinal influences that no longer exist in the slice. Moreover, any differences between slices of perirhinal cortex and slices of other areas may arise from the pattern of preserved and severed connections in the particular slice rather than any fundamental difference in *in vivo* physiology.

8.1.5. *Neural Modelling*

Computer modelling at the neuronal, network and systems levels would also produce valuable indications of the validity of hypotheses, the depth of understanding of the processes, and suggest further crucial experiments. The potential power and accuracy of such modelling will be greatly enhanced by the provision of detailed quantitative information concerning neuronal interconnectivity and plastic changes.

8.2. Correlating Neural Changes with Recognition Memory

It is necessary to continue to examine potential correlations between synaptic changes, neuronal response changes, and behaviour. Note that there are two successive sets of correlations here: (i) between synaptic plasticity and neuronal response changes on stimulus repetition, and (ii) between these neuronal response changes and recognition memory. In examining such correlations, it is essential that similar behavioural conditions are used, and the use of alternative behavioural strategies and neuronal substrates, and hence false negatives, are excluded.

Examining potential correlations between synaptic and neuronal response changes and behaviour is central to understanding the use made of the information available in repetition-sensitive responses. On the behavioural side very careful design is essential as recognition memory tasks may be solved using different types of information, i.e. there is likely to be more than one strategy that can lead to successful performance. This flexibility of strategy is especially pertinent to comparisons between results from humans and other species. The precise conditions used in testing may greatly influence strategy. In particular, the behavioural training given to animals in recognition memory tasks is typically such as to minimise the likely use of contextual information for the judgement of prior occurrence: the context is essentially unchanged day after day (Murray, 1996). In contrast, using stimulus items such as words that are typically very familiar and may often have been encountered recently can be expected to increase the use of contextual information (and being placed in a PET scanner is not an everyday occurrence). Recording studies during the performance of the *ABBA* task (Miller and Desimone, 1994) have demonstrated that strategy has a major influence on the generation of neuronal responses (see Section 6.2). Thus different strategies do indeed produce differences in neuronal activity. Accordingly, parallels can only be expected when testing conditions and strategy are the same for the compared situations. It is necessary to establish the type of information being used and how it is being employed to solve the task. It is additionally important to determine how practised the subject is at the task, as practice also leads to processing differences (e.g. Raichle *et al.*, 1994). Further, strategy is likely to be influenced by the stimulus materials, their confusability and their spatial composition. If encoding is automatic, any comparison task also becomes critical.

Establishing correlations between neuronal plastic changes and memory also requires very precise controls. Studies of neuronal response changes as a result of repeated exposure to or recognition memory for stimuli have included good controls for influences such as alertness, attention, emotion, motivation and movement (including eye movement); they additionally employ comparisons between the same numbers and types of novel and familiar sensory stimuli. There have been no published studies to date looking for specific anatomical, biochemical or molecular changes in perirhinal cortex that might provide explanation for the neuronal response changes, but it is essential that such studies are as closely controlled as the recording work. The paired-viewing procedure used in Fos studies in the rat provides one possible model for such work (see Fig. 5) (Zhu *et al.*, 1996).

There are many different ways in which parallels between plastic changes and behaviour may be sought and challenged. All of these approaches have potential application to the study of the mechanisms underlying the judgement of prior occurrence. In many cases appropriate combinations of these techniques may be expected to be particularly informative. The approaches may be grouped under five headings.

8.2.1. *Activation*

a) *Recordings.* Previous studies using this technique have been discussed above (Sections 2, 3 and 8.1). This work is likely to be greatly advanced by the simultaneous recording of individual neuronal spike trains, so allowing the study of neuronal interactions within and between regions.

b) *Immediate early genes.* To date such studies have successfully used c-fos as a marker of differential activation by novel and familiar stimuli (Zhu *et al.*, 1996) (see Sections 2.1 and 2.3.2). However, staining for the products of zif-268 does not show such a difference (X.O. Zhu and M.W. Brown, unpublished observations).

c) *Other markers.* There are no published studies on changes in any anatomical (synaptic contacts), biochemical or molecular factors, nor of changes in receptors or transmitter release. The discovery of a specific marker for the underlying plastic process would provide an ideal tool.

8.2.2. *Blockade*

a) *Ablation.* There have already been many ablation studies, but these have yet to explore the effects of lesions on the use of precise types of information (e.g. solely recency, or solely familiarity). Combined ablation and activation studies are likely to be useful in establishing the site of critical plastic synapses.

b) *Drugs*. There have been studies of pharmacological blockade with amnestic agents—scopolamine (Miller and Desimone, 1993; Tang and Aigner, 1996) and benzodiazepines (Wan *et al*., 1996)—but none so far with selective glutamate antagonists nor with selective agents that may prevent biochemical events necessary for synaptic changes such as long-term depression. However, one study has found a reduction in rats' spontaneous exploration of novel objects following chronic administration of a nitric oxide synthase inhibitor (Cobb *et al*., 1995). To provide a critical test, such drugs need to be delivered specifically into a particular region rather than being administered systemically. The possibility that continuing behavioural success or lack of effect on neuronal responses or other measures might be due to the use of an alternative cognitive strategy also needs to be remembered.
c) *Transgenic animals*. Selective gene knock-out animals have yet to be employed in this field.
d) *Electrical stimulation*. Localised, low intensity electrical stimulation given during acquisition and choice phases of delayed matching has been used to disrupt performance of recognition memory tasks (Ringo, 1995).

8.2.3. *Saturation*

Potentially, judgement of prior occurrence should be impaired if the repetition-sensitive mechanism could be saturated, for example by presenting very large numbers of sensory stimuli or by massively electrically stimulating perirhinal afferents in whatever might be the appropriate manner. However, such experiments may prove difficult. As judged by the response properties of perirhinal neurones, the information capacity of the system appears to be very large and this capacity may therefore be difficult to saturate. Additionally, it would be surprising if there were not control mechanisms to prevent inadvertent saturation of the system. At present a more immediate problem is that the appropriate means of stimulating perirhinal afferents remains to be discovered.

8.2.4. *Erasure*

This technique can only be used once the underlying synaptic plastic mechanism and a means for erasing its changes have been found.

8.2.5. *Artificial Induction*

The idea here would be to induce response changes by, for example, electrical or pharmacological stimulation of perirhinal cortex and then to demonstrate that these changes had induced appropriate alterations in behaviour (e.g. judging novel stimuli as familiar). Success would demonstrate the sufficiency of the induced change for producing the behaviour (e.g. McCabe *et al*., 1978), as opposed to techniques such as blockade which establish its necessity. However, until more evidence is available concerning how sensory items are encoded and how artificial stimulation might mimic this, this technique remains hypothetical.

8.3. Conclusions

This review has centred on neuronal response decrements on stimulus repetition in anterior inferior temporal cortex and their putative relation to recognition memory. Evidence has been presented that the properties of these neuronal response changes are sufficient to account for recognition memory capabilities of animals (recency and familiarity discrimination, rather than contextual discrimination). Thus these response changes: (i) provide information essential for judgement of prior occurrence of stimuli based on their recency and familiarity; (ii) demonstrate single trial learning; (iii) are stimulus selective; (iv) have a very large storage capacity; (v) are long-lasting; (vi) are not disrupted by other experiences; (vii) are endogenous and automatic (non-effortful); (viii) occur during performance of explicit memory tasks; (ix) can be demonstrated in neuronal population activity measures; and (x) occur in a region (perirhinal cortex) essential to judgement of prior occurrence. Further, the response changes are not specific to a particular experimental situation in that they occur for different types of stimuli in different recognition memory tasks and none, are found in monkeys and rats, and are consistent with PET changes described in humans making familiarity judgements. The response changes are not artefactual or trivial concomitants of the learning: they cannot be explained by differences in the reinforcement value of stimuli, the behavioural response emitted, eye movements or pupillary changes, alertness or attention.

It has been further argued that no other known response changes provide the necessary information to allow solution of a wide range of recognition memory tasks that do not require spatial or contextual discriminations. Thus the results of lesion studies indicate that the underlying changes critical to familiarity and recency discrimination must be found within a system centred on perirhinal cortex: ablation of perirhinal cortex produces major impairment in recognition memory tasks such as delayed non-matching to sample using individual stimulus items whereas ablation of the hippocampus and amygdala does not. Neuronal response changes capable of yielding the decremental responses in perirhinal cortex and the anterior part of area TE have not been found in regions providing afferents to them, including prefrontal cortex. Furthermore, other response changes found in anterior inferior temporal cortex cannot explain general recognition memory capabilities. Thus both enhanced responses to repeated stimuli and sustained or delay activity following a stimulus that must be remembered have yet to be shown to be capable of explaining recognition memory when more than one item must be remembered at a time or the memory must span a long and indeterminate interval. To date there has been no finding fatal to the hypothesis that the decremental neuronal response changes found in perirhinal cortex are central to judgement of the recency of occurrence and familiarity of individual stimuli.

Other neuronal response changes may be expected to be involved in other aspects of recognition mem-

ory. Thus, for example, there is evidence for the importance of the hippocampal formation in recognition memory judgements based on discrimination of spatial or contextual features.

There remain many unsolved problems concerning the neural bases of recognition memory. Thus, in particular, the synaptic plastic mechanisms underlying the response decrements are unknown and there is relatively little understanding of how the whole system operates to effect recognition memory. Suggestions are made concerning how solutions to some of these problems may be sought. Importantly, as recognition memory is not a unitary phenomenon, there must be more than one underlying substrate. Future experimentation needs to pay careful attention to which particular facet of recognition memory is under investigation.

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REFERENCES

Abeles, M. (1982) Role of cortical neuron: integrator or coincidence detector? *Isr. J. Med. Sci* **18,** 83–92.

Aggleton, J. P. and Brown, M. W. (1998) Episodic memory, amnesia and the hippocampal-anterior thalamic axis. *Behav. Brain. Sci.* in press.

Aggleton, J. P., Hunt, P. R. and Rawlins, J. N. P. (1986) The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. *Behav. Brain. Res.* **19,** 133–146.

Aggleton, J. P. and Shaw, C. (1996) Amnesia and recognition memory: a re-analysis of psychometric data. *Neuropsychologia* **34,** 51–62.

Alvarez, P., Zola-Morgan, S. and Squire, L. R. (1995) Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. *J. Neurosci.* **15,** 3796–3807.

Amari, S. (1989) Characteristics of sparsely encoded associative memory. *Neural Networks* **2,** 451–457.

Bachevalier, J. and Mishkin, M. (1986) Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys. *Behav. Brain. Res.* **20,** 249–261.

Baddeley, A. (1996) The fractionation of working memory. *Proc. Natl. Acad. Sci. USA* **93,** 13468–13472.

Baylis, G. C. and Rolls, E. T. (1987) Responses of neurons in the inferior temporal cortex in short term and serial recognition memory tasks. *Exp. Brain. Res.* **65,** 614–622.

Bodner, M., Kroger, J. and Fuster, J. M. (1996) Auditory memory cells in dorsolateral prefrontal cortex. *NeuroReport* **7,** 1905–1908.

Bonin, G. von, and Bailey, P. (1947) *The neocortex of Macaca mulatta.* University of Illinois Press: Urbana.

Brindle, P. M., Brown, M. W., Brown, J., Griffith, H. B. and Turner, G. M. (1991) Objective and subjective memory impairment in normal human pregnancy. *Psychol. Med.* **21,** 647–653.

Brown, M. W. (1982) Effect of context on the responses of single units recorded from the hippocampal region of behaviourally trained monkeys. In *Neuronal Plasticity and Memory Formation. IBRO Monograph Series* Vol. 9. pp. 557–573. Eds. C. Ajmone-Marsan and H. Matthies. Raven Press: New York.

Brown, M. W. (1990) Why does the cortex have a hippocampus? In *Learning and Computational Neuroscience: Foundations of Adaptive Networks.* pp. 233–282. Eds. M. Gabriel and J. Moore. M.I.T. Press: New York.

Brown, M. W. (1996) Neuronal responses and recognition memory. *Semin. Neurosci.* **8,** 23–32.

Brown, J. and Brown, M. W. (1990) The effects of repeating a recognition test in lorazepam-induced amnesia: evidence for impaired contextual memory as a cause of amnesia. *Quart. J. exp. Psychol. B* **42A,** 279–290.

Brown, M. W., Brown, J. and Bowes, J. B. (1989) Absence of priming coupled with substantially preserved recognition in lorazepam-induced amnesia. *Quart. J. exp. Psychol. B* **41A,** 599–617.

Brown, V. J., Desimone, R. and Mishkin, M. (1995) Responses of cells in the tail of the caudate nucleus during visual discrimination learning. *J. Neurophysiol.* **74,** 1083–1094.

Brown, M. W., Fahy, F. L., and Zhu, X. O. (1996) Studies of the recognition memory system. In *Perception,memory and emotion: frontiers in neuroscience.* pp. 111–123. Eds. T. Ono, B. L. McNaughton, S. Molotchnikoff, E. T. Rolls, and H. Nishijo. Elsevier: Amsterdam.

Brown, M. W. and Horn, G. (1977) Responsiveness of neurones in the hippocampal region of anaesthetised and unanaesthetised cats to stimulation of sensory pathways. *Brain. Res.* **123,** 241–259.

Brown, J., Lewis, V., Brown, M. W. and Horn, G. (1982) A comparison between transient amnesias induced by two drugs (diazepam or lorazepam) and amnesia of organic origin. *Neuropsychologia* **20,** 55–70.

Brown, M. W., Wilson, F. A. W. and Riches, I. P. (1987) Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory. *Brain. Res.* **409,** 158–162.

Brown, M. W., and Xiang, J.-Z. (1997) Information processing for novel and familiar visual stimuli in primate pregeniculate nucleus. *Soc. Neurosci. Abstr.* **23,** 194.13.

Buckley, M. J., Gaffan, D. and Murray, E. A. (1997) Functional double dissociation between two inferior temporal cortical areas: Perirhinal cortex versus middle temporal gyrus. *J. Neurophysiol.* **77,** 587–598.

Buckley, M. J. and Gaffan, D. (1997) Impairment of visual object-discrimination learning after perirhinal cortex ablation. *Behav. Neurosci.* **111,** 467–475.

Buckner, R. L. and Petersen, S. E. (1996) What does neuroimaging tell us about the role of prefrontal cortex in memory retrieval? *Semin. Neurosci.* **8,** 47–55.

Burwell, R. D., Witter, M. P. and Amaral, D. G. (1995) Perirhinal and postrhinal cortices of the rat: a review of the neuroanatomical literature and comparison with findings from the monkey brain. *Hippocampus* **5,** 390–408.

Caan, W., Perrett, D. I. and Rolls, E. T. (1984) Responses of striatal neurons in the behaving monkey. 2. Visual processing in the caudal neostriatum. *Brain. Res.* **290,** 53–65.

Cassaday, H. J. and Rawlins, J. N. P. (1995) Fornix–fimbria section and working memory deficits in rats: Stimulus complexity and stimulus size. *Behav. Neurosci.* **109,** 594–606.

Chow, K. L., Douville, A., Mascetti, G. and Gobstein, P. (1977) Receptive field characteristics of neurons in a visual area of the rabbit temporal cortex. *J. Comp. Neur.* **171,** 135–146.

Cobb, B. L., Ryan, K. L., Frei, M. R., GuelGomez, V. and Mickley, G. A. (1995) Chronic administration of L-NAME in drinking water alters working memory in rats. *Brain. Res. Bull.* **38,** 203–207.

Colombo, M. and Gross, C. G. (1994) Responses of inferior temporal cortex and hippocampal neurons during delayed matching to sample in monkeys (Macaca fascicularis). *Behav. Neurosci.* **108,** 443–455.

Constantinidis, C. and Steinmetz, M. A. (1996) Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task. *J. Neurophysiol.* **76,** 1352–1355.

Corkin, S., Amaral, D. G., Gonzalez, R. G., Johnson, K. A. and Hyman, B. T. (1997) H.M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. *J. Neurosci.* **17,** 3964–3979.

Crick, F. (1984) Function of the thalamic reticular complex: the searchlight hypothesis. *Proc. Natl. Acad. Sci. USA* **81,** 4586–4590.

Curran, T., Schacter, D. L., Norman, K. A. and Galluccio, L. (1997) False recognition after a right frontal lobe infarction: memory for general and specific information. *Neuropsychologia* **35,** 1035–1049.

Delay, J. and Brion, S. (1969) *Le syndrome de Korsakoff.* Masson: Paris.

Desimone, R. (1992) The physiology of memory: recordings of things past. *Science* **258,** 245–246.

Desimone, R. (1996) Neural mechanisms for visual memory and their role in attention. *Proc. Natl. Acad. Sci. USA* **93,** 13494–13499.

DeYoe, E. A., Felleman, D. J., Van Essen, D. C. and McClendon, E. (1994) Multiple processing streams in occipitotemporal visual cortex. *Nature* **371,** 151–154.

Di Pellegrino, G. and Wise, S. P. (1993) Visuospatial versus visuomotor activity in the premotor and prefrontal cortex of a primate. *J. Neurosci.* **13,** 1227–1243.

Doty, R. W. and Savakis, A. E. (1997) Commonality of processes underlying visual and verbal recognition memory. *Cognit. Brain. Res.* **5,** 283–294.

Eacott, M. J., Gaffan, D. and Murray, E. A. (1994) Preserved recognition memory for small sets, and impaired stimulus identification for large sets, following rhinal cortex ablations in monkeys. *Eur. J. Neurosci.* **6,** 1466–1478.

Eichenbaum, H. (1996) Is the rodent hippocampus just for 'place'? *Curr. Op. Neurobiol.* **6,** 187–195.

Eichenbaum, H., Otto, T. and Cohen, N. J. (1994) Two functional components of the hippocampal memory system. *Behav. Brain. Sci.* **17,** 449–518.

Eichenbaum, H., Schoenbaum, G., Young, B. and Bunsey, M. (1996) Functional organization of the hippocampal memory system. *Proc. Natl. Acad. Sci. USA* **93,** 13500–13507.

Ennaceur, A., Neave, N. and Aggleton, J. P. (1996) Neurotoxic lesions of the perirhinal cortex do not mimic the behavioural effects of fornix transection in the rat. *Behav. Brain. Res.* **80,** 9–25.

Erickson, C. A. and Desimone, R. (1996) Neural correlates of visual associative learning in inferior temporal cortex of the rhesus macaque. *Soc. Neurosci. Abstr.* **22,** 634.15.

Eskandar, E. N., Richmond, B. J. and Optican, L. M. (1992) Role of inferior temporal neurons in visual memory: I. Temporal encoding of information about visual images, recalled images, and behavioral context. *J. Neurophysiol.* **68,** 1277–1295.

Eslinger, P. J. and Grattan, L. M. (1994) Altered serial position learning after frontal lobe lesion. *Neuropsychologia* **32,** 729–739.

Fahy, F. L., Riches, I. P. and Brown, M. W. (1993a) Neuronal signals of importance to the performance of visual recognition memory tasks: evidence from recordings of single neurones in the medial thalamus of primates. *Progr. Brain. Res.* **95,** 401–416.

Fahy, F. L., Riches, I. P. and Brown, M. W. (1993b) Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. *Exp. Brain. Res.* **96,** 457–472.

Feigenbaum, J. D. and Rolls, E. T. (1991) Allocentric and egocentric spatial information processing in the hippocampal formation of the behaving primate. *Psychobiology* **19,** 21–40.

Fletcher, P. C., Dolan, R. J. and Frith, C. D. (1995) The functional anatomy of memory. *Experientia* **51,** 1197–1207.

Foote, S. L., Aston-Jones, G. and Bloom, F. E. (1980) Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. *Proc. Natl. Acad. Sci. USA* **77,** 3033–3037.

Fried, I., MacDonald, K. A. and Wilson, C. L. (1997) Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron* **18,** 753–765.

Fukuda, M., Masuda, R., Ono, T. and Tabuchi, E. (1993) Responses of monkey basal forebrain neurons during visual discrimination task. *Progr. Brain. Res.* **95,** 359–369.

Funahashi, S., Bruce, C. J. and Goldman-Rakic, P. S. (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* **61,** 331–349.

Funahashi, S., Inoue, M. and Kubota, K. (1997) Delay-period activity in the primate prefrontal cortex encoding multiple spatial positions and their order of presentation. *Behav. Brain. Res.* **84,** 203–223.

Funahashi, S. and Kubota, K. (1994) Working memory and prefrontal cortex. *Neurosci. Res.* **21,** 1–11.

Fuster, J. M. (1995) *Memory in the Cerebral Cortex*. MIT Press: Cambridge, Massachusetts.

Fuster, J. M. and Alexander, G. E. (1971) Neuron activity related to short-term memory. *Science* **173,** 652–654.

Fuster, J. M., Bauer, R. H. and Jervey, J. P. (1985) Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. *Brain. Res.* **330,** 299–307.

Fuster, J. M. and Jervey, J. P. (1981) Inferotemporal neurons distinguish and retain behaviorally relevant features of visual stimuli. *Science* **212,** 952–955.

Gaffan, D. (1974) Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *J. Comp. Physiol. Psychol.* **80,** 1100–1109.

Gaffan, D. (1991) Spatial organisation of episodic memory. *Hippocampus* **1,** 262–264.

Gaffan, D. (1994) Scene-specific memory for objects: a model of episodic memory impairment in monkeys with fornix transection. *J. Cognit. Neurosci* **6:4,** 305–320.

Gaffan, D. (1996) Associative and perceptual learning and the concept of memory systems. *Cognit. Brain. Res.* **5,** 69–80.

Gaffan, D. and Eacott, M. J. (1995) Uncinate fascicle section leaves delayed matching-to-sample intact, with both large and small stimulus sets. *Exp. Brain. Res.* **105,** 175–180.

Gaffan, D. and Murray, E. A. (1992) Monkeys (Macaca fascicularis) with rhinal cortex ablations succeed in object discrimination learning despite 24-hr intertrial intervals and fail at matching to sample despite double sample presentations. *Behav. Neurosci.* **106,** 30–38.

Gaffan, D. and Parker, A. (1996) Interaction of perirhinal cortex with the fornix–fimbria: Memory for objects and 'object-in-place' memory. *J. Neurosci.* **16,** 5864–5869.

Ghoneim, M. M. and Block, R. I. (1992) Learning and consciousness during general anesthesia. *Anesthesiology* **76,** 279–305.

Graf, P. and Schacter, D. L. (1985) Implicit and explicit memory for new associations in normal and amnesic subjects. *J. exp. Psychol. Learn. Mem. Cog.* **11,** 501–518.

Grafton, S. T. (1995) Mapping memory systems in the human brain. *Semin. Neurosci.* **7,** 157–163.

Graham, K. S. and Hodges, J. R. (1997) Differentiating the roles of the hippocampal complex and the neocortex in long-term memory storage: evidence from the study of semantic dementia and Alzheimer's disease. *Neuropsychology* **11,** 77–89.

Gross, C. G., Rochamiranda, C. E. and Bender, D. B. (1972) Visual properties of neurons in inferotemporal cortex of the macaque. *J. Neurophysiol.* **35,** 96–111.

Haenny, P. E. and Schiller, P. H. (1988) State dependent activity in monkey visual cortex. I. Single cell activity in V1 and V4 on visual tasks. *Exp. Brain. Res.* **69,** 225–244.

Haglund, M. M., Ojemann, G. A., Schwartz, T. W. and Lettich, E. (1994) Neuronal activity in human lateral temporal cortex during serial retrieval from short-term memory. *J. Neurosci.* **14,** 1507–1515.

Hamann, S. B. and Squire, L. R. (1997) Intact perceptual memory in the absence of conscious memory. *Behav. Neurosci.* **111,** 850–854.

Heit, G., Smith, M. E. and Halgren, E. (1988) Neural encoding of individual words and faces by the human hippocampus and amygdala. *Nature* **333,** 773–775.

Heit, G., Smith, M. E. and Halgren, E. (1990) Neuronal activity in the human medial temporal lobe during recognition memory. *Brain.* **113,** 1093–1112.

Herrera, D. G. and Robertson, H. A. (1997) Activation of c-fos in the brain. *Progr. Neurobiol.* **50,** 83–107.

Higuchi, S. I. and Miyashita, Y. (1996) Formation of mnemonic neuronal responses to visual paired associates in inferotemporal cortex is impaired by perirhinal and entorhinal lesions. *Proc. Natl. Acad. Sci. USA* **93,** 739–743.

Hodges, J. R., Patterson, K., Oxbury, S. and Funnell, E. (1992) Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. *Brain* **115,** 1783–1806.

Horel, J. A. (1978) The neuroanatomy of amnesia. A critique of the hippocampal memory hypothesis. *Brain* **101,** 403–445.

Horel, J. A., Pytkojoiner, D. E., Voytko, M. and Salsbury, K. (1987) The performance of visual tasks while segments of the inferotemporal cortex are suppressed by cold. *Behav. Brain. Res.* **23,** 29–42.

Horn, G. (1967) Neuronal mechanisms of habituation. *Nature* **215,** 707–711.

Horn, G. and Hill, R. M. (1964) Habituation of the response to sensory stimuli of neurons in the brain stem of rabbits. *Nature* **202,** 296–298.

Hubel, D. H. and Wiesel, T. N. (1965) Receptive fields and functional architecture in two non-striate visual areas (18 and 19) of the cat. *J. Neurophysiol.* **28,** 227–289.

Ito, M. (1989) Long-term depression. *Annu. Rev. Neurosci.* **12,** 85–102.

Jacoby, L. L. and Witherspoon, D. (1982) Remembering without awareness. *Can. J. Psychol.* **36,** 300–324.

Jagadeesh, B., Desimone, R. and Mishkin, M. (1996) Neuronal responses in macaque inferior temporal cortex during long term learning of object salience. *Soc. Neurosci. Abstr.* **22,** 634.16.

Johnstone, S. and Rolls, E. T. (1990) Delay, discriminatory, and modality specific neurons in striatum and pallidum during short-term memory tasks. *Brain. Res.* **522,** 147–151.

Jones, E. G. (1985) The ventral thalamus. In *The thalamus*. pp. 723–733. Eds. Anonymous Plenum Press: New York.

Jones, E. G. and Powell, T. P. S. (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain* **93,** 793–820.

Kandel, E. R. (1981) Calcium and the control of synaptic strength by learning. *Nature* **293,** 697–700.

Kandel, E. R. and Spencer, W. A. (1968) Cellular and neurophysiological approaches to the study of learning. *Physiol. Rev.* **48,** 66–134.

Kim, J. J. and Thompson, R. F. (1997) Cerebellar circuits and synaptic mechanisms involved in classical eyeblink conditioning. *Trends. Neurosci.* **20,** 177–181.

Koch, K. W. and Fuster, J. M. (1989) Unit activity in monkey parietal cortex related to haptic perception and temporary memory. *Exp. Brain. Res.* **76,** 292–306.

Kojima, S. and Goldman Rakic, P. S. (1982) Delay-related activity of prefrontal neurons in rhesus monkeys performing delayed response. *Brain. Res.* **248,** 43–50.

Konig, P., Engel, A. K. and Singer, W. (1996) Integrator or coincidence detector? The role of the cortical neuron revisited. *Trends. Neurosci.* **19,** 130–137.

Leonard, B. W., Amaral, D. G., Squire, L. R. and Zola-Morgan, S. (1995) Transient memory impairment in monkeys with bilateral lesions of the entorhinal cortex. *J. Neurosci.* **15,** 5637–5659.

Li, L., Miller, E. K. and Desimone, R. (1993) The representation of stimulus familiarity in anterior inferior temporal cortex. *J. Neurophysiol.* **69,** 1918–1929.

Liu, P. and Bilkey, D. K. (1996) Direct connection between perirhinal cortex and hippocampus is a major constituent of the lateral perforant path. *Hippocampus* **6,** 125–135.

Logothetis, N. K. and Sheinberg, D. L. (1996) Visual object recognition. *Ann. Rev. Neurosci.* 577–621.

Lueschow, A., Miller, E. K. and Desimone, R. (1994) Inferior temporal mechanisms for invariant object recognition. *Cerebral. Cortex* **4,** 523–531.

Maguire, E. A., Frackowiak, R. S. J. and Frith, C. D. (1996) Learning to find your way: a role for the human hippocampal formation. *Proc. R. Soc. Lond. B* **263,** 1745–1750.

Mandler, G. (1980) Recognizing: the judgment of previous occurrence. *Psychol. Rev.* **87,** 252–271.

Marr, D. (1971) Simple memory: a theory for archicortex. *Phil. Trans. Roy. Soc. Lond. B* **262,** 23–81.

McCabe, B. J., Horn, G. and Bateson, P. P. G. (1978) Effects of rhythmic hyperstriatal stimulation on chicks' preferences for visual flicker. *Physiol. Behav.* **23,** 137–140.

McLardy, T. (1970) Memory function in the hippocampi gyri but not in hippocampi. *Intern. J. Neuroscience* **1,** 113–118.

Merzenich, M., Wright, B., Jenkins, W., Xerri, C., Byl, N., Miller, S. and Tallal, P. (1996) Cortical plasticity underlying perceptual, motor, and cognitive skill development: implications for neurorehabilitation. *Cold. Spring. Harb. Symp. Quant. Biol.* **61,** 1–8.

Meunier, M., Bachevalier, J. and Mishkin, M. (1997) Effects of orbital frontal and anterior cingulate lesions on object and spatial memory in rhesus monkeys. *Neuropsychologia* **35,** 999–1015.

Meunier, M., Bachevalier, J., Mishkin, M. and Murray, E. A. (1993) Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *J. Neurosci.* **13,** 5418–5432.

Meunier, M., Hadfield, W., Bachevalier, J. and Murray, E. A. (1996) Effects of rhinal cortex lesions combined with hippocampectomy on visual recognition memory in rhesus monkeys. *J. Neurophysiol.* **75,** 1190–1205.

Mikami, A. and Kubota, B. (1980) Inferotemporal neuron activities and color discrimination with delay. *Brain. Res.* **182,** 65–78.

Miller, E. K. and Desimone, R. (1993) Scopolamine affects short-term memory but not inferior temporal neurons. *NeuroReport* **4,** 81–84.

Miller, E. K. and Desimone, R. (1994) Parallel neuronal mechanisms for short-term memory. *Science* **263,** 520–522.

Miller, E. K., Erickson, C. A. and Desimone, R. (1996) Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *J. Neurosci.* **16,** 5154–5167.

Miller, E. K., Gochin, P. M. and Gross, C. G. (1991a) Habituation-like decrease in the responses of neurons in inferior temporal cortex of the macaque. *Vis. Neurosci.* **7,** 357–362.

Miller, E. K., Li, L. and Desimone, R. (1991b) A neural mechanism for working and recognition memory in inferior temporal cortex. *Science* **254,** 1377–1379.

Miller, E. K., Li, L. and Desimone, R. (1993) Activity of neurons in anterior inferior temporal cortex during a short-term memory task. *J. Neurosci.* **13,** 1460–1478.

Mishkin, M. (1978) Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. *Nature* **273,** 297–298.

Mishkin, M. (1982) A memory system in the monkey. *Phil. Trans. Roy. Soc. Lond. B.* **298,** 85–95.

Mishkin, M. and Delacour, J. (1975) An analysis of short-term visual memory in the monkey. *J. Exp. Psychol.* **1,** 326–334.

Mishkin, M. and Murray, E. A. (1994) Stimulus recognition. *Curr. Op. Neurobiol.* **4,** 189–194.

Miyashita, Y. (1993) Inferior temporal cortex: where visual perception meets memory. *Ann. Rev. Neurosci.* **16,** 245–263.

Miyashita, Y. and Chang, H. S. (1988) Neuronal correlate of pictorial short-term memory in the primate temporal cortex. *Nature* **331,** 68–70.

Miyashita, Y., Okuno, H., Tokuyama, W., Ihara, T. and Nakajima, K. (1996) Feedback signal from medial temporal lobe mediates visual associative mnemonic codes of inferotemporal neurons. *Cognit. Brain. Res.* **5,** 81–86.

Moscovitch, M. and Melo, B. (1997) Strategic retrieval and the frontal lobes: evidence from confabulation and amnesia. *Neuropsychologia* **35,** 1017–1034.

Mumby, D. G. and Pinel, J. P. J. (1994) Rhinal cortex lesions and object recognition in rats. *Behav. Neurosci.* **108,** 11–18.

Mumby, D. G., Pinel, J. P. J., Kornecook, T. J., Shen, M. J. and Redila, V. A. (1995) Memory deficits following lesions of hippocampus or amygdala in rat: assessment by an object-memory test battery. *Psychobiology* **23,** 26–36.

Mumby, D. G., Wood, E. R., Duva, C. A., Kornecook, T. J., Pinel, J. P. J. and Phillips, A. G. (1996) Ischemia-induced object-recognition deficits in rats are attenuated by hippocampal ablation before or soon after ischemia. *Behav. Neurosci.* **110,** 266–281.

Murray, E. A. (1991) Medial temporal lobe structures contributing to recognition memory: the amygdaloid complex versus the rhinal cortex. In *The Amygdala: Neurobiological Aspects of Emotion, Memory and Mental Dysfunction*. pp. 453–470. Eds. J. P. Aggleton. Wiley-Liss, Inc., New York.

Murray, E. A. (1996) What have ablation studies told us about the neural substrates of stimulus memory? *Semin. Neurosci.* **8,** 13–22.

Murray, E. A. and Mishkin, M. (1996) 40-Minute visual recognition memory in rhesus monkeys with hippocampal lesions. *Soc. Neurosci. Abstr.* **22,** 116.9.

Nadel, L. and Moscovitch, M. (1997) Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Op. Neurobiol.* **7,** 217–227.

Nakamura, K. and Kubota, K. (1995) Mnemonic firing of neurons in the monkey temporal pole during a visual recognition memory task. *J. Neurophysiol.* **74,** 162–178.

Nakamura, K. and Kubota, K. (1996) The primate temporal pole: its putative role in object recognition and memory. *Behav. Brain. Res.* **77,** 53–77.

Naya, Y., Sakai, K. and Miyashita, Y. (1996) Activity of primate inferotemporal neurons related to a sought target in pair-association task. *Proc. Natl. Acad. Sci. USA* **93,** 2664–2669.

Nishijo, H., Ono, T. and Nishino, H. (1988) Topographic distribution of modality-specific amygdalar neurons in alert monkey. *J. Neurosci.* **8,** 3556–3569.

Nowicka, A., Ringo, J. L. and O'Neill, S. (1995) Saccadic eye movements (sem) enhance stimulus specific adaptation in inferotemporal (IT) units of macaque. *Soc. Neurosci. Abstr.* **21,** 661.

Nyberg, L., McIntosh, A. R., Cabeza, R., Habib, R., Houles, S. and Tulving, E. (1996) General and specific brain regions involved in encoding and retrieval of events: what, where, and when. *Proc. Natl. Acad. Sci. USA* **93,** 11280–11285.

O'Boyle, V. J., Murray, E. A. and Mishkin, M. (1993) Effects of excitotoxic amygdalo-hippocampal lesions on visual recognition in rhesus monkeys. *Soc. Neurosci. Abstr.* **19,** 186.4.

O'Keefe, J. (1993) Hippocampus, theta rhythms and spatial memory. *Curr. Op. Neurobiol.* **3,** 917–924.

O'Keefe, J. and Nadel, L. (1978) *The hippocampus as a cognitive map*. Eds. 1, Oxford University Press: Oxford.

Ojemann, G. A., Creutzfeldt, O., Lettich, E. and Haglund, M. M. (1988) Neuronal activity in human lateral temporal cortex related to short-term verbal memory, naming and reading. *Brain* **111,** 1383–1403.

Olton, D. S., Becker, J. T. and Handelmann, G. E. (1979) Hippocampus, space and memory. *Behav. Brain. Sci.* **2,** 313–322.

Otto, T. and Eichenbaum, H. (1992a) Complementary roles of the orbital prefrontal cortex and the perirhinal-entorhinal cortices in an odor-guided delayed-nonmatching-to-sample task. *Behav. Neurosci.* **106,** 762–775.

Otto, T., and Eichenbaum, H. (1992b) Neuronal activity in the hippocampus during delayed non-match to sample performance in rats: Evidence for hippocampal processing in recognition memory. *Hippocampus* **2,** 323–334.

Parkinson, J. K., Murray, E. A. and Mishkin, M. (1989) A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. *J. Neurosci.* **8,** 4159–4167.

Perkel, D. H., Gerstein, G. L. and Moore, G. P. (1967) Neuronal spike trains and stochastic point processes. II. Simultaneous spike trains. *Biophys. J.* **7,** 419–440.

Pollen, D. A., Nagler, M., Daugman, J., Kronauer, R. and Cavanagh, P. (1984) Use of Gabor elementary functions to probe receptive field structure of posterior inferotemporal neurons in the owl monkey. *Vision. Res.* **24,** 233–241.

Raichle, M. E., Fiez, J. A., Videen, T. O., MacLeod, A. M. K., Pardo, J. V., Fox, P. T. and Petersen, S. E. (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral. Cortex* **4,** 8–26.

Rao, S. C., Rainer, G. and Miller, E. K. (1997) Integration of what and where in the primate prefrontal cortex. *Science* **276,** 821–824.

Rawlins, J. N. P. (1985) Associations across time: the hippocampus as a temporary memory store. *Behav. Brain. Sci.* **8,** 479–496.

Riches, I. P., Wilson, F. A. W. and Brown, M. W. (1988) Neurones of the medial temporal lobes and recognition memory. In *Synaptic Plasticity in the Hippocampus*. pp. 193–197. Eds. H. L. Haas and G. Buzsaki. Springer-Verlag: Berlin.

Riches, I. P., Wilson, F. A. W. and Brown, M. W. (1991) The effects of visual stimulation and memory on neurons of the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of the primate. *J. Neurosci.* **11,** 1763–1779.

Richmond, B. J. and Sato, T. (1987) Enhancement of inferior temporal neurons during visual discrimination. *J. Neurophysiol.* **58,** 1292–1306.

Ringo, J. L. (1995) Brevity of processing in a mnemonic task. *J. Neurophysiol.* **73,** 1712–1715.

Ringo, J. L. (1996) Stimulus specific adaptation in inferior temporal and medial temporal cortex of the monkey. *Behav. Brain. Res.* **76,** 191–197.

Ringo, J. L. and Doty, R. W. (1985) A macaque remembers pictures briefly viewed six months earlier. *Behav. Brain. Res.* **18,** 289–294.

Ringo, J. L., and Nowicka, A. (1996) Long term memory for visual images in the hippocampus and inferotemporal cortex. *Soc. Neurosci. Abstr.* **22,** 116.7.

Rolls, E. T. (1995) Learning mechanisms in the temporal lobe visual cortex. *Behav. Brain. Res.* **66,** 177–185.

Rolls, E. T., Cahusac, P. M. B., Feigenbaum, J. D. and Miyashita, Y. (1993) Responses of single neurons in the hippocampus of the macaque related to recognition memory. *Exp. Brain. Res.* **93,** 299–306.

Rolls, E. T., Miyashita, Y., Cahusac, P. M. B., Kesner, R. P., Niki, H., Feigenbaum, J. D. and Bach, L. (1989) Hippocampal neurons in the monkey with activity related to the place in which a stimulus is shown. *J. Neurosci.* **9,** 1835–1845.

Rolls, E. T. and O'Mara, S. M. (1995) View-responsive neurons in the primate hippocampal complex. *Hippocampus* **5,** 409–424.

Rolls, E. T., Perrett, D. I., Caan, A. W. and Wilson, F. A. W. (1982) Neuronal responses related to visual recognition. *Brain* **105,** 611–646.

Sakai, K. and Miyashita, Y. (1991) Neural organization for the long-term memory of paired associates. *Nature* **354,** 152–155.

Saleem, K. S. and Tanaka, K. (1996) Divergent projections from the anterior inferotemporal area TE to the perirhinal and entorhinal cortices in the macaque monkey. *J. Neurosci.* **16,** 4757–4775.

Schacter, D. L., Chiu, C. Y. P. and Ochsner, K. N. (1993) Implicit memory:a selective reveiw. *Annu. Rev. Neurosci.* **16,** 183–205.

Scoville, W. B. and Milner, B. (1957) Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* **20,** 11–21.

Sharp, K., Brindle, P. M., Brown, M. W. and Turner, G. M. (1993) Memory loss during pregnancy. *Br. J. Obstet. Gynaecol.* **100,** 209–215.

Singer, W. and Gray, C. M. (1995) Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.* **18,** 555–586.

Sobotka, S. and Ringo, J. L. (1993) Investigations of long-term recognition and association memory in unit responses from inferotemporal cortex. *Exp. Brain. Res.* **96,** 28–38.

Sobotka, S. and Ringo, J. L. (1994) Stimulus specific adaptation in excited but not in inhibited cells in inferotemporal cortex of macaque. *Brain. Res.* **646,** 95–99.

Sobotka, S. and Ringo, J. L. (1996) Mnemonic responses of single units recorded from monkey inferotemporal cortex, accessed via transcommissural versus direct pathways: a dissociation between unit activity and behavior. *J. Neurosci.* **16,** 4222–4230.

Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O. and Raichle, M. E. (1992) Activation of the hippocampus in normal humans: a functional anatomical study of memory. *Proc. Natl. Acad. Sci. USA* **89,** 1837–1841.

Squire, L. R. and Zola, S. M. (1996) Memory, memory impairment, and the medial temporal lobe. *Cold. Spring. Harb. Symp. Quant. Biol.* **61,** 185–195.

Steele, K. and Rawlins, J. N. P. (1993) The effects of hippocampectomy on performance by rats of a running recognition task using lists of non-spatial items. *Behav. Brain. Res.* **54,** 1–10.

Stewart, B. A., Schuster, C. M., Goodman, C. S. and Atwood, H. L. (1996) Homeostasis of synaptic transmission in *Drosophila* with genetically altered nerve terminal morphology. *J. Neurosci.* **16,** 3877–3886.

Suzuki, W. A. (1996a) The anatomy, physiology and functions of the perirhinal cortex. *Curr. Op. Neurobiol.* **6,** 179–186.

Suzuki, W. A. (1996b) Neuroanatomy of the monkey entorhinal, perirhinal and parahippocampal cortices: organization of cortical inputs and interconnections with amygdala and striatum. *Semin. Neurosci.* **8,** 3–12.

Suzuki, W. A., Miller, E. K. and Desimone, R. (1995) Object and place memory in the monkey entorhinal cortex. *Soc. Neurosci. Abstr.* **21,** 19.

Suzuki, W. A., Zola-Morgan, S., Squire, L. R. and Amaral, D. G. (1993) Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities. *J. Neurosci.* **13,** 2430–2451.

Tanaka, K. (1996) Inferotemporal cortex and object vision. *Annu. Rev. Neurosci.* **19,** 109–139.

Tang, Y. and Aigner, T. G. (1996) Muscarinic receptor blockade in perirhinal cortex impairs visual recognition memory in monkeys. *Soc. Neurosci. Abstr.* **22,** 443.9.

Thompson, R. F. and Spencer, W. A. (1966) Habituation: a model phenomenon for the study of neuronal substrates of behaviour. *Psychol. Rev.* **73,** 16–43.

Tollworthy, L. J., Brown, M. W., Surmon, D. and Wilcock, G. K. (1991) The amnesia of Alzheimer's disease: a specific impairment in memory for context. *Eur. J. Neurosci. Suppl.* **4,** 175.

Tulving, E. and Markowitsch, H. J. (1997) Memory beyond the hippocampus. *Curr. Op. Neurobiol.* **7,** 209–216.

Tulving, E. and Schacter, D. L. (1990) Priming and human memory systems. *Science* **247,** 301–306.

Ungerleider, L. G. and Haxby, J. V. (1994) 'What' and 'where' in the human brain. *Curr. Op. Neurobiol.* **4,** 157–165.

Vandenberghe, R., Dupont, P., Bormans, G., Mortelmans, L. and Orban, G. (1995) Blood flow in human anterior temporal cortex decreases with stimulus familiarity. *NeuroImage* **2,** 306–313.

Van Essen, D. C. and Gallant, J. L. (1994) Neural mechanisms of form and motion processing in the primate visual system. *Neuron* **13,** 1–10.

Van Hoesen, G. W. (1995) Anatomy of the medial temporal lobe. *Magnetic Resonance Imaging* **13,** 1047–1055.

Vankov, A., HerveMinvielle, A. and Sara, S. J. (1995) Response to novelty and its rapid habituation in locus coeruleus neurons of the freely exploring rat. *Eur. J. Neurosci.* **7,** 1180–1187.

Verfaellie, M. and Keane, M. M. (1997) The neural basis of aware and unaware forms of memory. *Semin. Neurol.* **17,** 153–161.

Vinogradova, O. S. (1975) Functional organisation of the limbic system in the process of registration of information: facts and hypotheses. In *The Hippocampus Volume 2: Neurophysiology and Behaviour*. pp. 3–67. Eds. R. L. Isaacson and K. H. Pribram. Plenum Press: London.

Vogels, R., Sary, G. and Orban, G. A. (1995) How task-related are the responses of inferior temporal neurons? *Vis. Neurosci.* **12,** 207–214.

Wan, H., Aggleton, J. P. and Brown, M. W. (1997a) Differential expression of c-fos produced by novel and familiar items or arrangements of items in the rat rhinal and hippocampal cortices. *Soc. Neurosci. Abstr.* **2317,** 623.12.

Wan, H., Aggleton, J. P., McCabe, B. J. and Brown, M. W. (1997b) Differential expression of the immediate early gene c-fos in rat hippocampus and perirhinal cortex in relation to recognition memory. *Internatl. Congr. Physiol. Sci.* **33,** 99.01.

Wan, H., Zhu, X. O., Crabtree, J. W., Aggleton, J. P., McCabe, B. J. and Brown, M. W. (1996) Mapping recognition memory: perirhinal and hippocampal neuronal expression of c-fos evoked by novel and familiar visual stimuli. *Soc. Neurosci. Abstr.* **22,** 443.7.

Warrington, E. K. (1975) The selective impairment of semantic memory. *Quart. J. exp. Psychol.* **27,** 635–657.

Wiener, S. I. (1996) Spatial, behavioral and sensory correlates of hippocampal CA1 complex spike cell activity: implications for information processing functions. *Progr. Neurobiol.* **49,** 335–361.

Wiig, K. A. and Bilkey, D. K. (1995) Lesions of rat perirhinal cortex exacerbate the memory deficit observed following damage to the fimbria-fornix. *Behav. Neurosci.* **109,** 620–630.

Wilson, F. A. W., Brown, M. W. and Riches, I. P. (1988) Neuronal activity in the inferomedial temporal cortex compared with that in the hippocampal formation. Implications for amnesia of medial temporal lobe origin. In *Cellular mechanisms of conditioning and behavioral plasticity*. pp. 313–328. Eds. C. D. Woody, D. L. Alkon, and J. L. McGaugh. Plenum Press: New York.

Wilson, F. A. W. and Goldman-Rakic, P. S. (1994) Viewing preferences of rhesus monkeys related to memory for complex pictures, colours and faces. *Behav. Brain. Res.* **60,** 79–89.

Wilson, F. A. W. and Rolls, E. T. (1990) Neuronal responses related to the novelty and familiarity of visual stimuli in the substantia innominata, diagonal band of Broca and the periventricular region of the primate basal forebrain. *Exp. Brain. Res.* **80,** 104–120.

Wilson, F. A. W. and Rolls, E. T. (1993) The effects of stimulus novelty and familiarity on neuronal activity in the amygdala of monkeys performing recognition memory tasks. *Exp. Brain. Res.* **93,** 367–382.

Wilson, F. A. W., Scalaidhe, S. P. O. and Goldman-Rakic, P. S. (1993) Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science* **260,** 1955–1958.

Wilson, F. A. W., Scalaidhe, S. P. O. and Goldman-Rakic, P. S. (1994) Functional synergism between putative γ-aminobutyrate-containing neurons and pyramidal neurons in prefrontal cortex. *Proc. Natl. Acad. Sci. USA* **91,** 4009–4013.

Xiang, J.-Z. and Brown, M. W. (1997a) Processing visual familiarity and recency information: neuronal interactions in area TE and rhinal cortex. *Brain. Res. Abstr.* **14,** 69.

Xiang, J.-Z. and Brown, M. W. (1997b) Neuronal encoding of the prior occurrence of visual stimuli in rhinal cortex and area TE of the monkey. *Brain. Res. Abstr.* **14,** 42.

Xiang, J.-Z., and Brown, M. W. (1998) Differential neuronal encoding of novelty and familiarity in the anterior medial temporal lobe. *Neuropharmacol.* in press.

Young, B. J., Otto, T., Fox, G. D. and Eichenbaum, H. (1997) Memory representation within the parahippocampal region. *J. Neurosci.* **17,** 5183–5195.

Zhu, X. O., Brown, M. W., and Aggleton, J. P. (1995a) Neuronal signalling of information important to visual recognition memory in rat rhinal and neighbouring cortices. *Eur. J. Neurosci.* **7,** 753–765.

Zhou, Y. D. and Fuster, J. M. (1996) Mnemonic neuronal activity in somatosensory cortex. *Proc. Natl. Acad. Sci. USA* **93,** 10533–10537.

Zhu, X. O. and Brown, M. W. (1995) Changes in neuronal activity related to the repetition and relative familiarity of visual stimuli in rhinal and adjacent cortex of the anaesthetised rat. *Brain. Res.* **689,** 101–110.

Zhu, X. O., Brown, M. W., McCabe, B. J., and Aggleton, J. P. (1995b) Effects of novelty or familiarity of visual stimuli on the expression of the immediate early gene c-fos in rat brain. *Neuroscience* **69,** 821–829.

Zhu, X. O., McCabe, B. J., Aggleton, J. P. and Brown, M. W. (1996) Mapping visual recognition memory through expression of the immediate early gene c-fos. *NeuroReport* **7,** 1871–1875.

Zhu, X. O., McCabe, B. J., Aggleton, J. P. and Brown, M. W. (1997) Differential activation of the hippocampus and perirhinal cortex by novel visual stimuli and a novel environment. *Neurosci. Lett.* **229,** 141–143.

Ziakopoulos, Z., Brown, M. W. and Bashir, Z. I. (1996) The induction of long-term depression of synpatic transmission in the perirhinal cortex *in vitro*. *Brain. Res. Abstr.* **13,** 74.

Ziakopoulos, Z., Brown, M. W., and Bashir, Z. I. (1998) Input-dependent short- and long- term synaptic plasticity in the rat perirhinal cortex *in vitro*. Submitted to *J. Neurosci.*