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 perirhinal 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 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...
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; Gaflan, 1996; Murray, 1996; Squire and Zola, 1996;}

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**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).
There have been radical reassessments 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 supplement 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).

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
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 definitions. 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 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; Suleem 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 neurons 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.

![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.](image-url)
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).

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 neurons 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., 1988; 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.

### 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 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 (Vandenbergh 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 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-
decrements do not vary consistently with the size of the stimulus, but this recency 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.

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 shorter than 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 3.1.1.1). 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). The neurones that signal recency for unfamiliar but not weakly to repeat presentations of these stimuli, and novelty neurones have been identified. The cells with these responses have been termed novelty neurones as they respond strongly to first presentations of novel or unfamiliar stimuli, 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-
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. 13. Responses of a monkey novelty neurone. Histograms are shown of the summed 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.](image)

![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.](image)
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 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.

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
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

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

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 perirhinal 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 (Magueire 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
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) 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., 1988, 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); (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 stimuli.

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 medio-dorsal 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
et al. repetition-sensitive neuronal responses are found in impairs delayed non-matching to sample tasks and provide adequately detailed signals to perirhinal cortex. 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).

Amongsst 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-
vior 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 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 possibilities it should be noted that there are many more neurones with short latencies in area TE than in perirhinal 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 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 then becomes specific to a whole cell.

![Fig. 20. Different mechanisms that might underlie repetition-sensitive response decrements.](image-url)
are familiar. Such additional processing could assist stimuli when they are novel compared to when they is likely to lead to additional processing of these sensitive responses to the first presentations of stim-

ones with repetition-sensitive responses. However, of that stimulus to be held in the activity of neur-

ones; it does not require the representation (perhaps in comparison to repetition-invariant 
ticipation 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 po-
tentials 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 recep-

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 re-
sponses themselves could form the representation of a new stimulus because the stimulus would generate different activity when it was subsequently encoun-
tered, even though it remained the same stimulus. It is difficult to imagine how perceptual stimulus con-

stancy 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 decre-

ment (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 neur-
ones with repetition-sensitive responses. However, the increased activity of neurones with repetition-
sensitive responses to the first presentations of stim-
uli 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 rep-

resentations of unfamiliar stimuli. However, the ad-

titional 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 synap-
tic connections. However, there does need to be a mechanism to determine whether a particular pat-

tern of activity has been encountered previously, i.e. whether a particular exemplar of a class (a particu-
lar face) has been encountered before: this is prec-
isely 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 neur-

onal assembly, though if information storage ca-
pacity is to be maximised, the proportion of synapses (and hence, probably, neurones) under-

going 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 counterba-

lancing increments to be very large. However, if re-
sponses averaged across all presented stimuli are considered, then the observed proportions of neur-
ones with net incremental responses on stimulus rep-

etition 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 popu-
lation of 1122 visually responsive neurones in an-
terior 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 mark-
edly 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.](image-url)
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. 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).

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 neverth-
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 attributable to the occurrence 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 changes 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).

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 of standard recognition memory tasks. However, 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, 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 potentials between parts of the system are necessary for the conscious registration, though certain patients with prefrontal damage appear to have 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 signalling 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
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.

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 inter-relationship 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 judgments 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


