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Review

# Object recognition memory: Neurobiological mechanisms of encoding, consolidation and retrieval

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ABSTRACT

Tests of object recognition memory, or the judgment of the prior occurrence of an object, have made substantial contributions to our understanding of the nature and neurobiological underpinnings of mammalian memory. Only in recent years, however, have researchers begun to elucidate the specific brain areas and neural processes involved in object recognition memory. The present review considers some of this recent research, with an emphasis on studies addressing the neural bases of perirhinal cortex-dependent object recognition memory processes. We first briefly discuss operational definitions of object recognition and the common behavioural tests used to measure it in non-human primates and rodents. We then consider research from the non-human primate and rat literature examining the anatomical basis of object recognition memory in the delayed nonmatching-to-sample (DNMS) and spontaneous object recognition (SOR) tasks, respectively. The results of these studies overwhelmingly favor the view that perirhinal cortex (PRh) is a critical region for object recognition memory. We then discuss the involvement of PRh in the different stages – encoding, consolidation, and retrieval – of object recognition memory. Specifically, recent work in rats has indicated that neural activity in PRh contributes to object memory encoding, consolidation, and retrieval processes. Finally, we consider the pharmacological, cellular, and molecular factors that might play a part in PRh-mediated object recognition memory. Recent studies in rodents have begun to indicate the remarkable complexity of the neural substrates underlying this seemingly simple aspect of declarative memory.



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## 1. Introduction

This article reviews the neural substrates of object recognition memory in non-human primates and rats with a focus on recent work studying the neurobiological basis of object recognition memory in the rat perirhinal cortex (PRh). Recognition – a judgement of the prior occurrence – of objects is thought to be a critical component of human declarative memory. Object recognition is commonly impaired in human patients affected by neurodegenerative diseases or who have suffered brain injury (Buffalo et al., 1998; Hajilou and Done, 2007; Holdstock, 2005; Irle et al., 1987; Laatu et al., 2003; Lee et al., 2003; Manns and Squire, 1999; Purdy et al., 2002; Reed and Squire, 1997). It is thus important that we gain a better understanding of the brain mechanisms underlying this vital cognitive function. The present review will first briefly consider the various operational definitions of object recognition in the laboratory setting and the tasks most commonly used to study object recognition memory in rats and monkeys. We will then consider at the systems level the primary brain regions implicated in object recognition memory, with special emphasis on the importance of the perirhinal cortex (PRh). The specific temporal involvement of PRh circuitry in the various phases of object recognition memory will then be examined, followed by a consideration of the possible pharmacological, cellular, and molecular mechanisms involved in PRh-mediated object recognition memory.

## 2. Object recognition memory – a common test of declarative memory

Declarative memory is defined as the conscious memory for facts and events and is often further divided into episodic memory (memory for personal events) and semantic memory (memory for general information) (Squire and Zola-Morgan, 1988; Squire and Zola, 1996). In contrast to non-declarative memory, such as procedural memory for habits or skills, which often requires an extensive acquisition phase, declarative memory is thought to be acquired with relatively few exposures to the material to be learned. This aspect of declarative memory is a feature of the most common tests of object recognition memory, described below. For this and other reasons, tests of object recognition enjoy widespread use by researchers studying the neurobiology of mammalian declarative memory. It must, however, be noted that declarative memory consists of a variety of putative cognitive processes necessitated by the integration of multimodal information. These processes, for example, may involve functions related to familiarity and recollection, which likely have dissociable neural substrates (Eichenbaum et al., 2007; Yonelinas, 2001). Clearly, successful performance of the object recognition tasks discussed below may only require a subset of the cognitive processes involved in normal declarative memory. The purpose of the present review is not to suggest that object recognition memory is the only way in which declarative memory can be measured. Rather, we view object recognition as an excellent model for research into the neural substrates of aspects of mammalian memory. The material that follows demonstrates the great contribution that object recognition research has made to our understanding of medial temporal lobe (MTL) mnemonic functions, and particularly the insights that this work has provided in recent years into the specific functions of PRh with regard to object memory. Obviously, an extensive network of brain areas mediates normal declarative memory, but a comprehensive consideration of these brain areas is beyond the scope of the present review. The memory for specific object information, however, constitutes an important element of certain declarative memories, and it is this aspect of memory function with which the present review is primarily concerned.

### 2.1. Delayed (non)matching-to-sample

Object recognition memory in non-human primates is most commonly tested in the delayed nonmatching-to-sample (DNMS) task or its counterpart, the delayed matching-to-sample (DMS) task. Work with these tasks proliferated in the 1970s and 1980s (Bachevalier et al., 1985a,b; Gaffan, 1974; Mahut et al., 1982; Mishkin, 1978; Mishkin and Delacour, 1975; Saunders et al., 1984; Zola-Morgan and Squire, 1985, 1986), when researchers sought to reproduce the kind of profound memory deficits observed in MTL-damaged patients such as H.M. (Scoville and Milner, 1957). A D(N)MS trial consists of two discrete stages – a sample presentation followed by a choice test – which are separated by a retention delay of variable duration. In the sample phase of a given trial, the monkey is presented with a 'junk' object over a central baited food well. The monkey must displace this object to obtain the food reward. Following a retention delay, which can vary from only a few seconds up to many minutes, the monkey is presented with the sample object and a novel junk object, each presented over a lateral food well. In the DNMS task, the monkey must displace the novel (i.e., nonmatching) object to obtain reward; in the DMS task, the original sample (i.e., matching) object must be displaced for reward. On a given trial a correct response according to the specific rule (match or nonmatch) of the task is taken as indication of the monkey's recognition of the sample object. The procedure is repeated for several trials per session with different object pairs for each trial. The use of trial-unique or pseudo-trial-unique stimuli discourages the formation of stimulus-reward associations during testing, thereby rendering the results easier to interpret in terms of 'pure' recognition memory. More recently, D(N)MS has been run in much the same way, but with computer-graphic stimuli presented on touchscreen monitors (e.g., Ogura and Aigner, 1993; Parker et al., 1997; Parker and Gaffan, 1998).

The D(N)MS task has also been adapted to test recognition memory for objects (Aggleton, 1985; Kesner et al., 1993; Mumby et al., 1990; Rothblat and Hayes, 1987) and odours (Hudon et al., 2002; Mair et al., 1998; Otto and Eichenbaum, 1992a,b; Ramus and Eichenbaum, 2000; Winters et al., 2000) in rats. Although these studies have used a variety of testing procedures, the rat versions of object D(N)MS generally resemble the monkey version in many facets, including the use of large sets of junk objects, the requirement for rats to displace these stimuli from food wells for reward, and the use of discrete trials consisting of sample and choice phases separated by a variable retention delay (Mumby, 2001).

### 2.2. Spontaneous object recognition task

A further variation on the DNMS paradigm for rodents is the simpler spontaneous object recognition (SOR) task (Ennaceur and Delacour, 1988). Indeed, the SOR task has become the test of choice for assessing aspects of declarative memory in rodents and has contributed greatly to our current understanding of the neurobiological basis of object recognition memory. The SOR task exploits the natural tendency of rats to explore novel stimuli in preference to familiar stimuli. A major advantage of the SOR task is the fact that it requires no pre-training and involves no explicit reinforcement; object recognition can thus be studied in a relatively 'pure' manner without the potential complications of interpretation introduced by, for example, extensive training phases of rule (e.g., nonmatching-to-sample) acquisition, or motivational considerations.

Typically, the SOR task is run in an open field arena, although recent efforts to address certain controversial aspects of the literature have prompted the introduction of a novel Y-shaped apparatus for testing SOR (see below) (Forwood et al., 2005; Winters et al., 2004). The SOR paradigm is similar to the DNMS task. A single SOR trial consists of sample and choice phases, separated by a variable retention delay. In the sample phase, the rat is introduced into the testing apparatus, which contains two identical junk objects (A1 and A2). The rat is allowed to explore these objects for a limited amount of time before being removed from the apparatus. At the end of the retention delay, the rat is reintroduced to the apparatus, which now contains a triplicate copy of the sample object (A3) and a novel object (B) never before seen by the rat. Normal rats will preferentially explore the novel object in this choice phase, and this behaviour is taken as the index of recognition of the familiar sample object (Fig. 1).

The DNMS and SOR tasks have in common the fact that the behaviour of normal animals in the test or choice phase is driven by a single exposure to a sample object and its subsequent recognition. As noted earlier, this ability to judge the prior occurrence of an object has been the subject of much investigation, and great strides have been made in recent years in uncovering the neural substrates of this cognitive function. The following section discusses studies from monkeys and rats that have elucidated one of the critical brain regions involved in object recognition memory.

## 3. Perirhinal cortex vs. hippocampus – functional dissociation within the MTL

### 3.1. Early studies on the role of the MTL in object recognition memory

Findings from studies of H.M. (Corkin, 1984; Scoville and Milner, 1957) and similar amnesic patients prompted intensive analysis of the role of the MTL in learning and memory in humans and non-humans. These studies have resulted in a vast literature implicating the structures of the mammalian MTL specifically in the mediation of declarative memory processes. These structures include the hippocampus, as well as the anatomically related entorhinal, perirhinal, and parahippocampal cortices, all of which have been suggested to function within a putative "medial temporal lobe memory system" (Squire and Zola-Morgan, 1991) (Fig. 2A). While it is clear that the MTL structures contribute to various memory processes, the extent to which they perform homogeneous or dissociable mnemonic functions remains up for debate.

Early animal studies suggested that the hippocampus and/or amygdala were vital for object recognition memory (Mishkin, 1978; Murray and Mishkin, 1984; Saunders et al., 1984; Zola-Morgan and Squire, 1985; Zola-Morgan et al., 1982). Subsequent research, however, suggested a contributing role for adjacent MTL cortical regions in the performance of object recognition tasks (Mahut et al., 1982; Murray and Mishkin, 1986; Zola-Morgan and Squire, 1986; Zola-Morgan et al., 1989a,b, 1993). Indeed, Zola-Morgan et al. (1989c) reported that lesions restricted to the perirhinal and parahippocampal cortices were sufficient to cause DNMS deficits as large as those observed following combined hippocampus and amygdala lesions, lesions that also included MTL cortical tissue. Importantly, this result and others (Murray and Mishkin, 1986) indicates that damage to perirhinal and related cortex is a crucial factor in the severe DNMS impairment caused by MTL lesions and that serious object recognition memory deficits can result from damage to this region even when the hippocampus is fully intact.

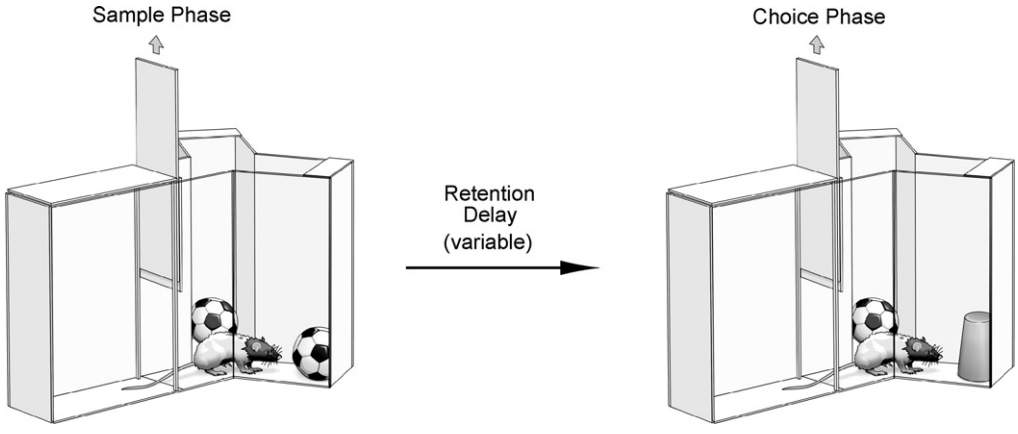


**Fig. 1.** Spontaneous object recognition (SOR). Diagram of the phases of the SOR task as run in the Y-shaped apparatus. The nearest wall of the apparatus appears transparent for illustrative purposes. At the beginning of the sample or choice phase, the rat is released from the start box when the experimenter manually raises the guillotine door. In the sample phase, the rat is exposed to identical versions of the same object, one at the end of each exploration arm. The rat explores these objects for a pre-determined amount of time before being removed from the apparatus for the variable retention delay. Following the retention delay, the rat is reintroduced to the apparatus, which now contains an identical copy of the sample object at the end of one exploration arm and a novel object at the end of the other arm. Spatial information is irrelevant as the side of the sample and novel objects is counterbalanced in the choice phase. Normal rats spend more time exploring the novel object, and a recognition score, often referred to as the discrimination ratio, is calculated on the basis of relative sample and novel object exploration [D.R. = (novel − sample)/(novel + sample)].

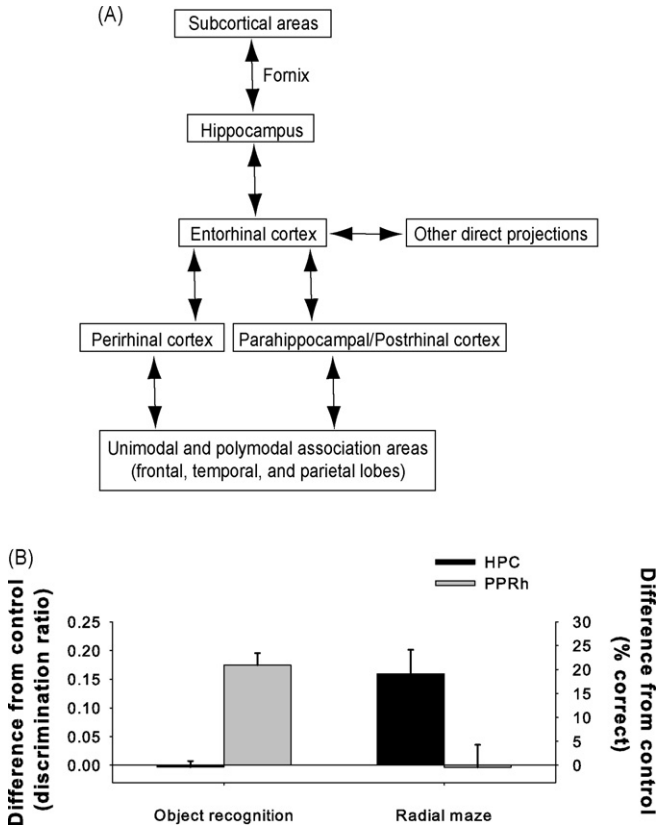


**Fig. 2.** Medial temporal lobe. (A) A schematic of the interrelationship between the structures of the putative medial temporal lobe "memory system" (adapted from Squire and Zola-Morgan, 1991). The rat postrhinal cortex is considered analogous to the primate parahippocampal cortex (Burwell and Amaral, 1998). (B) Graph illustrating the functional double dissociation between the effects of peri-postrhinal cortex (PPRh) and hippocampal (HPC) lesions on object recognition and spatial memory in the radial maze (Winters et al., 2004). Difference scores were calculated for each lesion group by subtracting performance on each task from the mean control group performance levels. PPRh lesions significantly impaired object recognition memory, but not spatial memory. HPC lesions had the opposite effect.

### *3.2. Perirhinal cortex is more important than other temporal lobe regions for object recognition memory*

Monkeys with rhinal (combined perirhinal plus entorhinal) cortex lesions are severely impaired on visual DNMS (Meunier et al., 1993) and DMS (Eacott et al., 1994) tasks. This impairment is delay-dependent in that lesioned animals can perform well with very short retention delays (~10 s), but suffer when the delays are made much longer (60 s or more). Moreover, Murray and Mishkin (1998) have shown that combined excitotoxic lesions of the hippocampus and amygdala that spare surrounding cortex do not disrupt DNMS performance in monkeys. This pattern of results suggests that the detrimental effects of rhinal cortex lesions on DNMS task performance is due to a direct role for these cortical areas in object recognition memory, independent of the hippocampus. Furthermore, of the MTL cortical regions considered, PRh dysfunction causes the most substantial object recognition impairment (Buffalo et al., 1999; Horel et al., 1987; Meunier et al., 1993). Indeed, lesions of PRh alone yield DNMS deficits similar in magnitude to those caused by combined rhinal cortex lesions, whereas the impairment associated with selective entorhinal cortex lesions is mild and transient (Leonard et al., 1995; Meunier et al., 1993).

Although few dispute the crucial role played by PRh, the debate continues over the contribution of the hippocampus to object recognition memory. While there have been several reports of object recognition impairment in humans (McKee and Squire, 1993; Pascalis et al., 2004; Squire et al., 1988; Zola-Morgan et al., 1986), monkeys (Alvarez et al., 1995; Beason-Held et al., 1999; Nemanic et al., 2004; Zola-Morgan et al., 1992; Zola et al., 2000), and rodents (Baker and Kim, 2002; Broadbent et al., 2004; Clark et al., 2000, 2001; de Lima et al., 2006; Gaskin et al., 2003; Hammond et al., 2004; Mumby et al., 1995b; Mumby et al., 1992; Prusky et al., 2004; Rampon et al., 2000; Rossato et al., 2007) with hippocampal dysfunction, there have also been many failures to observe substantial or lasting deficits in subjects with hippocampal system damage (Aggleton et al., 1986; Bachevalier et al., 1985b; Bussey et al., 2000; Cassaday and Rawlins, 1995, 1997; Duva et al., 1997; Forwood et al., 2005; Gaffan, 1994; Jackson-Smith et al., 1993; Kesner et al., 1993; Mumby, 2001; Mumby et al., 1992, 1995a, 1996; Murray and Mishkin, 1998; Rawlins et al., 1993; Rothblat and Kromer, 1991; Shaw and Aggleton, 1993; Steele and Rawlins, 1993; Winters et al., 2004; Yee and Rawlins, 1994). Even in those cases where hippocampal damage disrupts object recognition, this impairment is often much less severe than the deficit caused by PRh lesions (Murray et al., 2000; Prusky et al., 2004). Furthermore, in some cases, the extent of damage to the hippocampus and the magnitude of recognition impairment in DNMS for monkeys with excitotoxic lesions have actually been negatively correlated (Murray and Mishkin, 1998). Thus, although there does seem to be clear evidence that the hippocampus contributes to the performance of certain object recognition tasks, the equivocal nature of the literature regarding this contribution combined with the robust impairment consistently reported following PRh lesions strongly suggests a direct role for PRh in the actual recognition of object information and a role for the hippocampus that is ancillary at best.

Some of the clearest evidence against a direct role for the hippocampus and for a major role for PRh in object recognition memory comes from recent work with rats demonstrating dissociable functions between these two temporal lobe structures. In line with results from monkey studies discussed above, early analyses of parahippocampal cortex function in rats suggested a role in learning and memory tasks requiring object information (Kornecook et al., 1999; Myhrer and Wangen, 1996; Rothblat et al., 1993; Wiig et al., 1996). Furthermore, studies with rats in a non-recurring items version of the DNMS task indicated that rhinal (entorhinal plus perirhinal) cortex damage or disruption with the sodium channel blocker lidocaine significantly impaired object recognition memory (Barnes et al., 2000; Mumby and Pinel, 1994). The large effects of rhinal cortex damage in the rat DNMS task stand in contrast with the mild but significant impairment observed in the same task following bilateral combined lesions of the hippocampus and amygdala (Mumby et al., 1992).

Neurotoxic lesions of PRh or PRh plus postrhinal cortex have been shown to disrupt object recognition memory in the SOR task in a delay-dependent manner while leaving performance on standard allocentric spatial memory tasks (e.g., Morris water maze, delayed nonmatching to position, and delayed spatial alternation in the t-maze) relatively intact (Bussey et al., 2000; Bussey et al., 1999; Ennaceur et al., 1996). Indeed, studies by Ennaceur et al. (1996) and Bussey et al. (2000) were suggestive of doubly dissociable functions between PRh and the hippocampus; both of these papers reported impaired object recognition memory in the SOR task following neurotoxic PRh damage that was insufficient to disrupt spatial memory performance. In the same studies, fornix lesions impaired spatial memory but not object recognition memory, suggesting that hippocampal system function was not critical for recognition memory in the SOR task.

Although the fornix provides a crucial conduit to and from the hippocampus, it is not considered part of the MTL memory system (e.g., Clark et al., 2000). Winters et al. (2004) therefore set out to demonstrate a clear double dissociation between the hippocampus and PRh by comparing the effects of direct neurotoxic lesions of these structures in spatial and object recognition memory tasks. Rats with bilateral lesions of either the hippocampus or perirhinal plus postrhinal cortex (PPRh) were assessed in a standard radial maze spatial memory task and the SOR test of object recognition memory. Use of the SOR task for object recognition provided an extra benefit because this task requires no pretraining, which has been an issue in previous monkey studies demonstrating the absence of hippocampus lesion effects in DNMS. For example, the finding by Murray and Mishkin (1998) of spared recognition memory in monkeys with hippocampal lesions has been criticized on the grounds that the extensive pretraining used in that experiment might have hidden an impairment in subsequent recognition tests with longer delays (Zola et al., 2000). This explanation cannot apply to the study of Winters et al. (2004). The SOR task in the Winters et al. (2004) study was also run in an apparatus specially designed to minimize the influence of spatial or contextual information, because it has been suggested that the hippocampus may be recruited when such factors become relevant to task performance (Aggleton and Brown, 1999; Bussey and Aggleton, 2002; Cassaday and Rawlins, 1997; Gaffan, 1994; Nadel, 1995; Zola et al., 2000), and this may help to explain why hippocampal system damage sometimes disrupts SOR task performance when tested in an open field. The results provided a clear functional double dissociation, with PPRh lesioned rats demonstrating impaired object recognition memory and unimpaired radial maze performance and the opposite pattern of effects being observed in the hippocampus lesioned animals, who were unimpaired in object recognition even with a 24-h retention delay between sample and choice phases (Fig. 2B). This result provides unequivocal evidence for heterogeneity and independence of function between these two important mnemonic structures. Thus, while numerous studies indicate a role for the hippocampus in some aspect of object recognition task performance (Alvarez et al., 1995; Baker and Kim, 2002; Beason-Held et al., 1999; Broadbent et al., 2004; Clark et al., 2000, 2001; de Lima et al., 2006; Gaskin et al., 2003; Hammond et al., 2004; McKee and Squire, 1993; Mumby et al., 1992, 1995b; Nemanic et al., 2004; Pascalis et al., 2004; Prusky et al., 2004; Rampon et al., 2000; Rossato et al., 2007; Squire et al., 1988; Zola-Morgan et al., 1986, 1992; Zola et al., 2000), the double dissociation reported by Winters et al. (2004) strongly suggests that this role is not specific to the recognition of objects *per se*. Moreover, this study indicates the importance of considering procedural differences across studies when discussing the contributions of brain regions. Winters et al. (2004) changed the paradigm to address a possible explanation for the equivocal nature of the literature, and this change resulted in a double dissociation that is inconsistent with the suggestion that the hippocampus is particularly important for recognizing objects.

Evidence consistent with a functional double dissociation between PRh and hippocampus has also been provided by imaging experiments using the products of the immediate early gene *c-fos* as an index of neuronal activation in response to stimulus exposure. Specifically, Wan et al. (1999) found that PRh was activated significantly more by novel than familiar pictures of objects, whereas the hippocampus was not sensitive to the different conditions. Conversely, pictures of novel spatial arrangements of familiar objects significantly activated area CA1 of the hippocampus compared to familiar spatial arrangements, and PRh was not differentially activated. Along with the above studies, this result suggests an important role for PRh in the representation of individual object information useful for recognition processes, whereas the hippocampus plays a specific role in more spatial (O'Keefe and Nadel, 1978) and possibly other relational (Eichenbaum et al., 1992) functions.

Although the issue of hippocampal involvement in object recognition memory remains controversial, the Winters et al. (2004) double dissociation demonstrates that, under rigorous testing conditions, an intact hippocampus is not essential for the judgement of the prior occurrence of an object. Indeed, a follow-up study found results in support of this view using the same Y-shaped SOR testing apparatus to limit the influence of spatial factors (Forwood et al., 2005). In this study, rats with complete bilateral hippocampal lesions were as good as sham controls at recognizing objects even with a very stringent 48-h retention delay between the sample and choice phases, despite failing in a spatial nonmatching-to-location task. This is not to suggest that the hippocampus may not normally be involved in some aspects of recognition memory tasks as they are commonly run, but that for the recognition of object information *per se*, the hippocampus is not essential. Rather, PRh is the temporal lobe structure most important for object recognition memory in the SOR task.

## 4. Examining the time course of PRh-mediated object recognition memory

Studies involving permanent PRh damage have proven invaluable in elucidating the anatomical locus of object recognition memory. There are certain questions, however, that permanent lesion analyses cannot adequately address, such as for what *phase* of the memory process – encoding/acquisition, consolidation/storage, or retrieval – a particular brain region is necessary. Brain cannulation methods allow for the direct delivery of pharmacological agents into specific brain areas, and the effects of these drugs are often time-limited. Thus, cannulating techniques can facilitate the temporal analysis of the contributions of PRh to object recognition memory by allowing us to study the behavioural effects of transient pharmacological manipulations at various phases within a given object recognition trial. Indeed, the discrete one-trial nature of the SOR paradigm lends itself nicely to this kind of analysis, and a recent study tested the effects of transient lidocaine-induced PRh inactivation during sample presentation (encoding/acquisition), during the choice phase (retrieval), and during the retention interval (consolidation/storage) (Winters and Bussey, 2005c) (Fig. 3). The results of this study provided evidence that PRh is critically involved in these three distinct stages of object recognition memory.

### 4.1. Encoding/acquisition

Infusions of the sodium channel blocker lidocaine into PRh immediately before the sample phase in the SOR task significantly impaired object recognition memory, and this effect was seen with a very short ($\leq$30 s) retention delay, as well as with delays of 5, 20, and 180 min (Winters and Bussey, 2005c) (Fig. 3B). These results suggest a significant role for PRh in the initial encoding and acquisition of the object trace. The delay-independent nature of impairment caused by intra-PRh pre-sample lidocaine infusions suggests an effect of pre-sample infusions on the encoding of the perceptual representation of the sample object required for recognition memory regardless of the length of the retention interval. It is important to note that Winters and Bussey (2005c) did not test the effects of pre-sample infusions with a zero-second delay, and memory may not be affected under such conditions. Nonetheless, the minimal delay used in the study was very short ($\leq$30 s) and the fact that the magnitude of impairment was

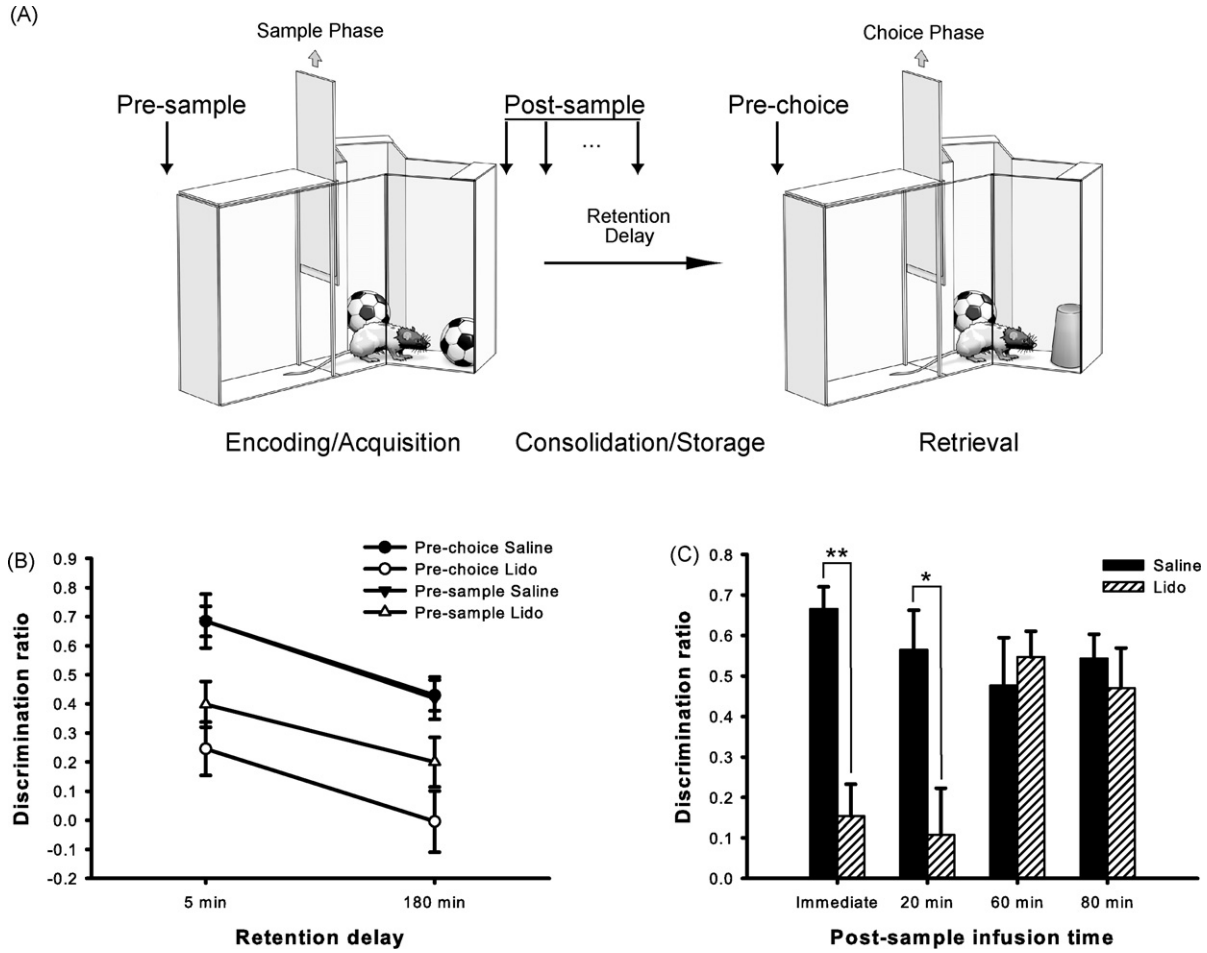


**Fig. 3.** Encoding, consolidation, and retrieval in PRh. (A) Illustration of the SOR task with vertical arrows indicating time points at which intracranial infusions can be delivered within a trial. Winters and Bussey (2005c) examined the effects of intra-PRh lidocaine (lido) on encoding (pre-sample infusions), consolidation (post-sample infusions at various time points), and retrieval (pre-choice infusions) in the SOR task. (B) Both pre-sample and pre-choice intra-PRh lidocaine infusions impaired object recognition memory with both short and long retention delays. (C) Intra-PRh lidocaine infused immediately or 20 min after the sample phase impaired object recognition memory. No disruption was observed when post-sample infusions were given 40 min or later after the sample phase. $^{*}p < 0.05$; $^{**}p < 0.01$.

equivalent at the minimum, 5 min, and 180 min retention delay is suggestive of an effect of pre-sample infusions on encoding or acquisition processes in addition to maintenance of the memory trace over the retention delay.

The putative effect of intra-PRh lidocaine on encoding and acquisition is consistent with the growing view that PRh plays a strong role in object identification and perceptual representation (Bartko et al., 2007; Buckley and Gaffan, 1998; Bussey and Saksida, 2002; Bussey et al., 2002a,b; Murray and Bussey, 1999; Murray et al., 2007), and it is well established that PRh lesions can disrupt visual discrimination, as well as object recognition memory (Buckley et al., 2001; Buckley and Gaffan, 1997; Bussey et al., 2003; Eacott et al., 2001; Saksida et al., 2007) (but see, Hampton, 2005; Hampton and Murray, 2002). Moreover, we have recently reported data that support the notion that the object representational functions of PRh contribute to performance in both object recognition and perceptual tasks (Bartko et al., 2007). In this study, rats with perirhinal plus postrhinal cortex lesions were significantly impaired in a zero-delay version of the SOR task when the objects used were perceptually similar, but not when the objects were easy to discriminate. Furthermore, a similar perceptual difficulty-dependent impairment was observed in rats with PRh lesions performing a spontaneous oddity task in which all objects were presented simultaneously, thereby minimizing mnemonic demands (Bartko et al., 2007). Such findings suggest that PRh houses complex representations of objects and that these representations are important for both memory and difficult perceptual discriminations. The effect of pre-sample intra-PRh lidocaine in the Winters and Bussey (2005c) study therefore may reflect impairment in the encoding and early acquisition of the perceptual representation of the object.

### 4.2. Retrieval

Winters and Bussey (2005c) also reported that inactivation of PRh with lidocaine immediately before the choice phase of the SOR task disrupted object recognition memory in a delay-independent manner similar to the effects of pre-sample infusions (Fig. 3B); impairment was observed with pre-choice infusions following 5, 20, and 180 min retention delays. Thus, neuronal activity within PRh is also required at the retrieval stage of object recognition memory. As PRh is implicated in the encoding and consolidation (see below) of the sample object trace and also in aspects of perceptual discrimination, it is possible that the behavioural effect of intra-PRh lidocaine at the retrieval stage is the result of blocking the activation of the sample object representation. This representation, which seems to be stored in PRh, is crucial for the identification of the sample object in the choice phase and would therefore facilitate discrimination between the sample and novel objects on the basis of familiarity. Further research is warranted to

examine the specific role of PRh at the retrieval stage of object recognition memory. Nonetheless, the detrimental effects of intra-PRh pre-choice lidocaine in the Winters and Bussey (2005c) study indicates the importance of PRh neuronal activity at the actual recognition stage of testing, consistent with other transient inactivation (Hannesson et al., 2004) and lesion (Mumby et al., 2002) studies.

### 4.3. Consolidation/storage

Perhaps the most intriguing finding reported by Winters and Bussey (2005c), and that most clearly supportive of a direct role for PRh in mnemonic processing specifically, was the pattern of impairment caused by intra-PRh infusions of lidocaine within the retention delay in the SOR task (Fig. 3C). Many types of memory remain labile and sensitive to disruption shortly after acquisition, stabilizing progressively over time (McGaugh, 2000). Winters and Bussey (2005c) provided evidence that PRh is critical to such a consolidation process for object memory traces.

Inactivation of PRh immediately or up to 20 min following the sample phase disrupted subsequent object recognition memory, whereas inactivation at 40, 60, or 80 min post-sample had no such effect. Note that PRh function is not disrupted during the encoding or retrieval stages in these post-sample infusion conditions. These results indicate an important role for PRh neuronal activity in the maintenance of the sample object trace during the retention delay. For some time between 20 and 40 min after the sample phase, the sample object trace, presumably encoded within PRh (see above), remains labile and sensitive to disruption of PRh activity. The trace apparently becomes resistant to lidocaine-induced disruption between 20 and 40 min after the sample object presentation. This period of PRh-dependent consolidation may represent a phase of active memory maintenance within PRh during which cellular and molecular processes required for long-term memory retention are established (Dudai, 1996; Goelet et al., 1986; Martin et al., 2000). Indeed, there is accumulating evidence that synaptic plasticity mechanisms associated with long-term memory in other brain regions also operate within PRh and may influence long-term object recognition memory (Bilkey, 1996; Brown and Bashir, 2002; Cho et al., 2000; Massey et al., 2001; Warburton et al., 2005; Warburton et al., 2003; Winters and Bussey, 2005a; Ziakopoulos et al., 1999) (see below). Thus, the effects of post-sample intra-PRh lidocaine infusions reported by Winters and Bussey (2005c) indicate that successful encoding of the sample object information in PRh does not guarantee successful maintenance of the memory trace. Rather, the trace gradually moves from a labile state requiring continuous PRh neuronal activity to a more resistant condition following a period of consolidation.

Thus, the findings reported by Winters and Bussey (2005c) indicate a role for PRh neuronal activity in encoding, retrieval, and consolidation of the object memory trace that supports object recognition memory in the SOR task. This time course of PRh involvement throughout the discrete stages of object recognition memory is similar to the pattern of effects implicating hippocampal involvement through the various stages of spatial memory processing (Riedel et al., 1999). It is interesting to speculate that, just as the anatomical organization of the hippocampus might render it particularly important for aspects of relational or spatial information processing, the anatomically downstream location of PRh in relation to the more posterior components of the ventral visual steam (Ungerleider and Mishkin, 1982) provide PRh with organizational properties conducive to the processing of object information, including the encoding, storage and retrieval of object memory traces (Gaffan, 2002; Murray and Bussey, 1999; Murray et al., 2007; Winters et al., 2004).

## 5. Pharmacological, molecular, and cellular factors regulating PRh-mediated object recognition memory

### 5.1. A neuronal substrate of familiarity judgement?

Dual-process accounts of recognition memory have suggested that there are separate component processes, namely recollection and familiarity judgement, which contribute to recognition memory (Brown and Aggleton, 2001; Eichenbaum et al., 2007; Rugg and Yonelinas, 2003; Yonelinas, 2001). Although such views remain contentious, electrophysiological studies in non-human primates and rats have provided support for a specific role of PRh in the putative familiarity judgement process (Brown and Aggleton, 2001; Brown and Bashir, 2002; Brown and Xiang, 1998). Specifically, electrophysiological recordings from neurons in the medial temporal lobe of monkeys or analogous regions in rats indicate that a large percentage of neurons (up to ~25%) in PRh and adjacent cortical areas respond less vigorously to familiar visual stimuli than to novel visual stimuli (Brown and Aggleton, 2001; Brown et al., 1987; Fahy et al., 1993; Riches et al., 1991; Xiang and Brown, 1998; Zhu et al., 1995). The responses of such cells are markedly reduced from the first to the second presentation of a visual stimulus. Such decremental responding is rarely observed in the hippocampus, but is commonly reported in inferotemporal cortical regions, particularly PRh (Brown and Bashir, 2002). Enhanced neuronal responding with repeated stimuli has also been observed in PRh, but such reports are less common and may be related to specific aspects of behavioural training, whereas response decrements are seen regardless of task demands (Brown and Bashir, 2002).

It remains to be seen if decremental neuronal responding to repeated stimuli constitutes the crucial mechanism for familiarity discrimination in PRh, but it is likely to be a major contributor to the object recognition process. Indeed, certain properties of decremental responses in PRh neurons strongly support this suggestion. First, the reduced neuronal responding occurs after a single exposure to a visual stimulus (Fahy et al., 1993; Xiang and Brown, 1998), consistent with the one-trial nature of object recognition memory. Second, there is evidence that such decremental responses could underlie long-term memory storage as they have been demonstrated even with delays of greater than 24 h between the first and second stimulus presentation (Brown and Bashir, 2002). Finally, the system mediating decremental responding appears to have quite a high capacity, as reduced responding on repetitions of specific stimuli occurs even when several objects must be remembered simultaneously or when an animal has previously been exposed to many similar stimuli (Xiang and Brown, 1998). Thus, decremental responding to previously encountered stimuli could represent at least part of the mechanism by which PRh neuronal activity could signal the familiarity of an object and store this information over relatively long intervals. Whether this is the case, as well as how synaptic plasticity mechanisms might mediate such a process, remains to be determined.

### 5.2. Synaptic plasticity in PRh

It is now widely believed that changes in synaptic strength support long-term memory storage in the brain (Martin et al., 2000). How might synaptic plastic changes in PRh contribute to the long-term maintenance of object memory traces? Electrophysiological studies of PRh slices *in vitro* have indicated that both incremental (long-term potentiation, LTP) and decremental (long-term depression, LTD) forms of long-term synaptic plasticity can be observed within PRh under the appropriate stimulation conditions

(Bilkey, 1996; Cho et al., 2000; Massey et al., 2001, 2004; Ziakopoulos et al., 1999). LTP, a persistent increase in synaptic efficacy resulting from high frequency stimulation of a post-synaptic neuron by a pre-synaptic neuron, has been studied extensively in other areas of the brain, such as the hippocampus, where it is consistently found to depend on glutamatergic transmission (Bliss and Collingridge, 1993; Bliss and Lomo, 1973). The excitatory neurotransmitter glutamate acts at a variety of receptor types throughout the brain to mediate aspects of fast synaptic transmission and synaptic plasticity. Of particular importance seems to be the glutamatergic NMDA (N-methyl-D-aspartic acid) receptor, the activation of which is required for the induction of synaptic changes throughout the brain (Martin et al., 2000). Consistent with these findings from other brain regions, Bilkey (1996) demonstrated that input-specific LTP could be induced in rat PRh slices and that this induction could be prevented by bath application of the NMDA receptor antagonist AP5. Subsequent studies of LTP in rat PRh slices have replicated and extended these findings, indicating a strong NMDA receptor component to certain aspects of PRh synaptic plasticity mechanisms (Massey et al., 2004; Ziakopoulos et al., 1999). The NMDA receptor is often regarded as a coincidence detector that is maximally active during concurrent pre-and post-synaptic activity; the fact that NMDA receptor dependent associative PRh LTP has been shown to require high contiguity of pre-and post-synaptic firing suggests that such a Hebbian mechanism might explain the role of NMDA receptors in PRh synaptic plasticity and memory (Bilkey, 1996) (see below). Thus, LTP may play an important role in refining PRh circuitry, and the resulting synaptic changes could contribute to the long-term maintenance of object information required for familiarity discrimination in object recognition tasks.

Although LTP may play an important role in PRh-mediated long-term object memory, some have argued that decremental synaptic changes, such as LTD, might be even more important considering the nature of neuronal responses reviewed above. The decreases in synaptic efficacy occurring in such processes as LTD could provide the mechanism underlying the decremental neuronal responses observed following exposure to familiar versus novel visual stimuli (Brown and Bashir, 2002; Cho et al., 2000). Accordingly, decremental synaptic changes have been reported to occur in PRh slices in response to a variety of stimulation and pharmacological manipulations (Brown and Bashir, 2002; Cho et al., 2000; Massey et al., 2001, 2004; McCaffery et al., 1999; Ziakopoulos et al., 2000). As with LTP, one form of LTD in PRh has been found to require glutamate receptor activation. Interestingly, unlike many forms of LTD in other brain areas, PRh LTD seems to require conjoint activation of both NMDA and metabotropic glutamate receptors (mGluRs) (Brown and Bashir, 2002; Cho et al., 2000; McCaffery et al., 1999). Specifically, group I and group II mGluRs seem to be important for aspects of PRh LTD. Interestingly, however, the involvement of these specific mGluRs is voltage dependent. Cho et al. (2000) showed that LTD induced by low frequency stimulation in PRh neurons voltage clamped at −70 mV required activation of group I and group II mGluRs as well as NMDA receptors. If, however, low frequency stimulation was delivered to PRh neurons depolarized to −40 mV, the resulting LTD required only NMDA and group I mGluR activation. Cho et al. (2000) suggest that this voltage dependence of group II mGluR involvement in PRh LTD results from a synergy between group I and group II mGluRs. Cho et al. (2000) posit that conjoint activation of NMDA and group I mGluRs is necessary and sufficient to induce LTD at depolarized potentials, when NMDA receptor activation is higher. At resting membrane potentials, when calcium influx through NMDA receptor channels is limited, the synergy between group I and group II mGluRs enhances calcium release from intracellular stores, thereby facilitating the induction of LTD (Cho et al., 2000). The requirement of concurrent mGluR activation for NMDA receptor-dependent PRh LTD is uncommon and may indicate specialized synaptic plasticity mechanisms that underlie the role of PRh in object recognition memory.

Although glutamate receptors are most commonly implicated in synaptic plasticity mechanisms, other neurotransmitters are known to affect synaptic efficacy under certain conditions. One such neurotransmitter is the neuromodulator acetylcholine (ACh). ACh has long been implicated in learning and memory, and electrophysiological studies have indicated that it may play important roles in cortical and hippocampal synaptic plasticity (Rasmusson, 2000; Segal and Auerbach, 1997). Interestingly, Massey et al. (2001) reported that activation of muscarinic cholinergic receptors in rat PRh slices induced a form of protein synthesis-dependent LTD, which did not require activation of NMDA receptors. Specifically, application of the cholinergic receptor agonist carbachol in an *in vitro* preparation of rat PRh neurons caused a long-lasting depression of synaptic transmission, which was prevented by co-application of the non-selective muscarinic receptor antagonist scopolamine or the M1 muscarinic receptor antagonist pirenzepine. Concurrent application of the NMDA receptor antagonist AP5 did not block the carbachol-induced LTD. Thus, a cholinergic mechanism of synaptic plasticity within PRh may play a role in the induction or expression of activity-dependent LTD. Cholinergic and glutamatergic mechanisms of synaptic plasticity within PRh may act synergistically and/or independently to influence different aspects of PRh-mediated object recognition memory processes.

### 5.3. Involvement of PRh glutamate receptors in object recognition memory

Although the foregoing review illustrates the existence of synaptic plasticity mechanisms in PRh, these findings do not address the question of whether such changes affect memory and behaviour directly. One approach to studying this question is to assess the behavioural effects of pharmacological, genetic, or molecular manipulations known to disrupt or facilitate synaptic plasticity (Martin et al., 2000). As the preceding section suggested, one such manipulation is the blockade of glutamatergic receptors. Indeed, recent work has begun to show that certain glutamatergic receptors are as important for PRh-mediated object recognition memory as they are for memory types that depend more strongly on other brain regions (Day et al., 2003; Riedel et al., 1999). For example, systemic injections of the NMDA receptor antagonist MK-801 before or after the sample phase in the SOR task significantly impaired object recognition memory with either a 1.5- or 24-h retention delay between the sample and choice phases (de Lima et al., 2005). These results suggest a role for NMDA receptors in both acquisition and consolidation of the object memory trace.

Accordingly, Winters and Bussey (2005a) reported involvement of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA glutamatergic receptors within PRh in several stages of object recognition memory (Fig. 4). AMPA and NMDA receptors contribute differentially to synaptic transmission and both are important for aspects of synaptic plasticity (Miyamoto, 2006; Rao and Finkbeiner, 2007; Riedel et al., 2003). Consistent with a role for AMPA receptors in fast synaptic transmission, Winters and Bussey (2005a) showed that intra-PRh infusions of the AMPA receptor antagonist CNQX disrupted three stages of object recognition memory in the SOR task in a similar manner to the sodium channel blocker lidocaine (Winters and Bussey, 2005c).

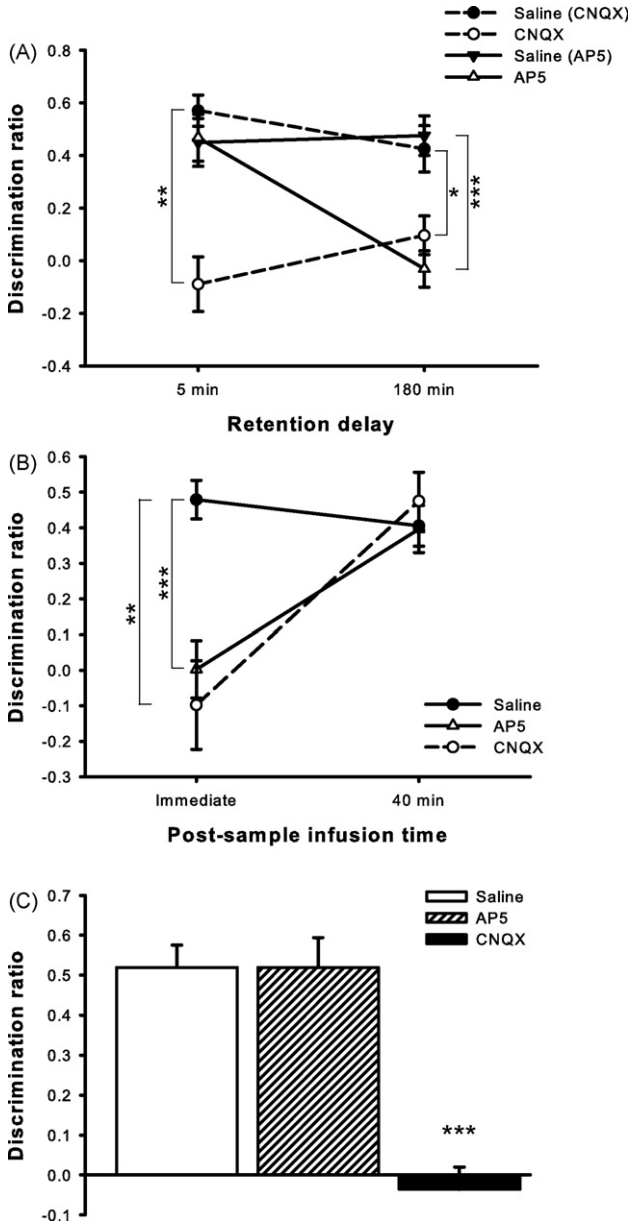


**Fig. 4.** Dissociable roles for AMPA and NMDA glutamate receptors in PRh-mediated object recognition memory. Winters and Bussey (2005a) reported involvement of AMPA and NMDA glutamate receptors in PRh in the various phases of the SOR task. (A) Pre-sample intra-PRh infusions of the AMPA receptor antagonist CNQX impaired object recognition memory with both short and long retention delays, whereas similar infusions of the NMDA receptor antagonist AP5 disrupted only long-term object recognition memory. (B) Intra-PRh infusions of either CNQX or AP5 immediately but not 40 min after the sample phase impaired object recognition memory with a 3-h retention delay. (C) CNQX but not AP5 disrupted object recognition memory when infused into PRh before the choice phase. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Infusions of CNQX before the sample phase impaired object recognition with short (5 min) and long (3 h) retention delays, suggesting a critical role for PRh AMPA receptors in the initial encoding and/or acquisition of the object representation. CNQX infused immediately, but not 40 min, after the sample phase abolished object recognition memory when tested with a 3-h retention delay, indicating a role for PRh AMPA receptors in the storage and/or consolidation of the object memory trace (Winters and Bussey, 2005a); this result is consistent with findings with lidocaine suggesting a role for PRh neural activity in the maintenance of the object trace during memory consolidation (Winters and Bussey, 2005c). Finally, intra-PRh infusions of CNQX before the choice phase also impaired recognition memory, again supporting conclusions from the lidocaine study that PRh neural activity is important at the retrieval stage in the SOR task.

The effects of NMDA receptor blockade in the same study indicated differential involvement of these glutamatergic receptors in the three stages of object recognition memory, but also supported the assertion that NMDA receptors are critically involved in aspects of synaptic plasticity underlying consolidation of long-term PRh-mediated object memory (Winters and Bussey, 2005a). Pre-sample intra-PRh infusions of the NMDA receptor antagonist AP5 impaired object recognition memory when tested with a long (3 h) retention delay, but not when the delay was relatively short (5 min). This result is consistent with delay-dependent memory effects of NMDA receptor antagonism in other tasks and brain areas and supports the idea that the contribution of NMDA receptors is related to their role in lasting synaptic changes that might be required for long-term memory retention. Moreover, Winters and Bussey (2005a) found that intra-PRh AP5 infusions disrupted long-term object recognition (3-h retention delay) when delivered immediately, but not 40 min, after the sample phase; this is the same time-course of consolidation revealed by infusions of lidocaine and CNQX. Again, this result supports the view that PRh NMDA receptors are involved in the consolidation of the object memory trace, perhaps via synaptic changes caused by a process like LTP or LTD. Finally, unlike the effects of PRh AMPA receptor blockade, NMDA receptor antagonism at the time of retrieval had no effect on object recognition memory, a result further suggestive of a specific role for PRh NMDA receptors in the consolidation process.

A recent study replicated and extended these findings (Barker et al., 2006b). Blocking NMDA receptors with intra-PRh infusions of AP5 impaired object recognition with a long (24-h) but not a short (20-min) retention delay when the infusions were made before the sample phase; there was no effect of AP5 infusions when given before the retrieval stage. Barker et al. (2006b) also reported that selective blockade of either NR2A or NR2B subunit-containing NMDA receptors in PRh was insufficient to disrupt object memory acquisition – long-term object recognition was impaired only when both an NR2A and NR2B antagonist were administered simultaneously. This finding is important because *in vitro* studies indicate that selective antagonism of NR2A or NR2B containing NMDA receptors blocks the induction of PRh LTP or LTD, respectively (Massey et al., 2004). Barker et al. (2006b) suggest that the requirement for combined NR2A and NR2B antagonism to disrupt long-term object recognition memory indicates that PRh-mediated object recognition does not rely exclusively on NMDA receptor-dependent LTP or LTD processes; both may normally be involved, but if one is disrupted the other seems capable of compensating to facilitate long-term object recognition memory.

In the same study, Barker et al. (2006b) also reported that blockade of kainate glutamate receptors in PRh disrupted object recognition with a short (20-min) but not a long (24-h) retention delay. This, combined with the reverse effect observed with NMDA receptor antagonism, is intriguing as it suggests that independent memory mechanisms may be operating within PRh: a kainate receptor-dependent, NMDA receptor-independent mechanism mediating memory with the 20-min retention delay, and an NMDA receptor-dependent, kainate receptor-independent mechanism responsible for longer term memory with the 24-h delay (Barker et al., 2006b). Finally, mGluRs have also recently been implicated in PRh-mediated object recognition memory. Barker et al. (2006a) report that simultaneous, but not separate, antagonism of PRh group I and II mGluRs during the sample phase

impaired object recognition memory with a 24-h but not a 20-min retention delay.

Thus, the studies reviewed above indicate that good progress is being made in the elucidation of the glutamatergic involvement in synaptic plasticity and object recognition memory in PRh. A growing body of data suggests that glutamate receptor-dependent synaptic plasticity processes operate within PRh and may underlie the role of this cortical region in object recognition memory. Much work, however, is still required to gather a complete picture of the specific contributions made by various glutamatergic receptor types and subtypes and the nature and extent of plasticity processes that might underlie PRh-mediated object recognition memory.

### 5.4. Muscarinic cholinergic receptors – a neuromodulatory role in PRh-mediated object recognition memory?

As noted above, there is now evidence that ACh can influence synaptic plasticity within PRh (Massey et al., 2001). Such findings may be linked to a cholinergic role in PRh-mediated object recognition as behavioural work has implicated ACh in recognition memory processes. Systemic administration of the cholinergic muscarinic receptor antagonists scopolamine or atropine impairs visual recognition in humans (Robbins et al., 1997), monkeys (Aigner and Mishkin, 1986; Aigner et al., 1991; Penetar and McDonough, 1983), and rats (Bartolini et al., 1996; Ennaceur and Meliani, 1992; Huston and Aggleton, 1987; Pitsikas et al., 2001; Vannucchi et al., 1997). Moreover, systemic treatment with the acetylcholinesterase (AChE) inhibitor physostigmine facilitates performance on visual recognition tasks in monkeys (Aigner and Mishkin, 1986) and humans (Furey et al., 2000), and administration of either of the AChE inhibitors metrifonate or tetrahydroaminoacridine attenuates the SOR task deficit seen in aged rats (Scali et al., 1997a,b).

More specifically, recent research with cholinergic immunotoxins has implicated the cholinergic basal forebrain input to PRh in object recognition memory in rats and monkeys. Permanent cholinergic denervation of PRh with 192 IgG-saporin in rats (Winters and Bussey, 2005b) and ME20.4-SAP in monkeys (Turchi et al., 2005) impairs object recognition in the SOR and DNMS tasks, respectively. In both of these studies the immunotoxin was infused locally into PRh to lesion selectively the cholinergic basal forebrain projections to PRh, leaving intact the widespread basal forebrain projections to other cortical regions. These findings indicate that the cholinergic input to PRh is important for some aspect of object recognition memory, but do not indicate which type(s) of cholinergic receptors might be involved or at which stage(s) of the object recognition process the cholinergic contribution is necessary.

To address these questions researchers have turned to the cannulation method, which permits localized infusion of specific pharmacological agents into PRh at various times throughout the learning and memory process (see above). There is now accumulating evidence from such studies that muscarinic cholinergic receptors are important for object recognition memory in both the rat and monkey. Infusions of the muscarinic receptor antagonist scopolamine into monkey PRh disrupts DNMS object recognition, a result that is consistent with the finding that PRh ACh release increases significantly in monkeys performing the DNMS task (Tang and Aigner, 1996; Tang et al., 1997). Furthermore, an elegant study by Warburton et al. (2003) demonstrated a remarkable confluence of scopolamine effects on PRh plasticity and object recognition memory in rats. Systemic injections or intra-PRh infusions of scopolamine before the sample phase in the SOR task significantly impaired object recognition memory with a 15–20-min retention delay. Systemic scopolamine also disrupted the normal decremental responses of PRh neurons to familiar versus novel pictures as measured with Fos expression (but see, Miller and Desimone, 1993, in which systemic scopolamine impaired monkeys' DNMS performance, but did not affect decremental responses in inferotemporal cortex). Finally, PRh LTD, but not LTP, was prevented by scopolamine bath application *in vitro*, consistent with previous reports (Massey et al., 2001). This collection of findings, though correlational, strongly supports the notion that cholinergic mechanisms mediate PRh synaptic plasticity processes and that these processes may be necessary for aspects of object recognition memory.

As for the specific temporal involvement of PRh ACh in object recognition, two recent studies have strongly suggested that the primary function of PRh muscarinic receptors is to facilitate acquisition of the object representation (Fig. 5). Winters et al. (2006) found that intra-PRh infusions of scopolamine before the sample phase disrupted recognition in the SOR task with a 24-h retention delay, whereas infusions before the retrieval stage did not affect performance. This result is consistent with Warburton et al. (2003), as well as current views regarding the role of cortical ACh in information acquisition (Hasselmo and Bower, 1993; Hasselmo and McGaughy, 2004; Sarter and Bruno, 1997). Intriguingly, Winters et al. (2006) also reported that infusions of scopolamine within the retention delay not only failed to impair object recognition memory, but actually *facilitated* performance relative to trials on which rats received saline infusions at the same time points (Fig. 5A). This effect, which was replicated multiple times, was observed with infusions given immediately, 8, 16, or 20 h after the end of the sample phase and suggests that PRh ACh is not necessary for consolidation in the SOR task. Winters et al. (2006) suggested that the particularly poor performance of rats receiving saline infusions within the retention delay might be the manifestation of an interference effect, which was blocked by scopolamine infusions. We suggested that with a relatively long retention delay (24 h), information acquired around the time of the infusion episode might be sufficient to interfere retroactively with the sample object memory trace, thereby disrupting object recognition. Indeed, we found that merely omitting the infusion recovered object recognition performance to normal levels. Moreover, the same effects were observed when infusions were performed 3 h prior to the sample phase, suggesting that the putative interference effect could operate retroactively and proactively and that intra-PRh scopolamine could prevent this effect, thereby facilitating memory, in both conditions. Blockade of the proactive interference effect by intra-PRh scopolamine provides further support against an interpretation in terms of a direct facilitative effect of scopolamine on consolidation or some other process operating during the delay period.

In a follow-up study, Winters et al. (2007) tested the interference hypothesis more explicitly by modifying the SOR task to allow for the presentation of additional objects within the retention delay or before the sample phase (Fig. 5B). It was found that an irrelevant object presented between the sample and choice phases or 3 h before the sample phase abolished object recognition memory with a 3-h retention delay in the same way that saline infusions had done in the previous study when object recognition was tested with a 24-h delay. These retroactive and proactive interference effects were completely blocked by intra-PRh infusions of scopolamine before the irrelevant object presentation (Fig. 5C). Winters et al. (2007) posited that scopolamine, by blocking the acquisition of object information, could facilitate or disrupt object recognition memory depending on the task relevance of the information being blocked. Thus, intra-PRh scopolamine infused just before the sample phase impairs object

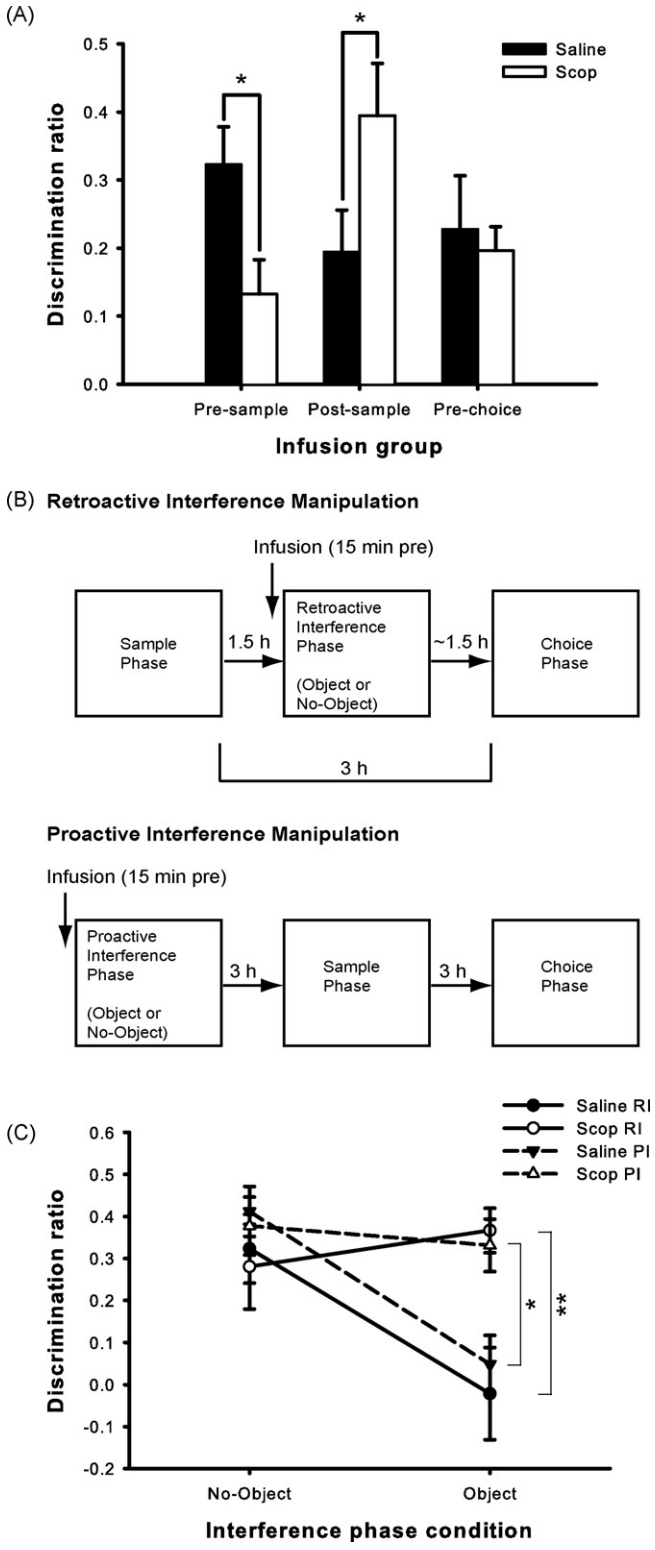


**Fig. 5.** Muscarinic cholinergic receptors in PRh mediate object memory acquisition. (A) Winters et al. (2006) reported object recognition impairment with a 24-h retention delay following pre-sample infusions of the muscarinic receptor antagonist scopolamine (Scop) into PRh. Paradoxically, intra-PRh infusions of scopolamine within the retention delay significantly *facilitated* object recognition memory. (B) In a follow-up study, Winters et al. (2007) examined the role of PRh muscarinic receptors in retroactive and proactive object interference. The SOR task was modified to allow presentation of irrelevant objects either 1.5 h after the sample phase within the retention delay (retroactive interference phase) or 3 h before the sample phase (proactive interference phase). Intra-PRh infusions of scopolamine or saline were given before the interference phases. (C) Intra-PRh infusions of scopolamine before the interference phase prevented the detrimental effect of an irrelevant object presentation in either the retroactive (RI) or proactive (PI) interference condition. These data indicate the vital importance of muscarinic receptors in PRh for the acquisition of object information. $^{*}p < 0.05$; $^{**}p < 0.01$.

recognition memory because muscarinic receptors facilitate the acquisition of sample object information within PRh. Conversely, scopolamine infused within the retention delay or sufficiently long before the sample phase might block the acquisition of other information which does not contribute to task performance. In the case of Winters et al. (2007), for example, activation of muscarinic receptors would help to acquire information about irrelevant objects that might interfere with the sample object trace and therefore could be detrimental to task performance. Scopolamine therefore facilitated object recognition memory by blocking acquisition of task-irrelevant object information within PRh.

It is interesting to note that the retroactive interference effect observed in the Winters et al. (2007) study is inconsistent with electrophysiological data indicating that the decremental responding of PRh neurons to recently presented stimuli is observed even when several objects must be remembered simultaneously (Xiang and Brown, 1998). While the testing conditions in these experiments differ substantially, and so direct comparison is impossible, the finding that the object recognition performance of rats is impaired with just a single intervening object presentation suggests that the aforementioned decremental responding to familiar stimuli may not be a sufficient neuronal mechanism for successful object recognition memory in cases of retroactive interference. This suggestion is also consistent with previous reports of dissociations between drug effects on object recognition memory and neuronal responses in inferotemporal cortex (Miller and Desimone, 1993).

In summary, whereas AMPA glutamate receptors appear to mediate aspects of acquisition, consolidation, and retrieval, and NMDA receptors seem to be crucial for consolidation, the evidence to date supports a specific role for PRh muscarinic cholinergic receptors solely in acquisition of object information. The results of the studies discussed above, analysing the effects of direct administration of glutamatergic and cholinergic receptor antagonists into PRh in the SOR task, are summarized in Table 1. A priority of future work will be to clarify the nature of cholinergic contributions to PRh synaptic plasticity and the relative involvement of muscarinic receptor subtypes in object recognition memory.

### 5.5. Molecular mechanisms involved in object recognition memory

At present, systematic molecular analyses of PRh-mediated object recognition memory are lacking in the literature. Although plasticity-related molecular mechanisms have been assessed in rodent object recognition tasks, most of these studies have focused on the hippocampus for their molecular analyses. Some of these studies have implicated intracellular signalling cascades in synaptic plasticity and long-term object recognition memory tasks. For example, mutant mice with a targeted disruption of the immediate early gene *zif268* showed disrupted maintenance of late LTP in the dentate gyrus of the hippocampus and were impaired in several tests of learning and memory, including object recognition (Jones et al., 2001). PRh plasticity, however, was not analysed in this study. There is good evidence that *zif268* may be part of a signalling cascade involved in the regulation of synaptic plasticity processes required for aspects of object recognition memory. This cascade includes mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK) and the cAMP response element-binding protein (CREB). Research has indicated that

**Table 1**
Effects of glutamatergic and cholinergic drugs infused into rat PRh at different stages of the SOR task

| Drug | Action | Infusion stage | Effect | References |
|---|---|---|---|---|
| CNQX | AMPAR antagonist | Pre-sample | Impairment with 15-min or 3-h retention delay | Winters and Bussey (2005a) |
| | | Post-sample | Impairment with immediate, but not 40-min, post-sample infusion; 3-h retention delay | Winters and Bussey (2005a) |
| | | Pre-choice | Impairment with 3-h retention delay | Winters and Bussey (2005a) |
| AP-5 | NMDAR antagonist | Pre-sample | Impairment with 3- or 24-h, but not 5- or 20-min, retention delay | Barker et al. (2006b), Winters and Bussey (2005a) |
| | | Post-sample | Impairment with immediate, but not 40-min, post-sample infusion; 3-h retention delay. | Winters and Bussey (2005a) |
| | | | No effect with 2-min post-sample infusion; 20-min or 24-h retention delay | Barker et al. (2006b) |
| | | Pre-choice | No effect with 20-min, 3-, or 24-h retention delay | Barker et al. (2006b), Winters and Bussey (2005a) |
| NVP AAM077 | NR2A subunit-containing NMDAR antagonist | Pre-sample | No effect with 24-h retention delay | Barker et al. (2006b) |
| Ro 25-6981 | NR2B subunit-containing NMDAR antagonist | Pre-sample | No effect with 24-h retention delay | Barker et al. (2006b) |
| NVP AAM077 + Ro 25-6981 | | Pre-sample | Impairment with 24-h retention delay | Barker et al. (2006b) |
| UBP302 | Kainate ($GLU_{K5}$) receptor antagonist | Pre-sample | Impairment with 20-min, but not 24-h, retention delay | Barker et al. (2006b) |
| | | Post-sample | No effect with 2-min post-sample infusion; 20-min retention delay | Barker et al. (2006b) |
| MPEP | Group I mGluR antagonist | Pre-sample | No effect with 24-h retention delay | Barker et al. (2006a) |
| LY341495 | Group II mGluR antagonist | Pre-sample | No effect with 24-h retention delay | Barker et al. (2006a) |
| MPEP + LY341495 | | Pre-sample | Impairment with 24-h retention delay | Barker et al. (2006a) |
| MSOP | Group III mGluR antagonist | Pre-sample | No effect with 24-h retention delay | Barker et al. (2006a) |
| Scopolamine | Muscarinic cholinergic receptor antagonist | Pre-sample | Impairment with 20-min or 24-h retention delay | Warburton et al. (2003), Winters et al. (2006) |
| | | Post-sample | Facilitation with immediate, 20-min, 40-min, 8-, 16-, 20-h post-sample infusions; 24-h retention delay | Winters et al. (2006) |
| | | Pre-choice | No effect with 24-h retention delay | Winters et al. (2006) |
| | | 3-h pre-sample | Facilitation with 24-h retention delay | Winters et al. (2006) |

AMPAR, AMPA receptor; NMDAR, NMDA receptor; mGluR, metabotropic glutamate receptor.

manipulations that disrupt the functions of these molecules can prevent the expression of late phase, protein synthesis-dependent LTP in the hippocampus and produce deficits in long-term object recognition memory tasks (Bozon et al., 2003).

While such findings provide important insights into the general organization of memory, it is difficult to discern their specific implications for object recognition memory *per se*. Research reviewed earlier indicates that the hippocampus is not required for object recognition memory when task parameters are controlled to prevent the influence of spatial or contextual factors. Thus, findings regarding the molecular mechanisms of hippocampal involvement in certain object recognition tasks are more likely relevant to processes involved in spatio-contextual information processing that is secondary to the true purpose of the object recognition task. The foregoing review suggests that to study the molecular bases of object recognition memory processes *per se*, analyses must be made within PRh.

One recent study has demonstrated the importance of CREB protein phosphorylation in PRh LTP and long-term object recognition memory (Warburton et al., 2005). In this study, CREB inhibition within rat PRh impaired SOR performance with a long (24-h) but not a short (15-min) retention delay and also disrupted the normal decremental response of PRh neurons to familiar versus novel pictures. Moreover, PRh slices taken from rats treated with the CREB inhibitor had impaired LTP. These results are strikingly similar to the pattern reported in a previous study using scopolamine (Warburton et al., 2003) and strongly suggest that the PRh decremental neuronal response to familiar stimuli and long-term synaptic plastic processes are important for PRh-mediated object recognition memory. The results with CREB inhibition indicate that CREB-activated gene transcription may play an important role in PRh synaptic plasticity and long-term object recognition memory.

Interestingly, a recent study reported that expression of *zif268* mRNA is upregulated in PRh of monkeys following acquisition of a visual-pair association (Tokuyama et al., 2002), suggesting that similar molecular mechanisms may underlie hippocampal and PRh involvement in certain learning and memory tasks. It would be interesting to see if similar results are observed in PRh-mediated object recognition memory tasks. Further research is required to assess the possible involvement of the many documented molecular mechanisms of synaptic plasticity in PRh-mediated object recognition memory consolidation and related PRh plasticity processes.

## 6. Conclusion

Object recognition is an increasingly valuable memory paradigm. Research in this field is widespread and encompasses work with human subjects, non-human primates, and rodents. The practicality of many object recognition tasks, particularly the rodent SOR task, renders them attractive for use in basic and preclinical research into the neurobiology of aspects of mammalian declarative memory. This outward simplicity, however, belies the complex and intricate nature of neural mechanisms underlying object recognition memory. The research reviewed herein illustrates the valuable contributions that animal studies have made to our understanding of this important cognitive function and the specific role played by PRh. The foregoing review also demonstrates the importance of systematic and careful analysis of memory functions. Although the hippocampus and amygdala were once thought to be critical contributors to object recognition

memory, recent systematic studies have revealed the greater importance of temporal cortical areas, with particular emphasis on PRh. While the hippocampus clearly contributes to the performance of object recognition tasks under certain, as yet not fully understood conditions, it does not appear to be required for the familiarity-based recognition of object information *per se*. Lesion, electrophysiological, imaging, and localized pharmacological and molecular studies all point toward PRh as a vital region for object recognition memory.

Of course, no cognitive process or brain area operates in a vacuum, and an important research issue going forward will be how PRh interacts with other brain areas such as the hippocampus and amygdala to mediate other forms of cognition involving the integration of object and other types of information. For example, studies have indicated that intact PRh and hippocampal system functions are required for the successful performance of object-in-place tasks (Bussey et al., 2000; Gaffan and Parker, 1996), and it has been suggested that the hippocampus may be particularly important for helping to combine spatial or contextual information with the specific object information processed by PRh (Aggleton and Brown, 1999; Bussey and Aggleton, 2002; Eacott and Gaffan, 2005; Eichenbaum et al., 2007; Winters et al., 2004). Moreover, another MTL area with strong projections to the hippocampus, the postrhinal cortex (parahippocampal cortex in primates), receives anatomical inputs from cortical regions involved in visual and spatial information processing (Furtak et al., 2007) and has been implicated in learning about the positions of objects within scenes or contexts (Eacott and Gaffan, 2005). Perirhinal and postrhinal cortices project in parallel to the hippocampus. It thus is highly probable that the hippocampus is involved in the integration of highly processed object and visuospatial information supplied by PRh and postrhinal cortex, respectively, and that this integration underlies the formation of complex episodic memories (Bussey and Aggleton, 2002; Eacott and Gaffan, 2005; Eichenbaum et al., 2007). A better understanding of the operations of the components of such a memory network, both independently and interactively, at the systems, cellular, and molecular levels of analyses, will lead to greater insight into the nature of normal and impaired memory functions.

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