ELSEVIER

Experimental Gerontology 38 (2003) 61–69

Experimental Gerontology

www.elsevier.com/locate/expgero

The neurobiology of memory changes in normal aging

C.A. Erickson[a,b], C.A. Barnes[a,c,*]

[a]*Arizona Research Laboratory Division of Neural Systems, Memory and Aging, University of Arizona, Rm. 384, Life Sciences North Building, Tuscon, AZ 85724-5115, USA*

[b]*California Regional Primate Research Primate Center, University of California Davis, Davis, CA 95616, USA*

[c]*Departments of Psychology and Neurology, University of Arizona, Tuscon, AZ 85724, USA*

Received 6 June 2002; accepted 19 June 2002

Abstract

Cognitive alterations occur over the lifespan of every species studied and have been quantified carefully in humans, other primates and rodents. Correspondingly, changes in hippocampal function have been associated with a number of observed memory impairments across species. It appears that humans, alone, show Alzheimer's disease-like cognitive and neural pathology spontaneously. Thus, a comparison of normal age-related changes in cognition in other animals can help disambiguate the boundary between normal and pathological states of aging in humans. Another important contribution made from studying aging in non-human species is the ability to examine, in more detail, the basic neural mechanisms that may be responsible for brain aging in these species. So far, most of the functional neurobiological studies have been conducted in the aged rat. We propose that the link between rodent and human work can be made much stronger by combining neurophysiological and behavioral investigation of normal aging in the non-human primate.

Keywords: Normal aging; Learning and memory; Humans; Monkeys; Rats; Hippocampal plasticity; Ensemble dynamics

1. Introduction

The brain has remarkably enduring plasticity considering the wear and tear that comes with the natural life history of all beings. In normal aging, cognitive abilities tend to decline more slowly and to a lesser degree than do physical abilities. Despite this resilience, some level of cognitive impairment is expected as aging progresses, relative to performance levels at younger ages. The change with age in ability to remember certain types of information has been referred to as 'age-associated memory impairment' (Crook et al., 1986). Although changes in memory with age can be variable between individuals, and all types of memory are not affected equally, alterations in memory can be observed objectively at least by the fifth decade in humans (e.g. Albert et al., 1987), and many in this age group notice subtle changes in memory. It is clear that understanding how the brain changes during normal aging must be known before the boundary between normal and pathological conditions can be understood fully (Albert, 2002). Two powerful approaches have been used to reach such an understanding. One has been to compare the types of memory altered during normal aging with surgical or accidental lesions of specific brain regions. This allows identification of brain structures critical to functions most affected during the aging process. The other has been to assess memory and brain function across species in order to identify commonalities. Once the brain regions most responsible for age-related cognitive change are identified, then it is possible to study the underlying mechanisms at finer levels of analysis. Several examples of these approaches are reviewed below.

2. Medial temporal lobe involvement in age-related memory deficits in humans

There are certain types of memory that show no apparent decline during normal aging. For example, normal elderly do not forget how to write, drive a car, or make a cup of tea, and vocabulary actually increases throughout life (Owen, 1953). One way to determine which brain regions are most

* Corresponding author. Address: Arizona Research Laboratory Division of Neural Systems, Memory and Aging, University of Arizona, Rm. 384, Life Sciences North Building, Tuscon, AZ 85724-5115, USA. Tel.: +1-520-626-2616; fax: +1-520-626-2618.

E-mail address: carol@nsma.arizona.edu (C.A. Barnes).

0531-5565/03/$ - see front matter
PII: S0531-5565(02)00160-2

affected by the aging process is to compare cognitive changes that occur as a result of age, with the behavioral profile of individuals that have surgical removal or accidental damage to specific parts of the brain. Humans with the most profound memory changes are those individuals that experience medial temporal lobe damage. In the classic case of patient H.M., who underwent bilateral removal of the temporal lobes for intractable epilepsy, perceptual abilities and short-term memory for objects remain intact; however, he shows profound memory deficits for recognition of these same objects if delay intervals are imposed (e.g. Corkin 1984). H.M. also shows impaired spatial navigation, although he is able to learn topographical information slowly, after repeated exposure to some environments (Corkin, 2002). Some of these memory deficits are also observed in children that experienced anoxia at birth and have selective hippocampal lesions (Vargha-Khadem et al., 1997). These children are impaired in object/place recognition performance and in their ability to find their way in familiar environments. Qualitatively similar deficits have been observed in aged humans, monkeys, rats and mice (discussed below).

3. Deficits in recognition memory following medial temporal lobe damage and changes in recognition memory during normal aging

3.1. Humans

As discussed above, damage to medial temporal lobe structures results in a classic amnesic syndrome in humans, the severity of which can be objectively measured using one of a number of versions of standard visual recognition memory tasks (Correll and Scoville, 1965). Flicker et al. (1984) examined normal young and aged individuals, as well as demented subjects, on a delayed visuospatial recall task. This task is conceptually similar to the delayed non-matching-to-sample task, discussed in more detail in Section 3.2. The subjects were required to remember which room of a 25 room house, presented on a computer monitor, was illuminated over delays of 0–2 min. No differences were found in performance on immediate recall between the normal young and elderly groups. There was, however, a larger decline in recall accuracy in the normal elderly compared with the young group when the delay intervals were increased (Fig. 1(A)). An additional group with mild dementia exhibited more pronounced deficits at all delay intervals.

3.2. Non-human primates

In the search for tasks that capture memory deficits observed in human amnesics, the delayed matching or non-matching-to-sample (DNMS) tasks emerged as useful tools for studying such memory deficits in non-human primates (Gaffan, 1974; Mishkin and Delacour, 1975). In the DNMS task, each trial consists of a sample and a recognition phase. An object is placed in the middle hole of a stimulus tray, and an opaque screen is lifted to initiate a trial. The monkey is allowed to displace the object and obtain reward. The opaque screen is lowered and the sample object is placed over one lateral well, and a novel object is placed over the other lateral well. There is food reward below the novel object. If the novel object is displaced, the monkey is allowed to retrieve the food reward. New objects are used for each trial to prevent interference from prior experience. One strength of this task is that memory deficits can be

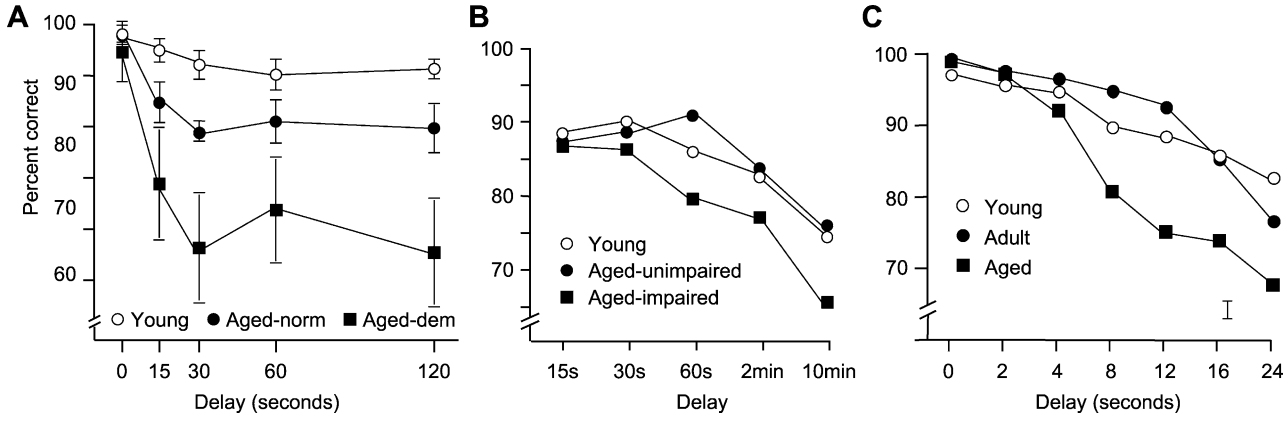

Fig. 1. Recognition memory tested over increasing delay intervals comparing young and aged humans, monkeys, and rats. In each of these experiments, memory is tested across a number of different delays. Performance is measured by percent correct on the *y*-axis of each graph, and the delay period is shown on the *x*-axis. (A) Normal aged humans (57–85 yr) tested on an object/place recognition task perform well at the shortest delays, but showed a more dramatic decline in performance than did the young group (18–42 yr) over longer delays. Performance was most impaired in those individuals (57–85 yr with mild dementia (modified with permission from Flicker et al., 1984, Fig. 1). (B) Performance of young and aged monkeys on the standard version of the delayed non-matching-to-sample task reveals that a subset of aged monkeys (aged-impaired, 24 yr) exhibited impaired performance, while another subset of aged (aged–unimpaired, 24 yr) and young monkeys (10 yr) performed similarly (modified with permission from Rapp and Amaral, 1991, Fig. 3). (C) Aged rats (24 months) showed deficits on a delayed non-match-to-place task compared to young (6 months) and middle-aged (15 months) rats (modified with permission from Dunnett et al., 1988, Fig. 1C, error bar shown in lower right, SEM).

demonstrated in the absence of perceptual deficits. Medial temporal lobe-lesioned monkeys are able to perform the task as well as control animals at the shortest delays between presentation of the sample and choice objects, but fail at longer delays (e.g. Mishkin, 1978).

Since these early studies, technical improvements in lesioning techniques have allowed analysis of the contributions made by subregions of the medial temporal lobe to the observed memory deficits. Neocortical inputs converge into the hippocampus from virtually every association area through the entorhinal cortex, and then diverge through a set of back-projecting pathways from the hippocampus via the entorhinal cortex to the areas that originally provided input to the hippocampus. There are two main cortico-hippocampal streams that flow into the entorhinal cortex: perirhinal cortex (area 35, 36) and parahippocampal cortex (area TH/TF in monkeys, postrhinal cortex in rats; e.g. Witter et al., 1989; Burwell and Amaral, 1998). The perirhinal cortex receives input from all sensory modalities and anterior association systems, including prefrontal areas thought to be involved in attention and working memory, as well as being connected with subcortical reward systems (e.g. Burwell, 2000). The parahippocampal cortex is heavily innervated by the visual modality and has connections with regions important for visuospatial orienting such as the parietal cortex and lateral posterior nucleus of the thalamus (e.g. Burwell, 2000).

A debate has arisen in the literature concerning whether the hippocampus is significantly responsible for visual recognition memory, as tested using the delayed non-matching-to-sample task (e.g. Baxter and Murray, 2001a,b; Zola and Squire, 2001). Of the three studies in which neurotoxic lesions of the hippocampus have been made in the monkey, two experiments show delay-dependent deficits in the DNMS task, and one does not (Table 1). The authors of these studies have offered the numerous variations in experimental procedure as explanations. In the perirhinal lesion studies listed in Table 1, all found delay-dependent effects of the lesion. One suggestion for a resolution of the apparent discrepancy concerning the hippocampus' role in the DNMS task can be offered. If the results are viewed in the context of the hypothesis that the hippocampus is only necessary for the initial acquisition of the highly specialized skill that performance of the DMNS task requires, then there are no discrepant findings. In the one study in which the monkeys were pretrained on the task before the hippocampal lesion (Murray and Mishkin, 1998), thereby permitting cortico-hippocampal interactions during training, there was no deficit. On the other hand, there is no effect of pretraining on perirhinal-lesioned monkeys. This suggests that the modification that takes place during the time that the monkey becomes a DNMS visual recognition 'expert', resides in the perirhinal cortex. In summary, intense training on the DNMS task appears to alter the circuitry of the perirhinal cortex so that it has the computational capacity to solve the problem on its own. This altered circuitry appears to come about through the engagement of the hippocampus during training. While other explanations may be possible, this one is internally consistent with the relevant data.

Table 1
Summary of the effects of selective hippocampal (HIP), amygdala (AMY) perirhinal (PR), and entorhinal (ENT) lesions on the delayed non-matching-to-sample (DNMS) task

Experiment	Lesion	Pretraining	DNMS
Murray and Mishkin, 1998	HIP + AMY	YES	No deficit
Beason-Held et al., 1999	HIP	NO	deficit
Zola et al., 2000	HIP	NO	deficit
Meunier et al., 1993	PR	YES	deficit
Buffalo et al., 1999	PR	NO	deficit
Baxter and Murray, 2001a,b	PR + ENT	YES	deficit

Like monkeys with damage to hippocampus and nearby cortical regions, aged monkeys show deficits on object recognition memory. Results from a number of laboratories have shown that aged monkeys show an impairment in the acquisition and performance in delayed response tasks (e.g. Bartus et al., 1978) and the delayed non-matching-to-sample task (Presty et al., 1987; Moss et al., 1988; Arnsten and Goldman-Rakic, 1990; Rapp and Amaral, 1989; Rapp and Amaral, 1991; Bachevalier, 1993), although the extent of the deficit in DNMS varies among the older monkeys. In the Rapp and Amaral, (1989) study, young and old monkeys showed performance levels over 85% at the 15 s delay, but one group of aged monkeys ('aged-impaired', Fig. 1(B)) showed significantly worse performance at delays from 1 to 10 min. Taken together with the lesion literature cited above, these data suggest that at least a subgroup of older monkeys have deficits that may arise from perirhinal/hippocampal dysfunction.

3.3. Rodents

Rats also learn object-guided, delayed non-matching-to-sample tasks, although, these tasks are difficult for them to learn. When rats are pretrained on the DNMS procedure, hippocampal lesions produce mild impairments (Mumby et al., 1990), while with no pretraining, perirhinal lesioned rats show clear delay-dependent deficits (Wiig and Bilkey, 1995). Spatial-guided versions of the DNMS task are learned more rapidly by rats, and perirhinal lesions also affect memory performance in this version of the task. Dunnett et al. (1988) tested young, middle-aged and old rats in a delayed non-matching-to-position task (Fig. 1(C)). The old rats show clear delay-dependent memory deficits in this task, again, reminiscent of hippocampal/perirhinal dysfunction.

4. Deficits in the visual paired-comparison task following medial temporal lobe damage and changes in performance of this task during normal aging

4.1. Medial temporal lobe damage and novelty preference behavior

The visual paired-comparison task exploits the tendency of novel objects to catch one's eye. The subject is presented with a stimulus for a familiarization period. After this, a pair of stimuli are presented for viewing, the familiar one and a novel one. Normal subjects show a viewing preference for the novel stimulus, and this preference has been taken to reflect recognition memory. McKee and Squire (1993) examined the stimulus viewing preference of medial temporal lobe amnesic patients and showed that at short delays there were no differences in time spent viewing the novel stimulus between amnesics and controls, but that at longer delays, this preference dropped off precipitously. The same pattern of results has been obtained in monkeys with lesions of the hippocampus (Pascalis and Bachevalier, 1999) or perirhinal cortex (Buffalo et al., 1999). The lesioned monkeys show less novelty preference at longer delays. Rats also have a natural tendency to explore novel objects more than familiar ones, and tests of this tendency are conceptually similar to the visual paired-comparison tasks used in humans and monkeys. In a recent study, this type of novelty preference was tested using objects, places or contexts as stimuli. Selective hippocampal lesions produced a reduction in novelty preference for the place and contextual stimuli, but not the object stimuli (Mumby et al., 2002). It will be interesting to examine performance of rats on the same series of tasks following perirhinal lesions.

4.2. Aged-related changes in performance of the visual paired-comparison or novelty preference tasks

To our knowledge, no studies have been conducted using the visual paired-comparison task in normal aged humans. Recently we have collected preliminary data from 2 young and 2 aged monkeys on a computerized version of the visual paired-comparison task (Erickson et al., 2001). An infrared eye tracking camera was used in order to monitor more precisely the eye movements of the monkeys (Fig. 2(A)). The monkeys sat facing a computer monitor in which digitized images of scenes or objects are displayed. First, a small spot appears at the center of the screen. When the monkey turns its gaze to the white spot, a picture comes up on the screen, followed by a variable delay (blank screen), and finally followed by the white spot again. When the monkey fixates the white spot again, two images are presented side by side (the previously viewed image and a novel image). There were no differences between age groups in fixation performance (Fig. 2(D)). All of the monkeys showed a preference for the novel stimulus, but

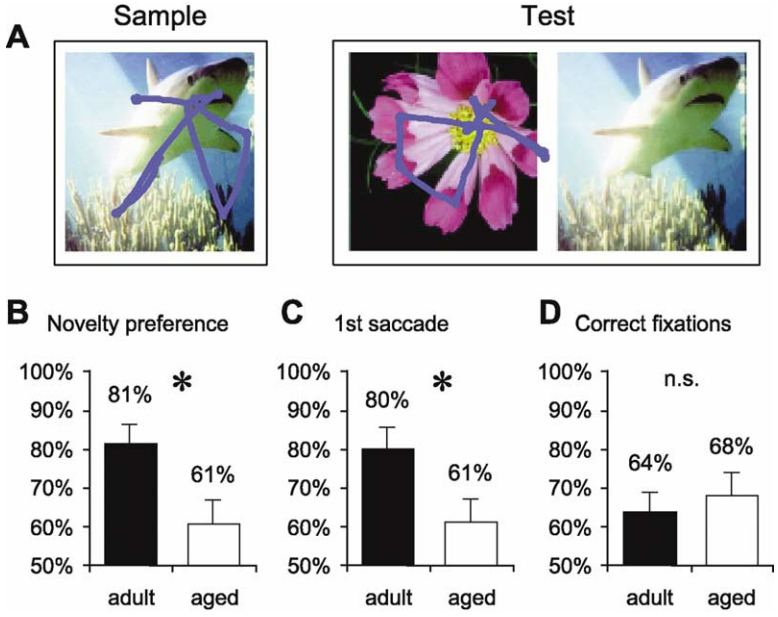

Fig. 2. Visual paired-comparison task used to test memory in young ($\bar{x}$ = 12 yr) and old ($\bar{x}$ = 28 yr) monkeys. (A) In the VPC task, monkeys are shown a sample image (*Sample*, left) at the center of a computer monitor. After a delay, they are shown the same image paired with a novel image (*Test*, right), and are rewarded for simply looking at the images presented. Eye movement data (blue line) superimposed over the image, illustrate the viewing preference for novelty. During the Test phase, the eye position begins midway between the stimuli, then typically moves first towards the novel image, as shown in this example. (B) In data collected from 2 young and 2 old monkeys, the young monkeys showed more novelty preference than did old monkeys as measured by the percent of time looking at the novel stimuli (50% is chance). (C) The young monkeys also made a higher percentage of first saccades to the novel image than did the old monkeys. (D) The percent of trials in which the monkeys maintained their gaze on the pictures (a measure of attention), however, did not differ between age groups (Erickson et al., 2001).

the young monkeys showed a much stronger preference than did the aged monkeys (Fig. 2(B)), and were more likely to make their first saccade toward the novel image (Fig. 2(C)). This age-related deficit is consistent with the hypothesis that the old monkeys have impaired hippocampal function. When young and old rats are tested in object exploration tasks, old rats show reduced exploration of objects that have been changed in space, but normal exploration of new objects inserted into a given space (Soffié et al., 1992; Cavoy and Delacour, 1993). Taken together, these data suggest that a closer examination of these tasks in aged rats, monkeys and humans would be fruitful.

5. Deficits in spatial memory after medial temporal lobe damage and changes in spatial memory with age

5.1. Spatial memory deficits after hippocampal lesions

Studies that have examined humans with neurological damage that include the hippocampus have reported deficits in these patients' ability to navigate, particularly when the environment had not been learned before the brain injury (e.g. see Section 2 above and Teng and Squire, 1999). Although there have been no studies of navigational ability in monkeys following hippocampal lesions, a number of studies have shown that hippocampal damage produces deficits in associating objects with their specific position in space (e.g., Parkinson et al., 1988; Angeli et al., 1993; Murray et al., 1998). There have been numerous studies conducted in rats that have shown altered spatial navigation following hippocampal damage (e.g. O'Keefe et al., 1975; Morris et al., 1982), in a variety of mazes. Together, these data suggest that the hippocampus is important for this type of memory across all species tested.

5.2. Age-related changes in spatial memory

Old, normal aged humans (e.g. Uttl and Graf, 1993; Wilkniss et al., 1997; Newman and Kaszniak, 2000), old monkeys (e.g. Lai et al., 1995; Rapp et al., 1997) old rats (e.g. Barnes, 1979; Markowska et al., 1989; Gallagher and Rapp, 1997) and old mice (Bach et al., 1999) all show spatial memory impairments compared with their younger counterparts. For example, Uttl and Graf (1993) studied the ability of groups of people from 15 to 74 yr of age to navigate through, and remember, spatial location information in a museum exhibit. The subjects showed an age-related decline in memory for the location of target exhibits, that began to appear during the sixth decade (Fig. 3(A)).

Rapp et al. (1997) designed a large scale spatial navigation task that takes advantage of the natural exploratory tendency of monkeys. Eight locations were baited around the perimeter of a large octagonal platform, food reward could only be obtained once in any location, and delays could be imposed between choices. Old monkeys became particularly impaired when delays of 30 min to 2 h were imposed between choices (Fig. 3(B)). It would be particularly interesting to examine this delay-dependent deficit while recording cells from hippocampus or surrounding structures, in young and old monkeys.

When young and old rats are compared on spatial navigational tasks, such as the Morris swim task, the clear and consistent finding between laboratories is that old rats do not remember the spatial location of the escape platform as well as do young rats. An example of this can be seen in

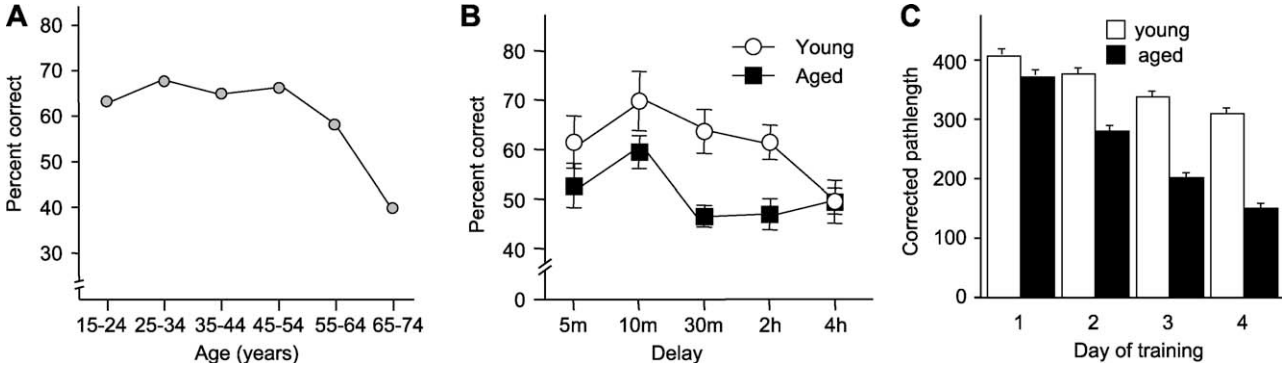

Fig. 3. Examples of spatial memory deficits observed in humans, monkeys, and rats. (A) Normal aged humans exhibited impairments on a task that required them to remember the location of exhibits in a science museum. The ability to remember the locations in this novel environment declined in individuals over 55 yr of age (modified with permission from Uttl and Graf, 1993, Fig. 3). (B) Young (7 yr) and aged (27 yr) monkeys were tested on a spatial working memory task in which they had to forage for food hidden in wells. (modified with permission from Rapp et al., 1997, Fig. 3). When increasing delays were imposed between choices, the old monkeys showed memory impairments—the old monkeys' performance was significantly worse than the young at the 30 min and 2 h delays. (C) Aged (~28 months) and young (~12 months) rats were tested on the spatial version of the Morris swim task, in which, rats are required to swim in a pool of cloudy water until they find the location of a hidden platform. Shown here is the average performance of six training trials on each of the four days of testing. Young rats become proficient at finding the hidden platform during this time, whereas on average, aged rats do not learn as quickly and never achieve the same level of performance as do the young rats. Corrected pathlength is the distance of the swim path corrected for distance to the target location and swim speed (modified with permission from Barnes et al., 1997, Fig. 3A).

Fig. 3(C), in which mean performance of young and old rats (about 100 in each group) is plotted over 4 consecutive days (6 trials averaged for each day). Clearly, old rats, as a group, do not learn this problem as well as do younger rats (Barnes et al., 1997), even when motor, motivational and visual problems are ruled out as major contributing factors. Again, in old humans, monkeys and rats, the data are consistent with the hypothesis that hippocampal dysfunction contributes to memory deficits observed during aging.

6. What are the underlying neural mechanisms that contribute to age-related changes in hippocampal-dependent memory?

6.1. Numbers of principle neurons in hippocampus does not change with normal aging

There is a common misconception that substantial neuronal loss is associated with aging. Part of this perception comes from the fact that neurons do die as a consequence of strokes, various degenerative processes and Alzheimer's disease. Careful anatomical studies, however, have shown that there is no loss of neurons in the primary CA fields of the hippocampus, nor do granule cell numbers change during normal aging in humans (West, 1993), monkeys (Rapp, 1995; Peters et al., 1996), rats (Rapp and Gallagher, 1996; Rasmussen et al., 1996), or mice (Calhoun et al., 1998). Furthermore, it is not only the case that neurons do not die in large numbers, but that they continue to be regenerated well into adulthood. For the granule cells of the hippocampus, at least some of the new neurons are known to be functional upon maturation (van Praag et al., 2002). Even though the numbers of new cells is very small (only a fraction of a percent of the total population), the potential to add functional neurons is remarkable. The fact that neurons are not dying as you read this manuscript might mean one of two things: it could be bad news, because if age-related cognitive decline was due to an indiscriminate loss of cells throughout the brain, then the therapeutic solution might be simple-find a drug that would keep cells from dying. On the other hand, lack of generalized cell death could be good news. If cell death is limited in the normal aged brain, then drug therapies can be targeted at promoting cell health and function, rather than at the harder problem of recreating cells in appropriate regions.

6.2. Why study age-related neurobiological changes in the hippocampus of the rat?

With recent advances in neural imaging, changes in brain function can be assessed throughout the lifespan of humans (e.g. Small et al., 2002); although the resolution of current imaging methods cannot resolve small structures or individual cells. Furthermore, the interpretation of what a given change might mean, using current imaging methods, remains unspecified. The advantages of age comparisons across species are clear, if age-related memory changes in mammals are consistent and predictable, then studying the neurobiological underpinnings of these cognitive changes in less complex species, should facilitate fundamental insights into these deficits in humans. Because there have, as yet, been no electrophysiological recordings in awake behaving young and old monkeys (and these experiments are not feasible in aged humans), the focus in this section is on the rat. There is a large literature on the functional consequences of brain aging in this species, and a selected overview is given below.

The hippocampus of the rat exhibits complex, region-selective changes in its functional organization during aging (for reviews, Rapp and Amaral, 1992a,b; Barnes, 1994, 1998; Geinisman et al., 1995). Two important changes include reduced persistence of experimentally induced, long-term potentiation (LTP) of hippocampal synapses, which is correlated with faster behavioral forgetting of spatial information (Barnes, 1979; Barnes and McNaughton, 1980, 1985). In addition, there is both direct (Geinisman et al., 1992) and indirect evidence (Barnes et al., 1992; Calhoun et al., 1998; Smith et al., 2000) for a loss of synaptic connectivity and integration among hippocampal cells in old rats, which can lead to a reduced probability or magnitude of LTP induction (Deupree et al., 1991; Moore et al., 1993; Rosenzweig et al., 1997). The ability of convergent inputs to cooperate in the induction of this phenomenon (McNaughton et al., 1978) has made LTP a prime candidate for a mechanism for associative memory and also a prime suspect in the etiology of age-related memory dysfunction (e.g. Landfield et al., 1978; deToledo-Morrell et al., 1988; Barnes et al., 1994).

While LTP provides one view of the cellular computation accomplished in hippocampal circuits, extracellular recordings of single and multiple cells in the hippocampus provide a window into the network dynamics of the system that may underlie associative memory. In rats, hippocampal pyramidal and granule cells ('place cells') fire spikes over limited portions of an environment through which the animal passes (the 'place field' of the cell; O'Keefe and Dostrovsky, 1971). With the advent of methods that allow recording of over 100 hippocampal cells simultaneously, it is now possible to reconstruct the position of the rat within an environment from the ensemble activity of place cell firing patterns alone (Wilson and McNaughton, 1993). It is proposed that the ensemble pattern of place-specific firing is stabilized by strong synaptic interactions among neurons with neighboring place fields in an environment, which result in 'attractor' dynamics. In different environments, the spatial relationships among the fields of the same ensemble of neurons change drastically. These distributions of ensemble activity are often referred to as 'maps' (as we do here for convenience), but these maps are not necessarily two dimensional or uniform, and, it must be emphasized that

they can depend on numerous other, non-spatial variables such as task requirements (Markus et al., 1995).

Place field stability and robustness in young rats is clearly enhanced rapidly with experience (Wilson and McNaughton, 1993). Just as predicted by theories of sequence learning (Levy, 1989; Blum and Abbott, 1996), when young rats traverse linear tracks, place fields expand in the direction opposite to the direction of motion of the rat, and firing rates increase over the first few traversals of the track on a given day (Mehta et al., 1997). Because of the temporal asymmetry of LTP (Levy and Steward, 1983), repeated traversals of a route can cause cells at a given location to activate subsequent cells in the sequence, before the rat actually reaches the original firing location. This hypothesis is given support from the observation that this experience-dependent hippocampal place field expansion is NMDA receptor-dependent (Ekstrom et al., 2001), as is LTP induction.

Consistent with known age-related changes in hippocampal plasticity, old rats fail to show robust experience-dependent place field expansion (Shen et al., 1997). The lack of field broadening in old rats might therefore be expected to lead to a failure to link together the spatial components of a route. Deficits in this form of plasticity may also contribute to the differences between age groups in the stability of map formation. Old rats sometimes show map retrieval failures, both in the sense that they retrieve different maps for identical stimulus configurations, or fail to retrieve a different map when stimuli are significantly changed (Barnes et al., 1997; Tanila et al., 1997a,b). The finding that failure of map retrieval (or 'remapping') is more prevalent in old than in young rats might be explained by faulty association of inputs. The evidence that supports this hypothesis includes the observations that LTP at hippocampal intrinsic or afferent synapses is less easily induced (e.g. Deupree et al., 1991; Moore et al., 1993; Rosenzweig et al., 1997), and less durable (e.g. Barnes, 1979, 1994; Bach et al., 1999). There is also a loss of rapid NMDA- and experience-dependent place field expansion in aged hippocampal CA1 paramidal cells (Shen et al., 1997). Furthermore, hippocampal map stabilization is impaired in young rats by $NMDA_R$ antagonism (Kentros et al., 1998), an effect reminiscent of the map retrieval errors observed in old animals (Barnes et al., 1997).

Taken together, the foregoing data indicate that disruption in functional connectivity of the hippocampus in old rats contributes to memory retrieval deficits. Such retrieval deficits could disrupt information processing widely in neocortical circuits receiving back projections from the hippocampus.

7. Summary and conclusions

The hippocampus and other medial temporal lobe structures are critical for normal memory operations in humans, monkeys, rats and mice. In fact, as long as language confounds are avoided, similar deficits can be illustrated across species when these structures are damaged or when they are altered more subtly during the normal aging process. Because the data support the hypothesis that the cognitive processes changed during normal aging are similar across species, it is tempting to suggest that mechanistic understanding of the neural alterations in the rat may lead to a deeper understanding of brain aging in humans. From our perspective the major link that is missing in this chain of logic is the fact that no functional non-human primate data currently exist. Recordings from young and old monkeys during cognitive tasks provide a bridge between the electrophysiological data in the rat with the functional imaging data in humans. The authors of the present manuscript are determined to fill this gap in the near future.

Acknowledgements

This chapter was prepared under the support of AG18890 and AG03376.

References

Albert, M.S., 2002. Memory decline: the boundary between aging and age-related disease. Ann. Neurol. 51, 282–284.

Albert, M.S., Duffy, F., Naeser, M., 1987. Non-linear changes in cognition with age and neurophysiological correlates. Can. J. Psychol. 41, 141–157.

Angeli, S.J., Murray, E.A., Mishkin, M., 1993. Hippocampectomized monkeys can remember one place but not two. Neuropsychologia 31, 1021–1030.

Arnsten, A.F.T., Goldman-Rakic, P.S., 1990. Analysis of α-2 adrenergic agonist effects on the delayed nonmatch-to sample performance of aged rhesus monkeys. Neurobiol. Aging 11, 583–590.

Bach, M.E., Barad, M., Son, H., Zhuo, M., Lu, Y.F., Shih, R., Mansuv, I., Hawkins, R.D., Kandel, E.R., 1999. Age-related defects in spatial memory are correlated with defects in the late phase of hippocampal long-term potentiation in vitro and are attenuated by drugs that enhance the cAMP signaling pathway. Proc. Nat. Acad. Sci., USA 96, 5280–5285.

Bachevalier, J., 1993. Behavioral changes in aged rhesus monkeys. Neurobiol. Aging 14, 619–621.

Barnes, C.A., 1979. Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat. J. Comp. Physiol. Psychol. 93, 74–104.

Barnes, C.A., 1994. Normal aging: regionally specific changes in hippocampal synaptic transmission. TINS 17, 13–18.

Barnes, C.A., 1998. Spatial cognition and functional alterations of aged rat hippocampus. In: Wang, E., Snyder, D.S. (Eds.), Handbook of the Aging Brain, Academic Press, New York, pp. 51–66.

Barnes, C.A., McNaughton, B.L., 1980. Spatial memory and hippocampal synaptic plasticity in middle-aged and senescent rats. In: Stein, D., (Ed.), The Psychobiology of Aging: Problems and Perspectives, Elsevier, Amsterdam, pp. 253–272.

Barnes, C.A., McNaughton, B.L., 1985. An age comparison of the rates of acquisition and forgetting of spatial information in relation to long-term enhancement of hippocampal synapses. Behav. Neurosci. 99, 1040–1048.

Barnes, C.A., Rao, G., Foster, T.C., McNaughton, B.L., 1992. Region-specific age effects on AMPA sensitivity: electrophysiological evidence for loss of synaptic contacts in hippocampal field CA1. Hippocampus 2, 457–468.

Barnes, C.A., Treves, A., Rao, G., Shen, J., 1994. Electrophysiological markers of cognitive aging: region specificity and computational consequences. Semin. Neurosci. 6, 359–367.

Barnes, C.A., Suster, M.S., Shen, J., McNaughton, B.L., 1997. Multistability of cognitive maps in the hippocampus of old rats. Nature 388, 272–275.

Bartus, R.T., Dean, R.L., Fleming, D.L., 1978. Aging in the rhesus monkey: effects on visual discrimination learning and reversal learning. J. Gerontol. 34, 209–219.

Baxter, M.G., Murray, E.A., 2001a. Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. Hippocampus 11, 61–71.

Baxter, M.G., Murray, E.A., 2001b. Effects of hippocampal lesions on delayed nonmatching-to-sample in monkeys: a reply to Zola and Squire 2001. Hippocampus 11, 201–203.

Beason-Held, L., Rosene, D.L., Killiany, R.J., Moss, M.B., 1999. Hippocampal formation lesions produce memory impairment in the rhesus monkey. Hippocampus 9, 562–574.

Blum, K.I., Abbott, L.F., 1996. A model of spatial map formation in the hippocampus of the rat. Neural Comput. 8, 85–93.

Buffalo, E.A., Ramus, S.J., Clark, R.E., Teng, E., Squire, L.R., Zola, S.M., 1999. Dissociation between the effects of damage to perirhinal cortex and area TE. Learn. Mem. 6, 572–599.

Burwell, R.D., 2000. The parahippocampal region: corticocortical connectivity. Ann. NY Acad. Sci. 911, 25–42.

Burwell, R.D., Amaral, D.G., 1998. Perirhinal and postrhinal cortices or the rat: interconnectivity and connections with the entorhinal cortex. J. Neurosci. 391, 293–321.

Calhoun, M.E., Kurth, D., Phinney, A.L., Long, J.M., Hengemible, J., Mouton, P.R., Ingram, D.K., Jucker, M., 1998. Hippocampal neuron and synaptophysin-positive bouton number in aging. Neurobiol. Aging 19, 599–606.

Cavoy, A., Delacour, J., 1993. Spatial but not object recognition is impaired by aging in rats. Physiol. Behav. 53, 527–530.

Corkin, S., 1984. Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. Semin. Neurol. 4, 249–259.

Corkin, S., 2002. What's new with the amnesic patient H.M. Nat. Rev. Neurosci. 3, 153–160.

Correll, R.E., Scoville, W.B., 1965. Performance on delayed match following lesions of medial temporal lobe structures. J. Comp. Physiol. Psychol. 60, 360–367.

Crook, T., Bartus, R.T., Ferris, S.H., Whitehouse, P., Cohen, G.D., 1986. Age-associated memory impairment: proposed diagnostic criteria and measures of clinical change–report of a National Institute of Mental Health work group. Dev. Neuropsychol. 2, 261–276.

Deupree, D.L., Turner, D.A., Waters, C.L., 1991. Spatial performance correlates with in vitro potentiation in young and aged Fischer 344 rats. Brain Res. 554, 1–9.

Dunnett, S.B., Evenden, J.L., Iversen, S.D., 1988. Delay-dependent short-term memory deficits in aged rats. Psychopharmacology 96, 174–180.

Ekstrom, A.D., Meltzer, J., McNaughton, B.L., Barnes, C.A., 2001. NMDA receptor antagonism blocks experience-dependent expansion of hippocampal place fields. Neuron 31, 631–638.

Erickson, C.A., Permenter, M., Rapp, P., Roberts, J.A., Barnes, C.A., 2001. Aged monkeys show diminished preference to novelty in the visual paired comparison task. Seventh Conference on the Neurobiology of Learning and Memory: Orchestration of Cells and Systems: Making Memories in the Brain. #79.

Flicker, C., Bartus, R.T., Crook, T.H., Ferris, S.H., 1984. Effects of aging and dementia upon recent visuospatial memory. Neurobiol. Aging 5, 275–283.

Gaffan, D., 1974. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. J. Comp. Physiol. Psychol. 86, 1100–1109.

Gallagher, M., Rapp, P.R., 1997. The use of animal models to study the effects of aging on cognition. Ann. Rev. Psychol. 48, 339–370.

Geinisman, Y., deToledo-Morrell, L., Morrell, F., Persina, I.S., Rossi, M., 1992. Age-related loss of axospinous synapses formed by two afferent systems in the rat dentate gyrus as revealed by the unbiased stereological disector technique. Hippocampus 2, 437–444.

Geinisman, Y., deToledo-Morrell, L., Morrell, F., Heller, R.E., 1995. Hippocampal markers of age-related memory dysfunction: behavioral, electrophysiological and morphological perspectives. Prog. Neurobiol. 45, 223–252.

Kentros, C., Hargreaves, E., Hawkins, R.D., Kandel, E.R., Shapiro, M., Muller, R.V., 1998. Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. Science 280, 2121–2126.

Lai, Z.C., Moss, M.B., Killiany, R.J., Rosene, D.L., Herndon, J.G., 1995. Executive system dysfunction in the aged monkey: spatial and object reversal learning. Neurobiol. Aging 16, 947–954.

Landfield, P.W., McGaugh, J.L., Lynch, G., 1978. Impaired synaptic potentiation process in the hippocampus of aged, memory deficient rats. Brain Res. 150, 85–101.

Levy, W.B., 1989. A computational approach to hippocampal function. In: Hawkins, R.D., Bower, G.H. (Eds.), Computational Models of Learning in Simple Neural Systems, vol. 23. Academic Press, New York, pp. 243–305.

Levy, W.B., Steward, O., 1983. Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. Neuroscience 8, 791–797.

Markowska, A.L., Stone, W.S., Ingram, D.K., Reynolds, J., Gold, P.E., Conti, L.H., Pontecorvo, M.J., Wenk, G.L., Olton, D.S., 1989. Individual differences in aging: behavioral and neurobiological correlates. Neurobiol. Aging 10, 31–43.

Markus, E.J., Qin, Y.-L., Leonard, B., Skaggs, W.E., McNaughton, B.L., Barnes, C.A., 1995. Interactions between location and task affect the spatial and directional firing of hippocampal neurons. J. Neurosci. 15, 7079–7094.

McKee, R.D., Squire, L.R., 1993. On the development of declarative memory. J. Exp. Psychol: Learn. Mem. Cogn. 19, 397–404.

McNaughton, B.L., Douglas, R.M., Goddard, G.V., 1978. Synaptic enhancement in fascia dentata: cooperativity among coactive afferents. Brain Res. 157, 277–293.

Mehta, M.R., Barnes, C.A., McNaughton, B.L., 1997. Experience-dependent, asymmetric expansion of hippocampal place fields. Proc. Nat. Acad. Sci., USA 94, 8918–8921.

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

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

Mishkin, M., Delacour, J., 1975. An analysis of short-term visual memory in the monkey. J. Exp. Psychol.: Anim. Behav. Process. 1, 326–334.

Moore, C.I., Browning, M.D., Rose, G.M., 1993. Hippocampal plasticity induced by primed burst, but not long-term potentiation, stimulation is impaired in area CA1 of aged Fischer 344 rats. Hippocampus 3, 57–66.

Morris, R.G.M., Garrud, P., Rawlins, J.N.P., O'Keefe, J., 1982. Place navigation impaired in rats with hippocampal lesions. Nature 297, 681–683.

Moss, M.B., Rosene, D.L., Peters, A., 1988. Effects of aging on visual recognition memory in the rhesus monkey. Neurobiol. Aging 9, 495–502.

Mumby, D.G., Pinel, J.P., Wood, E.R., 1990. Nonrecurring-items delayed nonmatching-to-sample in rats: a new paradigm for testing nonspatial working memory. Psychobiology 18, 321–326.

Mumby, D.G., Gaskin, S., Glenn, M.J., Schramek, T.E., Lehmann, H., 2002. Hippocampal damage and exploratory preferences in rats: memory for objects, places, and contexts. Learn. Mem. 9, 49–57.

Murray, E.A., Mishkin, M., 1998. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J. Neurosci. 18, 6568–6582.

Murray, E.A., Baxter, M.G., Gaffan, D., 1998. Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. Behav. Neurosci. 112, 1291–1303.

Newman, M.C., Kaszniak, A.W., 2000. Spatial memory and aging: performance on a human analog of the Morris water maze. Aging Neuropsychol. Cogn. 7, 86–93.

O'Keefe, J., Dostrovsky, J., 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. 34, 171–175.

O'Keefe, J., Nadel, L., Keightley, S., Kill, D., 1975. Fornix lesions selectively abolish place learning in the rat. Exp. Neurol. 48, 152–166.

Owen, N.A., 1953. Age and mental abilities: a longitudinal study. Gen. Psychol. Monogr. 40, 71–79.

Parkinson, J.K., Murray, E.A., Mishkin, M., 1988. A selective mnemonic role of the hippocampus in monkeys: memory for location of objects. J. Neurosci. 8, 4159–4167.

Pascalis, O., Bachevalier, J., 1999. Neonatal aspiration lesions of the hippocampal formation impair visual recognition memory when assessed by paired-comparison task but not by delayed nonmatching-to-sample task. Hippocampus 9, 609–616.

Peters, A., Rosene, D.L., Moss, M.B., Kemper, T.L., Abraham, C.R., Tigges, J., Albert, M.S., 1996. Neurobiological basis of age-related cognitive decline in the rhesus monkey. J. Neuropathol. Exp. Neurol. 55, 861–874.

van Praag, H., Schinder, A.F., Christie, B.R., Toni, N., Palmer, T.D., Gage, F.H., 2002. Functional neurogenesis in the adult hippocampus. Nature 415, 1030–1034.

Presty, S.K., Bachevalier, J., Walker, L.C., Struble, R.G., Price, D.L., Mishkin, M., Cork, L.C., 1987. Age differences in recognition memory of the rhesus monkey (*Macaca mulatta*). Neurobiol. Aging 8, 435–440.

Rapp, P.R., 1995. Cognitive neuroscience perspectives on aging in nonhuman primates. In: Nakajima, T., Ono, T. (Eds.), Emotion, Memory and Behavior, Japan Scientific Societies, Tokyo, pp. 197–211.

Rapp, P.R., Amaral, D.G., 1989. Evidence for task-dependent memory dysfunction in the aged monkey. The Journal of Neuroscience 9, 3568–3576.

Rapp, P.R., Amaral, D.G., 1991. Recognition memory deficits in a subpopulation of aged monkeys resemble the effects of medial temporal lobe damage. Neurobiol. Aging 12, 481–486.

Rapp, P.R., Amaral, D.G., 1992a. Evidence for task-dependent memory dysfunction in the aged monkey. J. Neurosci. 9, 3568–3576.

Rapp, P.R., Amaral, D.G., 1992b. Individual differences in the cognitive and neurobiological consequences of normal aging. TINS 15, 340–345.

Rapp, P.R., Gallagher, M., 1996. Preserved neuron number in the hippocampus of aged rats with spatial learning deficits. Proc. Nat. Acad. Sci., USA 93, 9926–9930.

Rapp, P.R., Kansky, M.T., Roberts, J.A., 1997. Impaired spatial information processing in aged monkeys with preserved recognition memory. NeuroReport 8, 1923–1928.

Rasmussen, T., Schliemann, T., Sorensen, J.C., Zimmer, J., West, M., 1996. Memory impaired aged rats: no loss of principal hippocampal and subicular neurons. Neurobiol. Aging 17, 143–147.

Rosenzweig, E.S., Rao, G., McNaughton, B.L., Barnes, C.A., 1997. Role of temporal summation in age-related LTP-induction deficits. Hippocampus 7, 549–558.

Shen, J., Barnes, C.A., McNaughton, B.L., Skaggs, W.E., Weaver, K.L., 1997. The effect of aging on experience-dependent plasticity of hippocampal place cells. J. Neurosci. 17, 6769–6782.

Small, S.A., Tsai, W.Y., DeLaPaz, R., Mayeux, R., Stern, Y., 2002. Imaging hippocampal function across the human life span: is memory decline normal or not? Ann. Neurol. 51, 290–295.

Smith, T.D., Adams, M.M., Gallagher, M., Morrison, J.H., Rapp, P.R., 2000. Circuit-specific alterations in hippocampal synaptophysin immunoreactivity predict spatial learning impairment in aged rats. J. Neurosci. 20, 6587–6593.

Soffié, M., Buhot, M.-C., Poucet, B., 1992. Cognitive and noncognitive processes involved in selective object exploration: comparison between young adult and old rats. Physiol. Behav. 52, 1029–1035.

Tanila, H., Shapiro, M., Gallagher, M., Eichenbaum, H., 1997a. Brain aging: changes in the nature of information coding by the hippocampus. J. Neurosci. 17, 5155–5166.

Tanila, H., Sipilä, P., Shapiro, M., Eichenbaum, H., 1997b. Brain aging: impaired coding of novel environmental cues. J. Neurosci. 17, 5167–5174.

Teng, E., Squire, L.R., 1999. Memory for places learned long ago is intact after hippocampal damage. Nature 400, 675–677.

deToledo-Morrell, L., Geinisman, Y., Morrell, F., 1988. Individual differences in hippocampal synaptic plasticity as a function of aging: behavioral, electrophysiological and morphological evidence. In: Petit, T., Ivy, G. (Eds.), Neural Plasticity: A Lifespan Approach, Alan R. Liss Inc, New York, pp. 283–328.

Uttl, B., Graf, P., 1993. Episodic spatial memory in adulthood. Psychol. Aging 8, 257–273.

Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, V., Mishkin, M., 1997. Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277, 376–380.

West, M.J., 1993. Regionally specific loss of neurons in the aging human hippocampus. Neurobiol. Aging 14, 287–293.

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

Wilkniss, S.M., Jones, M.G., Korol, D.L., Manning, C.A., 1997. Age-related differences in an ecologically-based study of route learning. Psychol. Aging 12, 372–375.

Wilson, M.A., McNaughton, B.L., 1993. Dynamics of the hippocampal ensemble code for space. Science 261, 1055–1058.

Witter, M.P., Groenewegen, H.J., Lopes de Silva, F.H., Lohman, A.H.M., 1989. Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog. Neurobiol. 33, 161–253.

Zola, S.M., Squire, L.R., 2001. Relationship between magnitude of damage to the hippocampus and impaired recognition memory in monkeys. Hippocampus 11, 92–98.

Zola, S.M., Squire, L.R., Teng, E., Stefanacci, L., Buffalo, E.A., Clark, R.E., 2000. Impaired recognition memory in monkeys after damage limited to the hippocampal region. J. Neurosci. 20, 451–463.