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An animal model of amnesia that uses Receiver Operating Characteristics (ROC) analysis to distinguish recollection from familiarity deficits in recognition memory

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Abstract

Here we review our development of an animal model of episodic memory and amnesia that employs on signal detection analyses to characterize recognition memory performance in rats. This approach aims to distinguish episodic recollection of studied items from mere familiarity for recently experienced stimuli, and then to examine the neural basis of these memory processes. Our findings on intact animals indicate that it is possible to distinguish independent components of recognition that are associated with features of recollection and familiarity in humans. Furthermore, we have found that damage limited to the hippocampus results in a selective deficit in recollection and not familiarity. Also, aging and prefrontal damage result in a similar pattern of impaired recollection and spared familiarity. However, whereas the recollection deficit following hippocampal damage can be attributed to the forgetting of studied materials, the impairment following prefrontal damage is due to false alarms, likely reflecting a deficit in source monitoring.

Keywords

Rat; hippocampus; prefrontal cortex; episodic memory; dual process theory; aging

There is strong consensus that, in humans, episodic memory depends on the hippocampal region. Furthermore, many observations from studies on human amnesia and functional imaging in healthy subjects have suggested that the hippocampus plays a selective role in episodic recollection, and not in mere familiarity for recently experienced stimuli (for reviews, see Davachi, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007). This distinction is important because comparisons between recollection and familiarity can be used to characterize different functional mechanisms of the hippocampus and other components of the medial temporal lobe memory system. However, this proposal is controversial in that other studies have argued that the hippocampus is involved in strong memories, regardless of whether they are based on recollection or familiarity (Squire, Wixted, & Clark, 2007). A definitive resolution of this controversy may not be possible from studies on humans, because it is difficult to assess with certainty the extent of brain damage in amnesic patients, and because distinguishing with

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certainty neighboring areas within the medial temporal lobe is currently beyond the anatomical resolution of functional imaging.

Studies using animals could be enormously useful in addressing this controversy, because in animals one can produce highly selective damage within particular brain areas and one can record selectively from neurons in identified brain areas. However, there is also a major challenge to animal models of episodic recollection, specifically in our ability to develop valid measures of this kind of memory in non-human species. To the extent that episodic memory is defined in terms of subjective experience, such as auto-noetic awareness (Tulving, 2002), it may indeed be impossible to test episodic memory in animals. Nevertheless, there have been several efforts to define episodic memory by its contents, including the “what”, “when”, and “where” of specific experiences. In this way, several studies have demonstrated that birds, mice, and rats have a capacity for episodic-like memory (Clayton & Dickinson, 1998); see for review (Dere, Kart-Teke, Huston, & De Souza Silva, 2006)).

Exploring episodic memory with ROC analysis

Another approach on which we have focused involves exploiting recent findings from cognitive science and neuroscience that employ signal detection analyses of recognition memory. This approach is based on the widely held view that recognition can be supported by two processes: episodic recollection of previous study events and/or a sense of familiarity for recently experienced stimuli. Our aim in using signal detection analysis is to characterize features of the Receiver Operating Characteristics (ROC) functions of recognition memory performance that distinguish the contributions of episodic recollection and familiarity (see for review Yonelinas & Parks, 2007).

In a typical ROC experiment on item recognition, human subjects study a list of words, faces, or other stimuli. Subsequently, they are tested with a list that includes both the old items (the items on the study list) and an equal number of new items, and subjects must distinguish each item as “old” or “new”. ROC curves then relate the proportion of “hits” (correct identifications of old items) to that of false alarms (incorrect identifications of new items as “old”) across a range of response criteria that vary from liberal (accepting an item as “old” based on a low threshold) to conservative (accepting items as “old” based on a high criterion). Performance is then plotted as two dimensional [P(hits) vs P(false alarms)] data points. Memory is reflected where $P(\text{hits}) > P(\text{false alarms})$, i.e., in data points that lie above the diagonal, which indicates chance accuracy at different thresholds (see Figure 1). In normal human subjects, the ROC function is typically characterized by two features: the curve is asymmetrical, involving an above-zero Y-intercept, and the shape of the function is curvilinear, such that it bows away from the chance line (Figure 1a). According to one interpretation, called the Dual Process Signal Detection (DPSD) model, the magnitude of the asymmetry reflects the contribution of recollection to recognition performance, whereas the curvilinearity measures the contribution of familiarity (Yonelinas, 2001). Confirming this view, under conditions where recollection is favored and the contribution of familiarity is decreased, the ROC function remains asymmetrical but becomes more linear (Figure 1b). Conversely, under conditions where familiarity is favored and recollection is decreased, the ROC function becomes more symmetrical (Figure 1c).

According to another view, called the Unequal Variance Signal Detection (UVSD) model, the bowing of an ROC curve reflects the strength of memories, and characterizes familiarity and recollection as weak and strong memories, respectively, along a continuum rather than as independent processes (Wixted, 2007). According to this view, the asymmetry of the ROC function occurs because the variability of the memory strength of old items is higher than that of new items. Whereas some unequal variance models explicitly predict that increasing

memory strength results in increases in both the curvilinearity and the variance of the ROC (Gillund & Shiffrin, 1984; Hintzman, 1988), Wixted's (2007) UVSD model is silent on this issue. The analyses described below were designed to determine whether the asymmetry and the curvilinearity of the ROC constitute distinct parameters of ROC curve for recognition memory in rats. Furthermore, our analyses were designed to determine whether the asymmetry and the curvilinearity can be manipulated independently by memory demands associated with characteristics of human memory that correspond to recollection and familiarity, respectively. If so, then in our view, these parameters reflect valid measures of recollection and familiarity that can be applied to examine the functional contributions of specific brain areas.

ROC analysis of recognition memory in rats

In our studies we have adopted a procedure that is similar to that used in humans, with modifications of relevance to our animal subjects (Fortin, Wright, & Eichenbaum, 2004). Specifically, the memory cues were composed of a large pool of ordinary household odors (e.g., lemon, thyme, cumin) mixed in sand within small plastic cups. During the study phase, a series of 10 stimuli are presented, and each stimulus is baited with a bit of sweetened cereal buried in the sand of each cup (Figure 2). On each successive stimulus presentation, animals are allowed to dig for that reward. After a 30 min delay, a series of 20 "target cups" is presented, consisting of a random ordering of 10 old odors (those presented in the sample phase) and 10 new odors taken from the pool. The test phase involves a non-match contingency, such that rats can obtain rewards by digging only in target cups containing *new* odors. In addition, rats can also obtain a reward in an alternate cup in the back of the cage if they refrain from digging in target cups that contain *old* odors. To manipulate the animal's bias for responding or not responding to target cups, we vary both the height of the target cup and the ratio of reward magnitude in the target cup versus that in the alternate cup. Under these conditions, rats are more likely to refrain from digging (i.e., identify this item as "old") in a target cup containing a new odor if it can obtain only a small reward or has to apply more effort (corresponding to a liberal threshold for "old" responses in humans). Conversely, rats are more inclined to dig in a target cup (i.e., identify item as "new") in which it can obtain a greater reward or exert less effort (corresponding to a conservative threshold in humans). We also control for the possibility that rats can smell the rewards buried in target cups using probe trials wherein the reward is not present in a cup with a new odor and instead is given only after digging commences.

ROC analysis of item recognition in rats

Our first application of this method involved testing normal adult rats on item recognition memory (Fortin et al., 2004). We found that the ROC curve of intact rats contained both an asymmetrical component (above-zero Y-intercept) and a strong curvilinear component (Figure 1d). This pattern is remarkably similar to the ROC of humans in verbal recognition performance (Fig 1a), and consistent with a combination of recollection-like and familiarity-based components of recognition in animals (see Yonelinas, 2001). It is important, however, to consider that the UVSD model would interpret these results as reflecting a single process characterized by both strong memory (bowing of the curve) and a greater variance of memory strength for old items compared to new items (asymmetry). Therefore, to test whether the performance of rats is supported by two distinct memory components, we have pursued extensions of the ROC analysis aimed at determining whether the asymmetry and curvilinearity components of the ROC can be dissociated in ways that relate to distinctions between recollection and familiarity.

ROC analysis of associative recognition

To examine whether the recollection (asymmetry) component of the ROC can be dissociated from the familiarity (curvilinearity) component, we developed a version of the associative recognition task (see Yonelinas, 2001). In the associative recognition protocol as used in humans, subjects are initially presented with a list of stimulus pairs, then later must distinguish the previously experienced (old) stimulus pairings from rearranged (new) pairs of the same stimulus elements. Assuming the pairs are processed as separate stimulus elements, performance should depend largely on recollection of the acquired associations because old and new pairs cannot be distinguished on the basis of differential familiarity for the individual elements (Parks & Yonelinas, 2007). Therefore, one would expect the ROC function to reflect strong recollection (asymmetry) with little or no contribution of familiarity, i.e., the ROC curve should be more linear than the standard item recognition ROC.

We developed a version of the associative recognition paradigm for rats using stimulus pairs composed of combinations of an odor mixed into one of several digging media (e.g., wood chips, beads, sand) contained in a cup (Sauvage, Fortin, Owens, Yonelinas, & Eichenbaum, 2008). Rats can readily learn to separately attend to odors and media as distinct stimulus dimensions (Birrell & Brown, 2000), so we expected the rats to distinguish these elements and rely on recollection of their associations (e.g., lemon is associated with wood chips). Each day the animals would initially sample a series of 10 odor-medium pairings, then following a 30 min delay, had to distinguish re-presentations of the 10 original (old) pairs from 10 rearranged (new) pairings of the same odors and media, using the same non-matching rule and manipulations of bias as in our study on item recognition described above. The resulting ROC function was highly asymmetric, indicating the presence of a strong recollection component (Fig 1e). Furthermore, the shape of the ROC was linear, indicating the absence of a significant familiarity component. This pattern is similar to the ROC function of human subjects when they rely selectively on recollection in associative recognition and source memory studies (Yonelinas, 1999; Parks & Yonelinas, 2007).

ROC analysis of item recognition in aged rats

To determine whether the familiarity (curvilinearity) component of the ROC can be dissociated from the recollection (asymmetry) component, we examined item recognition performance in aged rats. In humans, aging results in the pattern of memory deficit highlighted by a disproportionate loss in episodic recollection, and in particular, ROC analyses have revealed a striking dissociation between impaired recollection and spared familiarity (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006; Howard, Bessette-Symons, Zhang, & Hoyer, 2006; Prull, Dawes, Martin, Rosenberg, & Light, 2006). Therefore we expected that aged rats, particularly those with a broad memory deficit that extends to spatial and non-spatial memory, would show a selective loss of the recollection (asymmetry) component of the ROC function and sparing of the familiarity (curvilinearity) function. We performed an ROC analysis of recognition memory in 22–24 month old rats that had previously been characterized for spatial memory ability in the Morris water task (Robitsek, Fortin, Koh, Gallagher, & Eichenbaum, 2008) As has been previously reported, aged rats have a larger range of spatial memory performance than young rats, with some aged rats performing fully within the range of young adult rats and others performing outside the normal range (Gallagher, Burwell, & Burchinal, 1993). Our analyses focused on comparisons between young and aged rats on both the spatial and item recognition tasks.

Overall, aged rats were not significantly impaired in item recognition performance as measured by overall percent correct, which reflects the combined contribution of recollection and familiarity (Robitsek et al., 2008). Furthermore, there was only a modest correlation between recognition performance and spatial memory performance. However, the results of ROC

analyses revealed that aged rats had a significant and selective deficit in the recollection component of recognition, such that their ROC function was symmetrical and curvilinear (Fig 1f). Further analyses showed that the recollection impairment was limited to aged rats that were also impaired in spatial memory, and that the recollection component of the ROC was well correlated with spatial memory performance whereas the familiarity component was not. These observations suggest an important connection between episodic recollection and spatial memory. Furthermore, these results show that, as observed in aging humans, aging in rats is associated with a selective loss of episodic recollection, reflected in loss of the recollection (asymmetry) component of the ROC function and sparing of the familiarity (curvilinearity) component.

In rats, recognition memory is supported by two processes

The combined findings validate our animal model of the distinction between episodic recollection and familiarity, consistent with the dual process (DPSD) model of recognition memory. In these studies we found that normal young rats exhibit an asymmetrical and curvilinear ROC function, interpreted by the DPSD model as reflecting the contributions of recollection and familiarity, respectively. In associative recognition, normal young rats exhibit an asymmetrical but linear ROC function, consistent with the DPSD interpretation of performance that relies on recollection of stimulus associations and not on familiarity for the individual stimuli. Furthermore, while the observed linear shape of the ROC is entirely consistent with the predictions of the DPSD model, the UVSD account must struggle to explain a linear ROC (Wixted, 2007). In aging, rats exhibit a curvilinear but symmetrical ROC function, consistent with the DPSD interpretation of intact familiarity and selective loss of recollection, as observed in aged humans. Importantly, comparisons between these findings provide compelling evidence that the asymmetry and curvilinearity components of the ROC function can be manipulated independently. These results are inconsistent with the unequal variance signal detection (UVSD) model, which predicts that stronger memory results both in increased curvilinearity and equal or increased asymmetry. In contrast, these results are fully consistent with the DPSD model that interprets the asymmetry and curvilinearity as independent indices of recollection and familiarity, respectively. Therefore, whereas the controversy about ROC studies continues, it is clear that recognition memory in rats involves two distinct components: an asymmetrical component that is related to associative recognition, which relies on episodic recollection in humans, and a curvilinear component that is spared in aging, consistent with spared familiarity in aged humans.

The role of the hippocampus in episodic recollection

The above-described studies provide a strong foundation for examining the role of the hippocampus in episodic recollection. In the following studies, our hypothesis is that the hippocampus is selectively involved in recollection and not familiarity, and is also not involved in learning the basic rules of the non-matching task or in sensitivity to manipulations that affect response biases. ROC analyses then should show that rats with isolated hippocampal damage are able to perform the non-matching task and their response biases should not be affected. Furthermore, animals with hippocampal damage should have an intact familiarity (curvilinearity) component of the ROC function but a loss of the recollective (asymmetry) component. These expectations were fully supported by our findings.

Item recognition

In the item recognition task, rats with localized hippocampal damage have a fully symmetrical and curvilinear ROC function, consistent with the loss of recollection and sparing of familiarity, respectively (Figure 3a). Importantly, an alternative interpretation of these data, consistent with the UVSD model, is that hippocampal damage simply weakened memory and that the

recollection (asymmetry) component of the ROC function was more sensitive to this weakening than the familiarity (curvilinearity) component. To address this possibility, we examined the ROC function of normal rats with memory weakened by increasing the delay between study and test from 30 min to 75 min (Fortin et al., 2004). According to the single process (UVSD) model, one would expect the ROC to become symmetrical, similar to the effects of hippocampal damage. The DPSD model would predict a decrease in both recollection and familiarity, because both are presumably subject to forgetting over time, but does not necessarily imply that the ROC has to become more symmetrical. The ROC function with a long memory delay was consistent with the DPSD model and not with the UVSD model. Thus, under the long delay condition, the recollection (asymmetrical) component of the ROC function was decreased, such that the Y-intercept was reduced by approximately half (Figure 3b). The familiarity (curvilinearity) component was also decreased - indeed it was virtually eliminated. Furthermore, the shape of the ROC function in normal rats at the long delay was qualitatively different than that observed in rats with hippocampal damage, such that normal rats at the long delay exhibited an asymmetrical, more linear ROC function whereas rats with hippocampal damage at the short delay exhibited a symmetrical, curvilinear ROC function. This comparison is all the more striking considering that overall recognition performance (measured by percent correct), which combines the contribution of recollection and familiarity, was equivalent in these conditions (64% in normal rats at long delay; 66% in rats with hippocampal lesions at short delay). Thus, even in a comparison where the overall recognition performance was equivalent, normal rats and rats with hippocampal damage supported memory by distinct strategies, with normal rats exclusively using recollection and rats with hippocampal damage exclusively using familiarity. This double dissociation of strategies is entirely consistent with the DPSD model of recognition and inconsistent with the UVSD model.

Enhancement of familiarity under conditions of compromised hippocampal function

The conclusion that the hippocampus is selectively involved in episodic recollection and not in familiarity is further confirmed by observations that, under some conditions, familiarity is enhanced in the absence of normal hippocampal function. One of these conditions is the associative recognition task. This study was based on recent experiments that have suggested a way in which recollection and familiarity might be put into competition and consequently be affected in opposite directions by hippocampal damage (Diana, Yonelinas, & Ranganath, 2008; Giovanello, Keane, & Verfaellie, 2006; Quamme, Yonelinas, & Norman, 2007). In these studies, when the pairs are processed as distinct stimulus elements, it was found that performance might depend largely on recollection of the acquired associations, as described above. However, alternatively, when the elements of a pair are readily "unitized" into a single configuration, such as when the elements are features of a face or parts of a compound word, familiarity can support memory for stimulus pairings just as it does for single stimuli. In the case of odor-medium pairings in our associative recognition protocol, we expected that substantial experience during initial training and testing with many combinations of the same odor and medium elements would encourage the rats to distinguish these elements and rely on recollection of their associations (e.g., lemon is associated with wood chips). Alternatively, odors and media could readily be unitized into scented medium configurations (e.g., lemon smelling wood chips), allowing the use of familiarity to make recognition judgments.

As described above, the ROC function of normal rats was strongly asymmetrical and linear, consistent with strong recollection and absence of familiarity, respectively. This pattern is consistent with the interpretation that animals recalled the associations between items and their paired media and did not use the familiarity of the item-medium combinations to recognize stimuli. Animals with hippocampal damage suffered a significant decrease in the asymmetry of the ROC, indicating a deficit in recollection (Figure 4a). Although recollection was not reduced to zero, as observed in their performance on the item recognition task (Fig 3a), the

magnitude of reduction in the recollection component in the associative recognition task was actually larger than that in the item recognition task. Furthermore, after damage to the hippocampus, the shape of the ROC function became curvilinear, consistent with enhanced and compensatory use of familiarity. This observation is consistent with the possibility that, unlike normal rats, rats with hippocampal damage unitize the odor-medium combinations, allowing them to employ their intact familiarity capacity to support recognition. The double dissociation between reduced recollection and enhanced familiarity (Figure 4b) is entirely consistent with the DPSD model, and with the hypothesis that the hippocampus plays a selective role in recollection. This pattern of findings cannot be explained by the UVSD model.

Another experimental condition where enhancement of familiarity was observed was in our study on aged rats. As discussed above, the ROC of aged rats that were also impaired in spatial memory was symmetrical and curvilinear, consistent with a selective deficit in recollection and spared familiarity. These findings are similar to the effects of hippocampal damage (see Fig 3a) and consistent with many other results implicating compromised hippocampal function in aging (Barnes, 2003; Gallagher, Bizon, Hoyt, Helm, & Lund, 2003; Wilson, Gallagher, Eichenbaum, & Tanila, 2006). In addition to these findings, we observed a subset of aged rats that were impaired in spatial memory but paradoxically had overall (i.e., percent correct) intact recognition scores, that is, these animals performed as well overall as young adult rats. However, these aged animals had virtually no recollection component of the ROC function and, instead, the sparing of overall recognition performance was due to a compensatory enhancement of the familiarity (curvilinearity) component of the ROC function (Figure 5a). Thus, these aged animals had significantly enhanced familiarity compared to young rats at the same time as they exhibited decreased recollection (Figure 5b). The double dissociation between impaired recollection and enhanced familiarity components of the ROC function in aged rats is entirely consistent with the DPSD model and with the hypothesis that the hippocampus selectively supports recollection. Conversely, as found in associative recognition, this pattern of findings is particularly problematic for the UVSD model, which cannot account for the combination of an increase in one component of recognition performance (familiarity) and a decrease in another (recollection).

A complementary role for the prefrontal cortex in episodic recollection

So far our considerations have focused on the role of the hippocampus, either in animals with explicit damage to that structure or in the context of cognitive aging where loss of hippocampal function is prominent. In this section we will consider a rodent model of prefrontal function in episodic memory, using the ROC analysis described above. In humans, damage to the dorsolateral prefrontal area results in an impairment in episodic recollection (Alexander, Stuss, & Fansabedian, 2003; Gershberg & Shimamura, 1995; Janowsky, Shimamura, & Squire, 1989). In contrast, item recognition in patients with prefrontal damage is generally preserved (Swick & Knight, 1999). Furthermore, patients with prefrontal damage typically exhibit abnormally high false alarm rates (Curran, Schacter, Norman, & Galluccio, 1997; Parkin, Bindschaedler, Harsent, & Metzler, 1996; Schacter, Curran, Galluccio, Milberg, & Bates, 1996; Swick & Knight, 1999), an abnormality that is interpreted as misattribution of familiarity via impaired source monitoring (Johnson, 1997).

There is outstanding controversy about whether the rodent medial prefrontal cortical area (areas PL and IL, here designated as mPFC) is functionally homologous to the dorsolateral prefrontal cortex in humans and non-human primates. Previous studies have compared the effects of mPFC lesions in rats to those of dorsolateral prefrontal lesions in primates and humans by examining performance in working memory (Eichenbaum, Clegg, & Feeley, 1983; Granon, Vidal, Thinus-Blanc, Changeux, & Poucet, 1994), strategy switching (Birrell & Brown, 2000; Ragozzino, Detrick, & Kesner, 1999; Rich & Shapiro, 2007), and temporal ordering

(Kesner, 2000). All of these studies have supported the view that the rodent mPFC is functionally homologous to the primate dorsolateral prefrontal area. In our study, we employed ROC analysis to examine the effects of bilateral mPFC damage on performance in the item recognition task described above (Farovik, Dupont, Arce, & Eichenbaum, 2008). Based on the neuropsychological studies on humans, we expected that, in rodents, the mPFC would play a selective role in recollection and not familiarity, and that the recollection impairment would be attributed to an increase in false alarms.

We found that the ROC function of rats with mPFC lesions was remarkably similar to that of rats with hippocampal damage. The ROC curve in prefrontal rats, like that in hippocampal rats, was symmetrical and curvilinear, reflecting loss of the recollection component and sparing of the familiarity component (Figure 6a). These findings indicate that both the prefrontal cortex and hippocampus play selective roles in episodic recollection.

Further analyses of the ROC functions indicated that the nature of prefrontal involvement in recollection differed from that of the hippocampus. Specifically, analyses of hits and false alarms indicated that, in rats with hippocampal damage the deficit could be accounted for largely by reduction of hits that was particularly evident at the left side of the ROC function, which reflects the most conservative responses (compare data points at the same bias levels; see arrows in Figure 6b). The observation that rats with hippocampal damage are prone to identify old items as “new” is consistent with the view that they suffer an impairment of forgetting. By contrast, in rats with mPFC damage, the deficit could be accounted for largely by an increase in false alarms, again particularly evident at the left side of the ROC function (see arrows in Figure 6a). It is important to note that this deficit is not simply due to a failure of behavioural inhibition often associated with prefrontal damage, because an increase in the false alarm rate involves refraining from digging in the target cup (the “old” response) more often than controls.

The observation that rats with prefrontal damage are prone to identify new items as “old” is consistent with the view that they suffer an impairment of source monitoring. In this task, the same odor items were presented repeatedly across testing days, such that a central demand was to remember whether a particular odor was presented during the study phase on the same day as the test. A deficit in the ability to distinguish an odor that had occurred on the current day from previous occurrences on other days, or a deficit in distinguishing familiar from recollected odor, would be expected to result in an abnormally high false alarm rate, as observed. These observations indicate that the hippocampus and prefrontal cortex serve complementary roles, with the hippocampus involved in recalling old items and the prefrontal cortex involved in distinguishing the source of information that supports a recall judgment.

Discussion

Our ROC analyses provide an animal model that is useful for examining the roles of the hippocampus and other brain areas in distinct memory processes. Our results constitute strong evidence for the existence of two processes that support recognition memory in animals. One process is reflected in the asymmetry of the ROC, and is associated with a cardinal feature of episodic recollection in humans: the ability to remember once-presented associations. The other process is reflected in the curvilinearity of the ROC, and is associated with familiarity, here observed as intact familiarity in aged rats and as unitization of stimulus combinations. Furthermore, the results indicate distinct roles for the hippocampus and prefrontal cortex in episodic recollection. The hippocampus is critical for recollection of recently experienced stimuli and for associations of stimulus pairings. The prefrontal cortex also plays a selective role in episodic recollection, likely in supporting source monitoring. These findings

demonstrate functional specificity of distinct areas that support the capacity for episodic recollection.

Together, these observations support and extend the results from studies on humans. In addition, the findings discussed here provide a high degree of localization of specific brain areas, increasing our confidence about functional distinctions between neighbouring components of the medial temporal lobe. Thus, this animal model can be extended to examine the roles of other medial temporal and cortical areas in recollection and familiarity.

Dual process versus single process hypotheses of recognition memory

Our ability to manipulate experimental parameters to independently alter recollection and familiarity components of the ROC provide compelling evidence for the dual process theory and cannot be explained by a single process view. The evidence includes findings that the ROC is asymmetric and linear in associative recognition but symmetric and curvilinear in aging, and that, within associative recognition, hippocampal damage results in opposite effects on the asymmetry (decreased) and curvilinearity (increased) of the ROC. Furthermore, several findings indicate a selective role for the hippocampus in episodic recollection and not just in strong memories. These include the selective loss of recollection in item recognition that cannot be attributed to weakened memory and the contrast with intact familiarity and, under some conditions, as double dissociation between decreased recollection and increased familiarity in animals with compromised hippocampal function.

In studies on humans, there is currently considerable controversy about whether the DPSD or UVSD model better accounts for the ROC data, and about whether the hippocampus plays a selective role in episodic recollection and not familiarity or instead is involved in strong memories of either type (see reviews by Wixted, 2007) and Parks & Yonelinas, 2007). There is also considerable evidence favoring each view about the hippocampus both from studies on amnesic patients and from functional imaging (see reviews by (Eichenbaum et al., 2007; Squire et al., 2007)). Studies on amnesia in humans may not be able to resolve the issue because it is not possible to be sure that areas outside the hippocampus are not compromised in amnesic patients. Studies that employ functional imaging to show selective hippocampal activation for associative memory can be interpreted instead as reflecting a nonlinear response to strong memory, and conversely, studies showing hippocampal activation for strong familiarity can be interpreted instead as reflecting memory for untested, earlier learned associations of the familiar stimulus (Wais, Squire, & Wixted, 2009). Studies on animals can improve our understanding on these issues because the lesions can be highly selective and because experience with stimulus items is fully under experimental control. Furthermore, our protocols, which so clearly distinguish dual processes in recognition, provide suggestions for improvements in the testing protocols used on humans. We have directly manipulated the response criterion rather than rely on subjective confidence judgments, as typically used in studies on humans. Also, in studies of associative memory, we have used numerous contextual stimuli (media) that are distinct from the items to be remembered (odors), rather than typical studies on humans wherein the contexts are features of the items (e.g. the color or voice of word cues), which confuses the contexts and items. Furthermore, there are typically only two contexts, which results in massive interference between the associations between many items with one of two contexts.

Relation to other animal models of episodic memory

Multiple efforts to model hippocampal function in episodic memory in animals have focused on the contents of episodic memories, specifically on what happened, where, and when (Clayton & Dickinson, 1998; Dere et al., 2006), and these studies have generally supported the view that the hippocampus is critical to memory for a combination of these features of memory,

even when it is not critical for memory of individual stimuli (Mumby, 2001, but see Clark, Zola, & Squire, 2000). In a study designed to test whether the hippocampus is critical in memory for integrating what-where-when information, we trained rats on a task that assesses memory for events from single episodes involving a combination of odors (“what”) presented in unique places (“where”) in a specific order (“when”; Ergorul & Eichenbaum, 2004). On each trial, rats sequentially sampled a unique series of four rewarded odor stimulus cups, each in a different place along the periphery of a large open field. Then, memory for the order of those events was tested by presenting a choice between an arbitrarily selected pair of the odor cups in their original locations. Because rats could employ memory for the locations of the cups (“where”) without using odor information (“what”), we also measure responses based purely on location information in two ways: First, we recorded the initial stimulus the animal approached; we separately determined that rats can’t tell which odor is inside until they approach the odor cup. Second, we presented probe memory tests in which the odors were omitted and the rats had to use the locations only to identify which odor was presented earlier.

Normal animals performed well in the standard what-where-when tests. Furthermore, they performed above chance but less well than on the standard test in first approaching the correct cup. Therefore, it appears that normal rats make an initial good guess about which item occurred first (“when”) based on location information (“where”) and then they confirmed or disconfirmed their choice based on the odor in the cup (“what”). Furthermore, normal rats fall to chance performance in the probe tests that omitted the odors, providing strong evidence that normal rats form strongly integrated representations of what happened when and where, such that they considered items that lacked the correct “what” component distinct from either correct item. Rats with hippocampal damage were severely impaired on the standard what-where-when memory judgments, performing no better than chance. Interestingly, animals with hippocampal damage tended to first approach the most recently reinforced cup, in opposition to their training to approach the earlier presented cup, suggesting their performance was driven by an intact system guided by recent reinforcement. These observations indicate that normal rats can remember single episodes of what happened, where, and when, and that this ability is based on highly integrated what-where-when representations that are supported by the hippocampus. Confirming this conclusion, in a recent study we recorded from hippocampal neurons in rats performing a task in which they had to learn what happens where. We found that hippocampal neurons develop representations of particular events in specific places. Furthermore, the appearance of these representations, and not representations of individual items or places, parallels learning and predicts performance accuracy (Komorowski et al., 2009). These findings complement the results from our ROC analyses of recognition memory, such that the evidence from the ROC studies informs us about the retrieval dynamics of episodic recollection while the studies on what-where-when tests inform us about the contents of what is recollected.

Finally, the observations discussed here support recent proposals about the functional organization of the medial temporal lobe memory system, and suggest that the fundamental mechanisms of this system are conserved among mammalian species (Eichenbaum et al., 2007; Davachi, 2006). According to this view, familiarity for specific objects is processed by cortical areas of the MTL that receive predominant input from the so-called “what” stream of the neocortex, whereas spatial and other contextual information are processed by other MTL cortical areas that receive predominant input from the “where” stream of the neocortex. Outputs of these MTL cortical areas are then linked within the hippocampus to support recall of events in the context in which they occurred. While the identification of neocortical “what” and “where” streams originates in studies on primates, the anatomical organization of these streams into the MTL and their connections with the hippocampus is quite similar across all mammalian species that have been studied (Manns & Eichenbaum, 2006). The dynamics of memory revealed by our ROC analyses converge with both these anatomical findings and studies on

humans that posit within the hippocampus a critical role in binding event and context information in support of episodic recollection.

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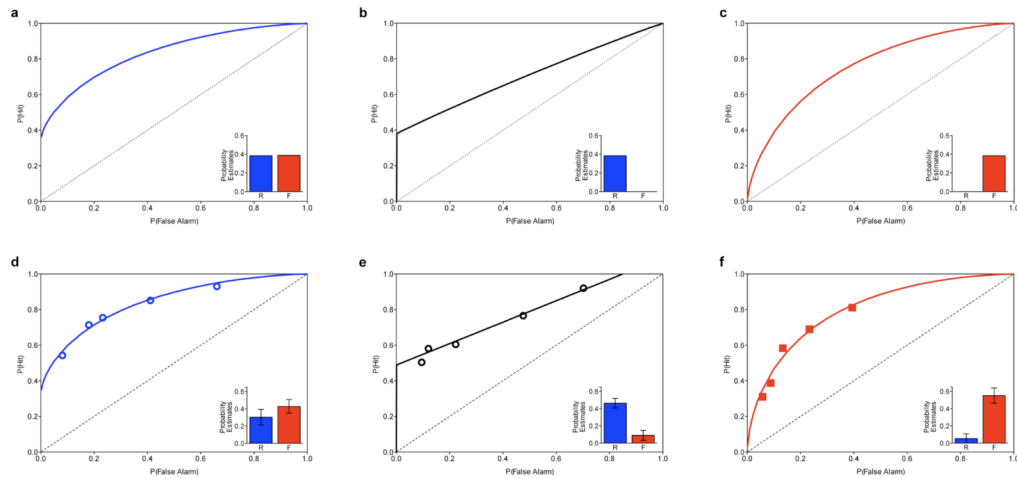


Figure 1.

Ideal ROC functions for human recognition memory predicted by Dual Process Signal Detection (DPSD) theory (see Yonelinas, 2001) and observed ROC functions for recognition memory in rats. a–c. Humans. a. Item recognition. The ROC curve is typically asymmetrical and curvilinear. Quantitative measurements of the contributions of recollection (R) and familiarity (F) are calculated as probability estimates shown in the inset of this and other figures (see Yonelinas et al., 2002). b. ROC function observed when performance is based only on recollection. c. ROC function observed when performance is based only on familiarity. d–f. Rats. d. Item recognition (data from Fortin et al., 2004). Recollection and familiarity components are both robust, similar to the ideal item recognition ROC in humans (panel a). b. Associative recognition (data from Sauvage et al., 2008). The ROC becomes linear, similar to the ideal ROC of humans when performance is based on recollection only (panel b). c. Item recognition in aged rats (data from Robitsek et al., 2008). The ROC becomes symmetrical and curvilinear, similar to the ideal ROC of humans when performance is based on familiarity only (panel c).

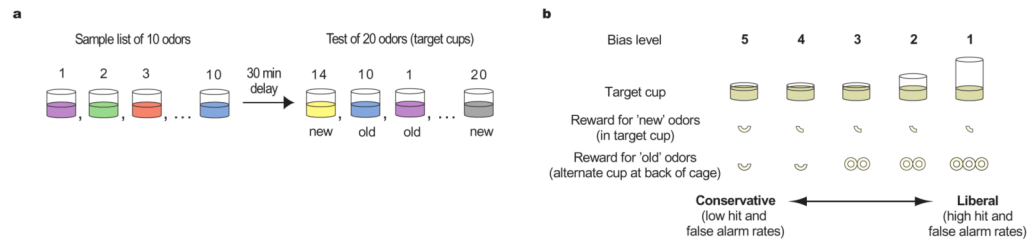


Figure 2.

The item recognition task developed for rats (from Fortin et al., 2004). a. Sequence of odor presentations on the sample and test phases. b. Bias levels determined by variations in cup height and payoff ratio of Froot Loop rewards.

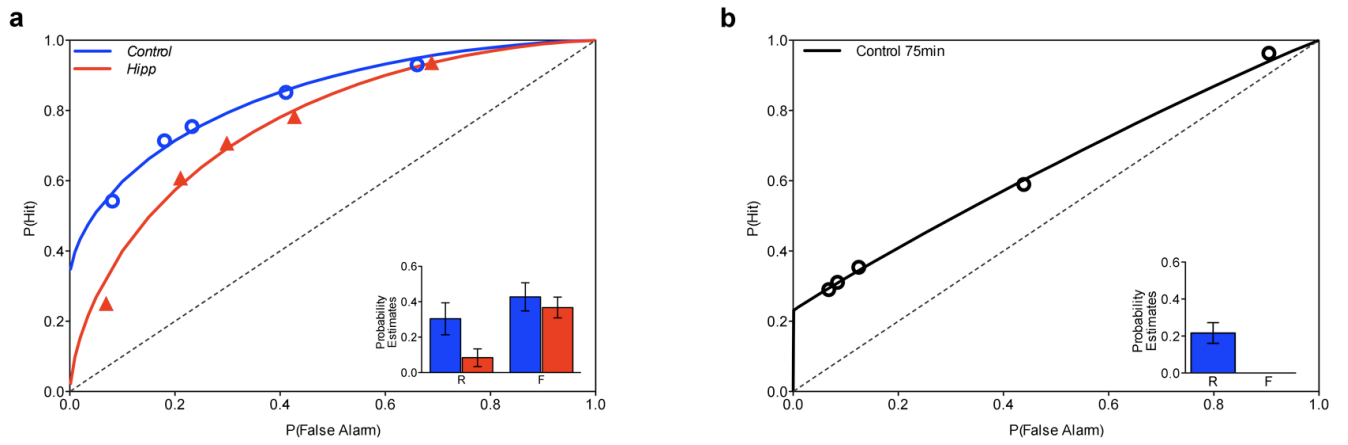


Figure 3. Item recognition ROC of rats with hippocampal damage (data from Fortin et al., 2004). a. Hippocampal damage eliminates recollection based performance and spares familiarity based performance. b. ROC function in normal rats with increased memory delay.

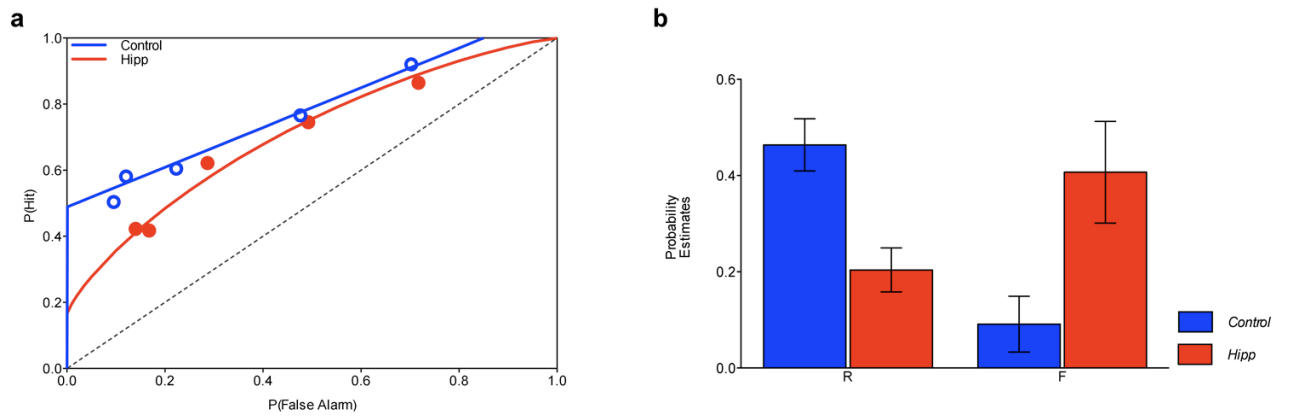


Figure 4. Associative recognition ROC of rats with hippocampal damage (data from Sauvage et al., 2008). a. Hippocampal damage reduces the asymmetry and causes the ROC function to become curvilinear. B. Comparison of probability estimates show a statistically significant double dissociation of decreased recollection and increased familiarity following hippocampal damage.

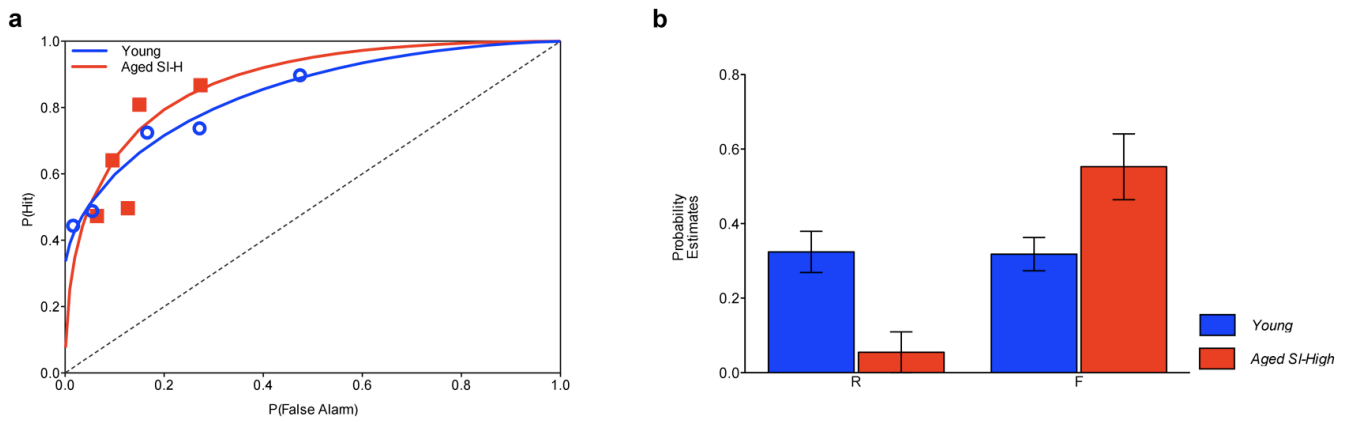


Figure 5.

Item recognition ROC in a subset of aged rats that perform exceptionally well in overall recognition (% correct; data from Robitsek et al., 2008). a. The ROC function of these aged rats is symmetrical but more curvilinear than that of young rats. b. Comparison of probability estimates show a statistically significant double dissociation of decreased recollection and increased familiarity in these aged rats (SI-High) compared to young rats.

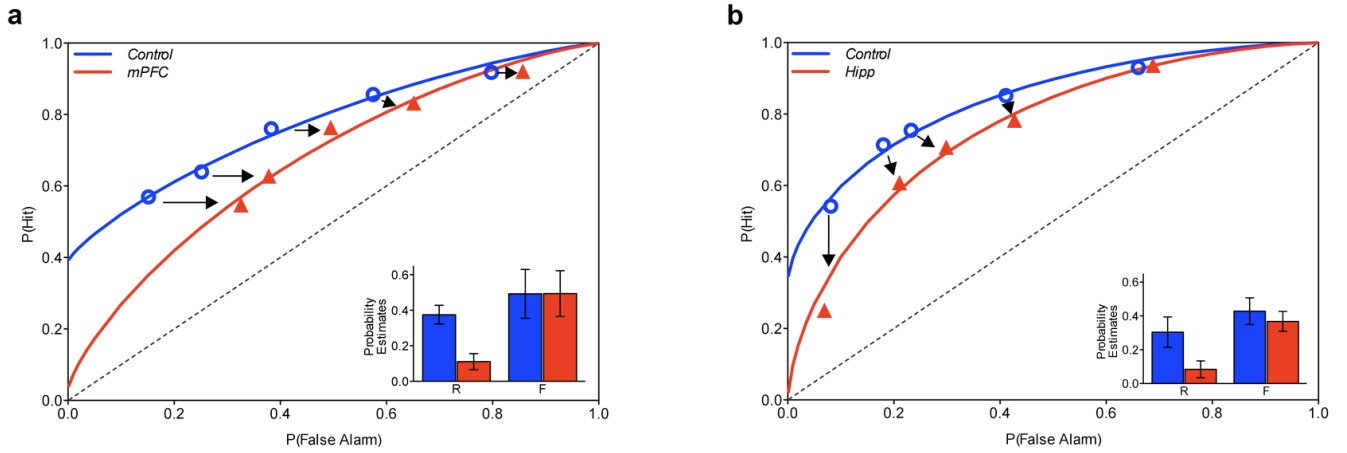


Figure 6. Item recognition ROC of rats with prefrontal damage as compared to that of rats with hippocampal damage. Arrows indicate comparisons between data points at the same bias level. a. Rats with prefrontal damage have selectively decreased recollection that can be attributed to a higher false alarm rate (data from Farovik et al., 2008). b. Rats with hippocampal damage also have selectively decreased recollection, but by contrast to prefrontal rats, the deficit following hippocampal damage is due to a lower hit rate (data from Fortin et al., 2004).