Evidence concerning how neurons of the perirhinal cortex may effect familiarity discrimination

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Many studies indicate that recognition memory involves at least two separable processes, familiarity discrimination and recollection. Aspects of what is known of potential neuronal substrates of familiarity discrimination are reviewed. Lesion studies have established that familiarity discrimination for individual visual stimuli is effected by a system centred on the perirhinal cortex of the temporal lobe. The fundamental change that encodes prior occurrence of such stimuli appears to be a reduction in the response of neurons in anterior inferior temporal (including perirhinal) cortex when a stimulus is repeated. The neuronal responses rapidly signal the presence of a novel stimulus, and are evidence of long-lasting learning after a single exposure. Computational modelling indicates that a neuronal network based on such a change in responsiveness is potentially highly efficient in information theoretic terms. Processes that occur in long-term depression within the perirhinal cortex provide candidate synaptic plastic mechanisms for that underlying the change, but such linkage remains to be experimentally established.

Keywords: recognition memory; familiarity discrimination; medial temporal lobe; perirhinal cortex; long-term depression; computational modelling

1. EVIDENCE FOR THE INVOLVEMENT OF THE PERIRHINAL CORTEX IN RECOGNITION MEMORY

Anyone who has known a friend or relative in the early stages of Alzheimer’s disease will be aware that one of the distressing manifestations of the condition is the constant repetition of questions and stories by the sufferer. In registering these repetitions the normal observer is using a mechanism that has been impaired in the disease sufferer. In the normal person, the ability to judge what is novel and what is familiar, what has occurred recently and what has never been encountered before, is commonplace and usually effortless. Such judgements of prior occurrence are the central process of recognition memory (Mandler 2001). Recent research has identified what appears to be at least part of the neuronal mechanisms underlying familiarity discrimination (Brown & Xiang 1998; Brown & Aggleton 2001).

This research has indicated a central role in familiarity discrimination for changes in neuronal responses in the perirhinal cortex of the temporal lobe when visual stimuli are seen more than once. The perirhinal cortex (classically, Brodmann’s area 35, but more recently redefined to include both areas 35 and 36; Amaral et al. 1987; Burwell et al. 1995) is a strip of cortex found anteriorly and inferiorly in the medial temporal lobe of primates. It lies lateral to the hippocampal formation to which it provides many inputs (Burwell et al. 1995; Suzuki 1996; Burwell & Amaral 1998; Lavenex & Amaral 2000). It also lies medial and anterior to area TE of von Bonin and Bailey (1947), a high-order visual processing area. The perirhinal cortex receives information from widespread areas of the cerebral cortex, including areas involved in visual (notably area TE in monkeys), auditory, somatosensory and olfactory processing, as well as return pathways from the hippocampal formation (Burwell et al. 1995; Suzuki 1996; Burwell & Amaral 1998; Lavenex & Amaral 2000). It is similarly placed with broadly equivalent connections in the rodent (Witter et al. 1989, 2000; Burwell et al. 1995; Shi & Cassell 1997). Thus, it is a multimodal area at the top end of the hierarchy of sensory processing areas (Felleman & Van Essen 1991; Lavenex & Amaral 2000; Witter et al. 2000). Indeed, one of its functions has been suggested to be a role in the perception of objects as entities in themselves (Buckley & Gaffan 1998a; Murray & Bussey 1999). Such regions, where the sensory processing streams provide information concerning stimulus identity, are well placed for involvement in processes to do with memory for the past history of the stimulus. Indeed, there is evidence that the perirhinal cortex is involved in paired associate learning, and aversive and appetitive conditioning as well as in recognition memory (Murray et al. 1993, 1998; Corodimas & LeDoux 1995; Higuchi & Miyashita 1996; Suzuki 1996; Buckley & Gaffan 1998b; Murray & Bussey 1999). It is with the functions of the perirhinal cortex in the familiarity discrimination component of recognition memory that this review is concerned. The potential contributions of the hippocampal system to spatial and recollective aspects of recognition memory have been reviewed elsewhere (Aggleton & Brown 1999; Brown & Aggleton 2001).

The crucial role of the perirhinal cortex in visual recog-
nition memory has been established by ablation studies, chiefly in the monkey (Zola-Morgan et al. 1989; Gaffan & Murray 1992; Meunier et al. 1993, 1996; Suzuki et al. 1993), but also in the rat (Otto & Eichenbaum 1992; Mumphry & Pinel 1994; Ennaceur et al. 1996). Thus, there is gross impairment of tasks, particularly visual delayed matching or non-matching to sample tasks, that depend for their successful performance upon judgement of the prior occurrence of infrequently repeated individual items (Murray 1996; Murray & Bussey 1999; Brown & Aggleton 2001). Although the degree of impairment following hippocampal lesions is still in dispute, all groups agree that the impairment following perirhinal lesions is far greater than that following either hippocampal, amygdalar or prefrontal lesions (Aggleton et al. 1986; Mumbry et al. 1992, 1995; Zola-Morgan & Squire 1993; Zola-Morgan et al. 1994; Alvarez et al. 1995; Murray 1996; Meunier et al. 1997; Murray & Mishkin 1998; Aggleton & Brown 1999; Seanson-Held et al. 1999; Murray & Bussey 1999; Zola et al. 2000; Baxter & Murray 2001; Brown & Aggleton 2001). By contrast, if task complexity is increased, particularly if a judgement dependent on spatial memory is required, then hippocampal lesions produce major impairments (O’Keefe & Nadel 1978; Morris et al. 1982; Aggleton et al. 1986; Eichenbaum et al. 1994, 1996; Gaffan 1994; Liu & Bilkey 1998; Murray et al. 1998; Aggleton & Brown 1999; Brown & Aggleton 2001). In summary, there is strong evidence from primate and rat ablation studies that the perirhinal cortex is a nodal point of a system that is concerned with judgements concerning the prior occurrence of individual visual items.

2. EVIDENCE CONCERNING CANDIDATE NEURONAL MECHANISMS OF FAMILIARITY DISCRIMINATION

Given the crucial involvement of the perirhinal cortex in familiarity discrimination, are there candidate neuronal mechanisms that could explain the behavioural results? Any mechanism must be capable of explaining learning that occurs in a single exposure, must be long-lasting, and must have high capacity, in particular the ability to remember the prior occurrence of potentially large numbers of complex stimuli at the same time. The mechanism should be manifest in both trained and untrained situations because familiarity discrimination itself (and correspondingly its counterpart process, novelty detection) should not need to be learned. It must also occur for stimuli encountered by the subject for the first and second times, and not merely for stimuli that are being frequently encountered and hence are highly familiar. Evidence for potential mechanisms comes from studies of the response characteristics of perirhinal neurons. Indeed, more than one potential substrate (correlate of relative familiarity) has been discovered by recording the responses of neurons during the performance of recognition memory tasks by monkeys (Gross et al. 1979; Fuster & Jervey 1981; Brown et al. 1987; Miller & Desimone 1994; Xiang & Brown 1997; Brown & Xiang 1998). These putative candidate substrates are response differences between match and mismatch trials, delay activity, response reductions or response increments on stimulus repetition, and synchronized neuronal firing; see figure 1. However, of these mechanisms, only one, response reductions on stimulus repetition, has so far been demonstrated to have the necessary properties and to occur in a variety of behavioural situations (Brown & Xiang 1998; Brown & Aggleton 2001). The first discovered difference in responsiveness of inferior temporal neurons in a recognition memory task was that between responses on match and mismatch trials while monkeys performed a delayed matching task (Gross et al. 1979). Such differences have been commonly reported in tasks where a match/mismatch judgement must be made to a single target stimulus on each trial and the target stimuli are selected from a small number of frequently repeating items (e.g. Gross et al. 1979; Mikami & Kubota 1980; Brown 1982; Riches et al. 1991; Nakamura & Kubota 1995; Young et al. 1997). However, such differences do not signal whether a particular stimulus is novel or familiar, merely that the trial type is match or non-match (Riches et al. 1991). Accordingly, such differences cannot provide a substrate of general familiarity discrimination (Riches et al. 1991; Brown & Xiang 1998; Brown & Aggleton 2001).

Figure 1. Schematic representation of types of neuronal activity change found in perirhinal cortex during performance of familiarity discrimination tasks. The size of letter represents the magnitude of response to an individual stimulus. A change in size denotes a change in response on repetition. (a) Match/mismatch response differences. Neuronal responses may be larger or smaller on match compared with non-match trials in tasks where the repetition of one target stimulus must be judged on each trial and small stimulus sets are used. (b) Delay activity. The sustained activity between the initial presentation of a stimulus and its repetition is represented by the arrows. (c) Response enhancement. When an animal is taught that responding to the repetition of a target stimulus leads to reward whereas other repeated stimuli do not, responses to the repetition of the target stimulus may be enhanced. (d) Response reductions. The response when a stimulus has been encountered before is reduced compared with its first presentation. In fact, there is more than one type of such response reductions, with there being three different, commonly found patterns of neuronal response on stimulus repetition (Xiang & Brown 1998). These different patterns of response imply that there is more than one underlying type of synaptic plasticity responsible for the response changes (Fahy et al. 1993; Brown & Xiang 1998; Xiang & Brown 1998). (e) Simultaneous firing. The approximate coincidence of the spikes of two individual neurons could carry information concerning the familiarity of a stimulus, for example if such coincidences varied between the first and second presentations of the stimulus.
The next discovered potential mechanism, delay activity, is a persistent change in neuronal firing that occurs in the delay interval after the presentation of a stimulus in the acquisition phase of a memory task, and lasts until the occurrence of the same or a different stimulus in the subsequent behavioral choice/decision phase (Fuster & Jervey 1981; Riches et al. 1991; Miller et al. 1993; Colombo & Gross 1994; Miller & Desimone 1994; Desimone 1996). Delay activity has not been demonstrated under conditions that require long-term rather than short-term memory—i.e. where more than one stimulus must be remembered at a time—or when the eventual occurrence of the choice phase of a task is unpredictable: i.e. may not occur until after a delay of many minutes filled with other activities (Desimone 1996; Brown & Xiang 1998; Brown & Aggleton 2001). Thus, delay activity has not been shown to persist over long periods of time, nor has it been shown that such a system has a high information storage capacity. It may rather represent a substrate of an attentive or short-term memory mechanism that could contribute to short-term recognition memory (Desimone 1996; Brown & Xiang 1998).

Similarly, responses that increment on repetition, i.e. are larger to a repeated stimulus than to one occurring for the first time, have only been observed when an animal has been trained to discriminate between a specific stimulus that, when repeated, signals the availability of reward and other stimuli that, when repeated, do not signal the availability of reward (Miller & Desimone 1994). Again, these response increments have only been demonstrated under conditions where only one stimulus need be held in the mind at a time. In such situations, as already indicated above, short-term memory and attentive mechanisms provide alternative means of solving the task (Brown & Xiang 1998; Brown & Aggleton 2001). Furthermore, response increments have not been shown to occur when time delays are long.

By contrast, response reductions on stimulus repetition have been found under a variety of conditions (Brown et al. 1987; Riches et al. 1991; Eskandar et al. 1992; Fahy et al. 1993; Li et al. 1993; Miller et al. 1993; Sobotka & Ringo 1993; Miller & Desimone 1994; Zhu et al. 1995; Xiang & Brown 1998b). An example is shown in figure 2. The detailed properties of such neuronal response reductions on stimulus repetition have been extensively reviewed elsewhere (Brown 1996; Desimone 1996; Eichenbaum et al. 1996; Ringo 1996; Brown & Xiang 1998; Suzuki & Eichenbaum 2000; Brown & Aggleton 2001) and so will be only briefly presented here. In monkeys they have been shown to occur under closely controlled conditions and are not explicable by changes in alertness, attention, motivation, eye movements or other behavioral changes (Brown & Xiang 1998). Such response reductions occur after a single exposure to an initially novel stimulus even if the ensuing delay before the recurrence of the stimulus is 24 h or more (Fahy et al. 1993; Xiang & Brown 1998b; e.g. figure 3). Critically, these reductions are found even when many stimuli must be remembered simultaneously and when intervals between repetitions are filled with presentations of other stimuli to which attention is being paid, so that long-term memory mechanisms are essential to task performance (Xiang & Brown 1998b). No other type of response change capable of signally information adequate to explain recognition memory processes has been reported in perirhinal cortex under conditions that necessitate the use of long-term memory. The high capacity of the system is demonstrated by the finding of such reductions for repetitions of new stimuli even when an animal has already seen many hundreds of such items (Xiang & Brown 1998b). Moreover, neuronal response reductions are found whether or not an animal is using the stimulus repetitions to obtain reward, and in rats as well as monkeys (Riches et al. 1991; Fahy et al. 1993; Zhu et al. 1995; Brown & Xiang 1998). As response reductions occur even in situations where an animal has received no specific training on a recognition memory task, they must be endogenous rather than induced by training. Personal experience indicates that any general familiarity discrimination mechanism needs to be able operate automatically and without direct or immediate feedback from reward systems.

Far less is known concerning the potential involvement

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**Figure 2.** Example response reduction on stimulus repetition. Illustrated are the cumulated peristimulus-time histograms and rasters showing the times of occurrence of individual action potentials for trials on each of which one of 10 different unfamiliar pictures was presented for either the first (a) or the second (b) time. Note the response reduction with stimulus repetition. The neuron’s activity was recorded from perirhinal cortex while pictures were presented to a monkey performing a serial recognition memory task in which juice rewards were obtained for left-sided presses for first presentations and right-sided presses for repeat presentations. One picture appeared on each trial and the types of trial were pseudorandomly ordered so that the occurrence of first and repeat presentations were not predictable by the monkey. Control trials (see Fahy et al. 1993) established that the response reduction was not explicable either by the animal’s behavioural responses or by changes in eye movements; all correct trials were rewarded. (Reproduced with permission from Fahy et al. (1993).)
of synchronized neuronal firing in familiarity discrimination. It has been hypothesized that such coincident or near coincident firing may carry important information in other systems (Abeles 1982; Singer & Gray 1995). Significant interactions have been revealed by cross-correlating the simultaneously recorded activity of pairs of neurons in monkeys (Gawne & Richmond 1993; Xiang & Brown 1997; Brown & Xiang 1998; Erickson et al. 2001). These interactions suggest that information of potential importance to recognition memory is being carried by relationships between the activities of perirhinal neurons. However, the incidence of simultaneous (within 6 ms) action potentials produced by simultaneously recorded pairs of neurons is very low. Moreover, more crucially, the timing of the occurrence of such simultaneous firing is typically late rather than early after stimulus onset, and is usually more closely related to the occurrence of an animal’s behavioural response than to the stimulus onset itself (Brown 2000; J.-Z. Xiang and M. W. Brown, unpublished observations). Accordingly, the information carried by such firing provides a much slower signal than is provided by the change in firing rate of the individual neurons.

3. EVIDENCE FOR SYNAPTIC CHANGES OCCURRING IN PERIRHINAL CORTEX

Although the ablation studies establish the importance of perirhinal cortex for familiarity discrimination, and the recording studies establish that there are neurons within this cortex whose response reductions on stimulus repetition signal the type of information that is required to judge prior occurrence for individual stimuli, none of the evidence reviewed so far establishes where the synaptic changes that underlie the neuronal response changes may first be generated. However, important evidence is provided by the speed and incidence of response reductions that survive over long delays between the first and subsequent occurrence of a stimulus. Although in monkeys neuronal response reductions are found more posteriorly, in earlier stages of the visual processing stream, these reductions do not survive more than some seconds or when more than a very few other stimuli are shown before a particular stimulus is repeated (Baylis & Rolls 1987; Maunsell et al. 1991; Miller et al. 1991; Vogels et al. 1995). Correspondingly, such response reductions cannot explain those found in anterior area TE and perirhinal cortex, that survive many intervening stimulus presentations and delay intervals of many hours (Xiang & Brown 1998b). Responses are reduced with stimulus repetition for ca. 25% of all recorded neurons in anterior TE, perirhinal cortex, and entorhinal cortex (Miller et al. 1993; Xiang & Brown 1998b). For over 50% of the neurons whose responses change on stimulus repetition, such reductions are found even after a 24 h delay, the incidence of such long memory spans being highest in perirhinal cortex (Xiang & Brown 1998b). Ablation of entorhinal cortex in monkeys produces only a transient impairment of delayed non-matching to sample (Meunier et al. 1993; Leonard et al. 1995), so that the critical change cannot be dependent on entorhinal cortex. Thus, the critical response changes must be first generated in anterior TE and perirhinal cortex, or be fed back to these areas from further on in the processing stream.

A remarkable property of the response reductions is the speed with which they signal prior occurrence. Latency measures across all the neurons displaying response reductions in anterior area TE in the monkey have established that within 90 ms of stimulus onset there is a significant difference in the population’s activity, dependent on whether the stimulus is novel or previously seen (Xiang & Brown 1998b). In many neurons the latency of the response change is the same (to within the experimental error of 10–20 ms) as the latency of the neuron’s visual response (Fahy et al. 1993; Miller et al. 1993; Xiang & Brown 1998b; e.g. figure 4). The speed of this change means that the initial change in response cannot be being generated as a result of feedback from areas such as the hippocampus or prefrontal cortex. Recordings in the monkey hippocampus and prefrontal cortex support this view. Thus, the incidence of response changes on the repetition of infrequently encountered individual stimuli in the hippocampus is less than 1% (Rolls et al. 1989, 1993; Riches et al. 1991; Xiang & Brown 1998b). As for inferior temporal cortex, it is important to note that other hippocampal changes have been shown in rats as well as monkeys for highly familiar, frequently repeated stimuli where the occurrence of only one stimulus need be remembered at a time (Riches et al. 1991; Colombo & Gross 1994; Eichenbaum et al. 1996; Hampson et al. 1999; Wiebe & Staubli 1999). However, it has been shown in monkeys that these responses do not reliably signal information about the familiarity or novelty of infrequently encountered individual stimuli (Riches et al. 1991), and so cannot form a basis for general familiarity discrimination. Moreover, the latencies of the changes in monkey hippocampal neuronal responses to infrequently repeated stimuli are long compared with those in anterior TE and perirhinal cortex (Rolls et al. 1993; Xiang & Brown 1998b). The incidence of response changes on stimulus repetition is much higher in certain parts of monkey prefrontal cortex, but again the latencies of these

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Figure 3. Population mean span. Illustrated are the population mean (+s.e.m.) responses of 43 neurons recorded in anterior inferior temporal and entorhinal cortex to the first presentations of novel stimuli (N) and their repetition after varying numbers of intervening trials on which other stimuli were shown. The final bar (24 h) represents the response to stimuli not seen since the previous day. An asterisk implies a significant reduction in response compared to N. Ordinate: mean firing rate in 0.5 s after stimulus onset normalized relative to prestimulus activity (=1). The data were obtained while monkeys performed a serial recognition memory task; for details see Xiang & Brown (1998b).

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changes are much longer than in temporal cortex (Miller et al. 1996; Xiang & Brown 1998a; Miller 1999). Again, although changes in neuronal responses on stimulus repetition have been described in subcortical regions, such as the monkey basal forebrain nucleus (Rolls et al. 1982; Wilson & Rolls 1990), these changes occur with a longer latency than those in anterior inferior temporal and perirhinal cortex (Brown & Xiang 1998). Additionally, it seems implausible that the relatively small number of neurons involved in such subcortical areas could have the information-processing capacity to themselves first discriminate amongst hundreds of complex visual stimuli: such capacity is a prerequisite for the judgement of the prior occurrence of such stimuli. (Indeed, it is important to note that there is evidence of such capacity for area TE and perirhinal cortex.) Thus, there is no evidence that the initial response reductions on stimulus repetition are fed back to anterior TE and perirhinal cortex from other brain regions.

Because, as indicated above, there is no evidence that the response reductions can arise as a result of feed-forward signals from more posterior visual areas, at least the initial reductions in response must be being generated in anterior TE and/or perirhinal cortex. For visual processing, ablation experiments cannot easily decide between anterior TE and perirhinal cortex as ablating TE de-aferents perirhinal cortex. The response changes occur at shorter latency in anterior TE than in perirhinal cortex, but the memory spans of the response changes tend to be longer in perirhinal cortex than anterior TE. Thus, there is good evidence from the monkey that response changes are generated within the region encompassing anterior TE and perirhinal cortex. Moreover, the recording data provide some evidence in favour of changes being generated in both anterior TE and perirhinal cortex. Alongside this, the available evidence from lesion studies provides the best evidence for the critical region being the perirhinal cortex, but without excluding the involvement of area TE.

4. EVIDENCE FROM COMPUTATIONAL MODELLING FOR THE FEASIBILITY OF USING NEURONAL RESPONSE REDUCTIONS AS A BASIS FOR FAMILIARITY DISCRIMINATION

Assuming that neuronal response reductions in perirhinal cortex provide the substrate for familiarity discrimination, could such a system explain human capabilities? Human abilities are very impressive in the laboratory as well as in everyday life, and include speed, accuracy and huge capacity (Standing 1973; Seeck et al. 1997; Hintzman et al. 1998). Recent computational modelling based on the observed properties of perirhinal response reductions has established the plausibility of such changes as a substrate (Bogacz et al. 1999, 2001). The basic premise of the modelling is that individual synapses undergo a plastic, use-dependent change upon their initial activation by a stimulus. This synaptic change stores the prior occurrence of the individual stimulus. In the models, the necessary synaptic changes could be effected by processes determined at individual synapses, such as those that are utilized by long-term potentiation or LTD (Ito 1989; Bliss & Collingridge 1993; Linden 1994; Bear & Abraham 1996; Kemp & Bashir 2001; figure 5). On this basis, such models can be made to operate using biologically plausible learning rules and connectivity.

Theoretical calculations and simulations indicate that under optimal conditions the capacity of such models to discriminate the familiarity of stimuli is potentially very
and on whether the types of responses simulated in the model mirror those observed in the real brain (Bogacz 2001; Bogacz et al. 2001). Simulations of different models have recently revealed that the capacity of a model depends crucially on the degree of correlation between the responses of the individual neurons to the incoming stimuli; see figure 6. Clearly, if all the neurons responded in the same way to each different stimulus, the capacity of the whole model could be no more than the capacity of one of the individual component neurons, and would be correspondingly very low. It is therefore essential that the mechanisms within the network act to de-correlate responses so that individual neurons can make independent calculations of the familiarity of a stimulus. All previously published computational networks for discriminating familiarity have used synaptic enhancement as the fundamental synaptic change (Bogacz et al. 1999, 2001; Sohal & Hasselmo 2000; Bogacz 2001; Norman & O’Reilly 2001). (The models also employ some form of synaptic weakening of relatively unstimulated synapses to maintain a constant overall level of network excitability.) In fact, within perirhinal cortex, response increments on stimulus repetition are unusual and unimpressive in magnitude (Li et al. 1993; Xiang & Brown 1998b). Such response increments are an essential feature of models that combine feature detection (learning a representation) with familiarity discrimination, as the increased responses are designed to signal (represent) the presence of a particular stimulus (Sohal & Hasselmo 2000; Norman & O’Reilly 2001). However, if the representation has not yet been learnt and hence feature extraction is incomplete, the responses of the network’s neurons are necessarily not independent (and hence are correlated). For this reason, simulations indicate that these models have a capacity that is greatly reduced compared with that theoretically possible when responses are uncorrelated (Bogacz 2001).

In the published Bogacz et al. (2001) model, the fundamental synaptic change was one of enhancement on stimulus repetition, with response increments being prevented by network connections that increased inhibition for repeated stimuli. This architecture was chosen as it used learning rules based on those that have been widely established in the real brain and resulted in neuronal responses that mimicked those observed in the real perirhinal cortex. Nevertheless, it remains necessary for correlations between responses to be very low ($r < 0.05$) for a high capacity to be achieved by this model (Bogacz 2001; see figure 6). However, if the primary synaptic change is decremental rather than incremental, the neuronal responses tend to become less rather than more correlated as a result of the synaptic change that stores the occurrence. Correspondingly, the capacity of the network is far less affected by initial correlations between the responses of its neurons (Bogacz 2001; see figure 6). The reason for this difference may be understood in principle from the following considerations. Fundamentally, if an incremental change is used the network moves in the direction of feature extraction, i.e. neurons responsive to a particular stimulus feature tend to become more responsive to it when it recurs in the future, while (through compensatory mechanisms) originally less responsive neurons become even less responsive. Such an outcome is favourable to building a representation by feature extraction. However,
as shown by simulations, a familiarity discrimination network is far more efficient if feature extraction has already been completed and the responses of its component neurons are de-correlated, i.e. essentially, the neurons of the network act to emphasize what is particular rather than what is commonplace in a stimulus (Bogacz 2001). Thus, modelling provides an explanation for the observed direction of response change (reductions rather than increments) on stimulus repetition in perirhinal cortex. The counterpart of this direction of change is that for a novel stimulus the system generates a large signal which can potentially be used to allow further processing of the novel stimulus elsewhere (possibly including the setting up of a new representation outside the familiarity discrimination network).

Thus, computational modelling demonstrates that neuronal response reductions in perirhinal cortex could potentially be used as a basis for familiarity discrimination: the necessary speed, accuracy and capacity are theoretically achievable. The models rely on activity-dependent, synapse-specific plasticity. Plastic mechanisms that do not produce changes that are localized to specific synapses would result in a catastrophic loss of capacity. Moreover, as measurements in perirhinal cortex indicate that there are many more excitatory than inhibitory synapses (Thompson et al. 2001), a high capacity can only be achieved by having modifiable excitatory synapses. Both long-term potentiation and LTD rely on activity-dependent, synapse-specific plastic mechanisms. The above-presented arguments based on computational modelling indicate that employing as the primary plastic mechanism one that reduces synaptic efficacy is likely to prove more efficient than employing one that enhances efficacy. This raises the question as to whether there is evidence for appropriate decremental candidate plastic mechanisms in perirhinal cortex.

5. EVIDENCE FOR DECREMENTAL SYNAPTIC PLASTIC CHANGES IN RAT PERIRHINAL CORTICAL SLICES

Activity-dependent LTD of synaptic transmission has been shown to occur in many different regions of the central nervous system (Linden 1994; Bear & Abraham 1996; Kemp & Bashir 2001), and to utilize a variety of different mechanisms of induction and expression. In this section mechanisms of LTD that have recently been identified in adult rat perirhinal cortex in vitro will be reviewed.

(a) Glutamate receptor-dependent LTD

Most fast synaptic communication within the central nervous system occurs via the release of the neurotransmitter glutamate acting on a variety of different receptors. Thus, the modulation of glutamatergic transmission is an appropriate starting point in addressing the mechanisms that may underlie the changes in signalling that occur during learning and memory. Glutamate receptors consist of ionotropic (AMPA, NMDA and kainate, named after their pharmacological agonists) and mGlu subgroups. Synaptic plasticity induced by various means and in different regions of the central nervous system is often dependent on the synaptic activation of NMDA receptors. Consistent with this, NMDA receptor activation in rat perirhinal cortical slices leads to the induction of synaptic plastic changes, either long-term potentiation or LTD according to the pattern of stimulation given (Bilkey 1996; Ziakopoulos et al. 1999). Interestingly, however, mGlu receptors play a vital role in perirhinal LTD.
perirhinal cortex (McCaffery et al. produced LTD of excitatory synaptic transmission in LTD. The G in a circle represents ‘signal, it does not block the induction of LTD because there is still a sufficient rise in calcium ion concentration to induce LTD. The G in a circle represents ‘G protein’.

and it is findings relating to the role of these receptors that will now be discussed. These receptors are G-protein coupled and consist of three classes: mGlu groups I, II and III based on their pharmacological profile, sequence homology and signalling cascades. Group I receptors are coupled to inositol phospholipid hydrolysis, while group II and group III receptors are negatively coupled to adenylyl cyclase (Conn & Pin 1997; De Blasi et al. 2001).

Activation of mGlu receptors by bath application of appropriate pharmacological agonists has been examined in vitro to test whether these receptors have a potential role in the induction of lasting synaptic depression (McCaffery et al. 1999). Agonists of group I (3,5-dihydroxyphenylglycine) and group II mGlu receptors ((2S,2’R,3’R)-2-(2’,3’-dicarboxycyclopropyl)glycine) each produced LTD of excitatory synaptic transmission in perirhinal cortex (McCaffery et al. 1999). The application of mGlu receptor agonists has also been shown to result in LTD in other regions of the central nervous system, including subfield CA1 of the hippocampus (Fitzjohn et al. 1999; Overstreet et al. 1997; Palmer et al. 1997; Schnabel et al. 1999; Huber et al. 2000), dentate gyrus (O’Mara et al. 1995; Huang et al. 1999) and prefrontal cortex (Otani et al. 1999). In CA1 it is most probable that this form of LTD relies on activation of the mGlu5 subtype receptor, because LTD is also induced by the selective mGlu5 agonist CHPG (Palmer et al. 1997). At present, however, it is not known which of the group I subtypes (mGlu1/5) or which of the group II subtypes (mGlu2/3) are involved in mGlu receptor-induced LTD in perirhinal cortex.

(b) Activity-dependent LTD

As pharmacological activation of mGlu receptors produced LTD, it was probable that synapse-specific, activity-dependent LTD would also involve activation of these receptors. Indeed, in perirhinal cortex in vitro, group I and group II mGlu receptor activation as well as NMDA receptor activation was not required for LTD when this was induced by LFS (1 Hz stimulation; 200 stimuli) in neurons voltage clamped at −70 mV (Cho et al. 2000). By contrast, group II mGlu receptor activation was not required for LTD when this was induced by LFS paired with depolarization to −40 mV. One explanation for the voltage dependence of the involvement of group II mGlu receptors in LTD is that a synergy exists between group I and group II mGlu receptors (Schoepp et al. 1996; Mistry et al. 1998). This synergy can enhance the calcium release from intracellular stores that normally results from activation of group I mGlu receptors (Cho et al. 2000). Thus, when calcium influx resulting from NMDA receptor activation is limited, e.g. at resting membrane potentials (−70 mV), the mGlu receptor synergy may provide the extra calcium.

Figure 7. The role of glutamate (glu) receptors in the induction of LTD (based on data from rat perirhinal slices). (a) At −70 mV calcium ion influx through NMDA receptor channels is minimized by a voltage-dependent magnesium block. Group II mGlu receptors (mGlu2/3) enhance the calcium mobilization due to group I mGlu receptor (mGlu1/5) activation by a mechanism that may rely on mGlu1/5 dephosphorylation. The combination of NMDA and mGlu receptor-mediated calcium mobilization results in the induction of LTD. Blocking group II mGlu receptors prevents the synergy between mGlu receptors and reduces the calcium signal. This prevents the induction of LTD. (b) At −40 mV calcium ion influx through NMDA receptor channels is increased due to the removal of the voltage-dependent magnesium block. Under these conditions, whilst blocking group II mGlu receptor activation with EGLU ((S)-alpha-ethylglutamate) reduces the mGlu-dependent calcium signal, it does not block the induction of LTD because there is still a sufficient rise in calcium ion concentration to induce LTD. The G in a circle represents ‘G protein’.
required for LTD. However, the mGlu receptor synergy may be unnecessary for LTD when calcium influx from NMDA receptor activation is enhanced, as it is at depolarized membrane potentials (−40 mV) (see figure 7).

Thus, the mechanisms of induction of LTD discovered in perirhinal cortical slices are interesting for a number of reasons. First, there is only one other report of activity-dependent LTD that requires activation of both NMDA and mGlu receptors; in the great majority of forms of LTD so far investigated, induction of LTD is dependent either on NMDA receptors alone or on mGlu receptors alone (Kemp & Bashir 2001). This may mean that the mechanisms of LTD that pertain in perirhinal cortex may be restricted to a specialized subset of brain regions. Second, differences in experimental conditions in perirhinal cortex can dramatically alter the mechanisms underlying the induction of LTD. Whilst this has not yet been tested in other brain regions, such a property may provide explanation for some of the discrepancies between the reported involvement or lack of involvement of different mGlu receptors in LTD both in vitro and in vivo (Kemp & Bashir 2001). Given the dependency on a neuron’s membrane potential of mGlu receptor involvement, it will be interesting to investigate in vitro whether fluctuations in membrane potential that occur under physiological conditions in vivo—such as during theta or gamma oscillations—will have similar determining effects on the involvement of group II mGlu receptors in LTD. Studies to date in vitro have utilized relatively prolonged stimulation (lasting minutes) in order to experimentally LTD. However, the decrement that occurs in vivo in monkeys with stimulus repetition is observable even when a stimulus is repeated within ca. 1 s (Miller et al. 1993). Thus, it will be important to test whether neuronal activity of the type that occurs in vivo can also induce LTD in vitro, and whether such differences in induction protocols alter the underlying mechanisms employed. Additionally, if the involvement of mGlu receptor-dependent LTD mechanisms in recognition memory is to be established, it will be crucial to test the role of mGlu receptors in tasks requiring such memory and in the neuronal response decrements that occur in these tasks.

(c) Acetylcholine receptor-dependent LTD

Although the majority of studies in a variety of regions of the central nervous system show that LTD can be blocked by either NMDA or mGlu receptor antagonists, there are some studies which show a requirement for activation of other, or additional, receptors (De Mendonça et al. 1997; Katsuki et al. 1997; Kemp & Bashir 1997; Berretta & Cherubini 1998; Kirkwood et al. 1999; Otani et al. 1999). Given the evidence suggesting that acetylcholine may play a crucial role in learning and memory (e.g. Drachman & Leavitt 1974; Everitt & Robbins 1997; Tang et al. 1997; Easton et al. 2001), the effects of acetylcholine receptor activation have been sought in perirhinal cortex in vitro. Application of the cholinergic agonist CCh resulted in a depression of evoked synaptic transmission that persisted long after agonist washout (Massey et al. 2001). The induction of this form of LTD was prevented by the selective M1 receptor antagonist pirenzepine. Furthermore, CCh–LTD required neither coactivation of NMDA receptors nor evoked synaptic transmission for its induction (see figure 8). These results indicate that appropriate activation of acetylcholine receptors can result in the induction of LTD (Massey et al. 2001). Preliminary in vitro data (K. Cho, M. W. Brown and Z. I. Bashir, unpublished observations) also indicate that synapse-specific, activity-dependent LTD is prevented by pharmacological blockade of muscarinic receptors by scopolamine. Scopolamine has been shown previously to impair object recognition memory in rats, monkeys and humans.

Figure 8. Muscarinic receptor-mediated LTD in rat perirhinal cortical slices. (a) The application of CCh results in long-lasting depression (CCh–LTD) of synaptic transmission that is (b) blocked by the M1 muscarinic receptor antagonist pirenzepine. The transient depression is, however, unaffected by M1 antagonism. (c) The NMDA receptor antagonist AP5 does not prevent CCh–LTD. (d) The induction of CCh–LTD does not require synaptic stimulation. Stimulation through one electrode (on the temporal side) was discontinued during and for 40 min after application of CCh; however, LTD still occurred in this input. Black circles, temporal; white circles, entorhinal; fEPSP, field excitatory post-synaptic potential.
Identification biologically realistic parameters that will perform familiar responses on stimulus repetition. Computational modeling has established the plausibility of such a neuronal substrate because it is possible to construct networks using biologically realistic parameters that will perform familiarity discrimination with the required high speed and high capacity. Moreover, candidate mechanisms have been identified, such as that resulting in LTD, which could produce synapse-specific reductions in neuronal responsiveness in perirhinal cortex.

Nevertheless, the presence of LTD in rat perirhinal slices studied in vitro does not establish that all mechanisms are used to effect familiarity discrimination in vivo. It is a necessary, though not a sufficient, condition that pharmacological or molecular genetic manipulations have effects that are consistent upon perirhinal LTD mechanisms, perirhinal neuronal response reductions on stimulus repetition, and familiarity discrimination as measured behaviourally, if the hypotheses presented are valid. Studies are now needed to test the consistency of the effects of such manipulations across the different levels of analysis, thereby seeking to establish some commonality of mechanisms, if the neuronal substrates of familiarity discrimination are to be further elucidated.

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**GLOSSARY**

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxalone propionic acid
CCh: carbachol
LFS: low-frequency stimulation
LTD: long-term depression
mGlu: metabotropic glutamate
NMDA: N-methyl-D-aspartate