

Hippocampal dysfunction during aging II: Deficits on the radial-arm maze☆

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Abstract

Middle-aged and aged rats received dorsal hippocampal lesions before performance was evaluated on the radial-arm maze. The maze task contained simultaneous spatial working memory and visually cued reference memory components. Both middle-aged and aged rats that received lesions committed more errors of both types than sham-operated rats. Moreover, an age-related deficit was found for working and reference memory errors. After 14 sessions of training, a probe session revealed that: (a) middle-aged sham rats relied on spatial cues, (b) middle-aged lesioned rats employed the visual cues at the ends of the maze arms, (c) aged sham rats relied predominately on spatial information, (d) aged lesioned rats could not use spatial information or the visual cues at the ends of the maze arms. The additive effect of lesion and age suggests continued reliance on the hippocampus despite age-related deficits in its functioning. These data are suggestive of reduction in flexible cue utilization during aging, resulting *paradoxically* in more dependence on the hippocampus for aged rats than younger animals. © 1999 Elsevier Science Inc. All rights reserved.

Keywords: Aging; Working memory; Reference memory; Radial-arm maze; Hippocampus; Lesion; Learning

1. Introduction

In the previous article, findings were presented that suggest a disruption of hippocampal memory consolidation during aging [29]. In the present paper, we examine how degraded processing within the aged hippocampus can affect the encoding of new memories. Ablation studies have linked hippocampal functioning to spatial working memory: Lesions to the hippocampal system selectively disrupt performance of tasks requiring spatial working memory [1,10,22,26]. Additionally, rats' age-related deficits in learning and memory are remarkably similar to the deficits found after hippocampal damage [7,8,18].

The present study attempts to extend these findings by examining the effect of hippocampal lesions on aged animals' maze performance. Though the effects of either lesions or aging on learning and memory are well established, no experiments to date have included aged rats with dorsal

hippocampal lesions. Comparing sham-operated and lesioned aged rats' performance should reveal the hippocampus' contribution during aging. Removing an aged rat's hippocampus could have one of three consequences on performance of memory tasks: facilitation, disruption, or no effect. First, during aging the dorsal hippocampus may provide irrelevant or erroneous output, impeding processing in other brain regions. Consequently, the removal of the hippocampus could facilitate overall memory performance. Ischemic damage to the CA1 region of hippocampus has been suggested to produce such an effect on the rest of the brain [2,17]. Second, if the aged hippocampus still contributes to encoding spatial working memory, ablation should disrupt memory performance beyond the age-related decline. Third, in aged rats, hippocampal functioning may have declined to such an extent that all learning occurs in a hippocampus-independent manner. In this case, hippocampal lesions would have no effect on memory performance of aged rats. The present study was designed to distinguish among these possibilities.

Intact aged rats manifest a selective deficit on the visuospatial working memory component of the radial-arm maze task while performing equivalently with young and middle-aged rats on a reference memory component that included

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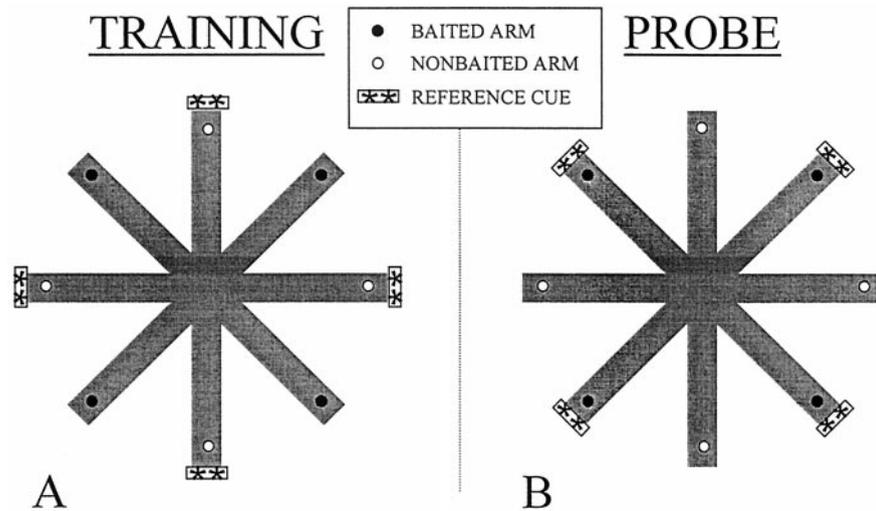


Fig. 1. Radial-arm maze configuration. (a) During training for the memory tasks, four alternating arms were baited. Nonbaited arms were cued with diodes and white cards attached to the ends of the arms perpendicular to the maze surface. (b) During the probe session, the location of the cues was rotated 45° to correspond with the baited arms.

tactile cues [3,18]. Arguably, the salience of the local tactile cues in previous studies could have overshadowed possible memory differences between the different age groups. To control for this possibility, rats in the present experiment performed a task similar to the previous studies except that local visual, rather than tactile, cues were attached to the end of the maze arms. Consequently, both the spatial/working and nonspatial/reference stimuli were visual.

2. Materials and method

2.1. Subjects

Twenty-six middle-aged (11–12 month) and 24 aged (24 month) lesion and sham rats from the 1- and 7-day groups of Ward et al. [29] were employed, 2 weeks and 1 week respectively, after completion of the retention tests. After completing the retention trials and shock sensitivity tests, the rats were food deprived to 80–85% of their ad lib body weight and given free access to water. Rats were singly housed in transparent cages and kept on a 12-h light/dark cycle.

2.2. Surgery

Rats received either a bilateral dorsal hippocampal electrolytic lesion or sham surgery (see ref. 29 for details).

2.3. Radial-arm maze procedure

2.3.1. Adaptation

Every other day, each rat was placed on a black Plexiglas maze with a central platform (24 cm dia.) and eight arms (60 cm × 10 cm). The end of each arm was baited with choc-

olate sprinkles in small metal cups. The maze was centered in a dimly lit room (4.5 m²) containing many stable extramaze cues including cabinets, furniture, equipment, and the experimenter. The rats' initial direction when placed onto the maze center was rotated three arms clockwise each day. After six arms were visited or 10 min elapsed, the rats were removed from the maze. Arms were rebaited each time an animal left an arm. Between rats, the maze was cleaned using 30% ETOH solution. To eliminate rats with overt motor or motivation dysfunction, on the ninth session all animals were screened for the ability to visit six arms in less than 10 min.

2.3.2. Memory tasks

Four alternating arms of the maze were baited. White note cards (9 × 8 cm), illuminated by 2 yellow light emitting diodes, were attached to the ends of the four non-baited arms perpendicular to the surface of the maze (see Fig. 1a). For 14 sessions, the rats were trained on the memory tasks every other day with the same configuration of cued and baited arms. Arms were not rebaited and the rats were removed from the maze after visiting all four baited arms or after 10 min. Three types of errors were defined. A *working memory error* was recorded when a rat revisited a previously baited arm. A *reference memory error* was recorded when a rat visited a non-baited, cued arm. A *repeated-reference memory error* was recorded when a rat revisited a non-baited, cued arm during a session. Repeated-reference memory errors are distinct from initial reference memory errors because repeating reference memory errors may indicate a working memory deficit (for a discussion see 18).

2.3.3. Probe session

On the fifteenth day, the cues were rotated 45° to correspond to the baited arms, whereas the previously cued arms

Table 1
The number of rats in each group

Surgery	Lesion	Sham
Middle-aged	9	13
Aged	8	11

were left unbaited (see Fig. 1b). This probe trial was conducted to examine which aspects of the environment were guiding the animals' behavior. Rats that were predominantly navigating spatially should continue to visit the baited arms regardless of the shift in cues, whereas rats that were predominantly guided by the local cues should avoid the cued arms regardless of their spatial orientation.

2.4. Histology

See Ward et al. [29] for details.

3. Results

Four middle-aged rats were excluded from all analyses, with the exception of the analysis of the relationship between lesion extent and maze performance, due to incom-

plete lesions. In addition, 6 aged (4 shams, 2 lesion) and 4 middle-aged (3 shams, 1 lesion) rats did not reach criterion during the adaptation sessions and were not trained on the memory tasks. Table 1 presents the number of rats retained in each group.

3.1. Lesion effects: middle-aged rats

For all three memory tasks, the number of errors that middle-aged rats committed decreased over training sessions and lesioned rats committed more errors than sham rats. In the working memory component of the task, a 2×14 repeated measures ANOVA found main effects for training session [$F(13, 260) = 1.92, p < 0.05$] and surgery [$F(1, 20) = 34.28, p < 0.001$] (Fig. 2a). In the reference memory component, main effects were found for training session [$F(13, 260) = 14.36, p < 0.001$] and surgery [$F(1, 20) = 16.75, p < 0.001$] (Fig. 2b). Similarly in the repeated-reference memory component, main effects were found for training session [$F(13, 260) = 9.68, p < 0.001$] and surgery [$F(1, 20) = 37.27, p < 0.001$] (Fig. 2c).

3.2. Lesion effects: aged rats

For each type of error, aged lesioned rats committed more errors than aged sham rats. In the working memory

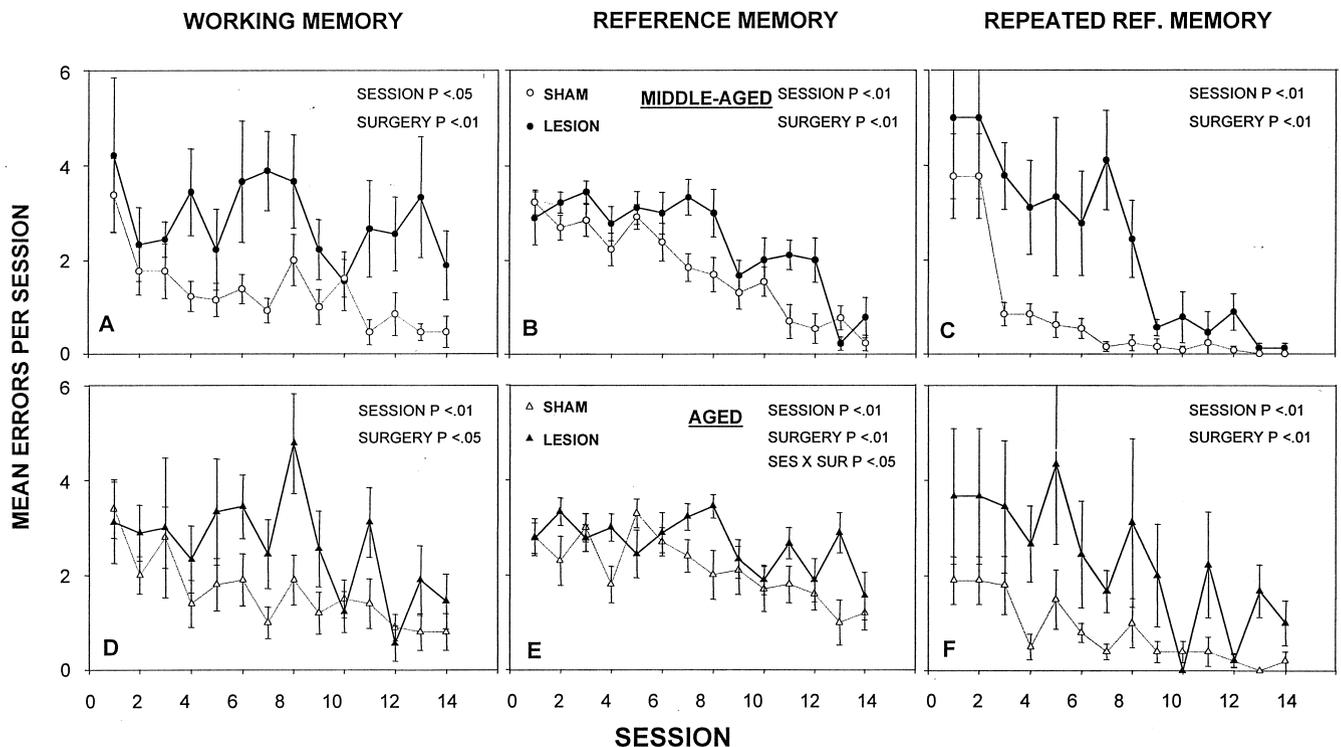


Fig. 2. Mean errors committed during acquisition of each memory task. (a) Middle-aged lesioned rats made more working memory errors than middle-aged sham rats. (b) Middle-aged lesioned rats made more reference memory errors than middle-aged sham rats. (c) Middle-aged lesioned rats made more repeated-reference memory errors than middle-aged sham rats. (d) Aged lesioned rats made more working memory errors than aged sham rats. (e) Aged lesioned rats made more reference memory errors than aged sham rats. (f) Aged lesioned rats made more repeated-reference memory errors than aged sham rats.

Table 2

Sessions to criterion on the radial-arm maze for adult and aged rats with sham surgery or hippocampal lesions^a

	Middle-aged		Aged	
	Sham	Lesion	Sham	Lesion
Working memory	7.5 (1.2)*	12.2 (1.4)*	9.8 (1.4)	11.6 (1.4)
Reference memory	12.1 (0.8)	13.7 (0.7)	12.9 (1.4)	15.8 (0.3)
Repeated-reference memory	6.2 (0.5)	7.6 (1.2)	6.6 (1.3)	8.3 (1.3)

* $p < 0.05$.

^a Means and SEM are represented.

component of the task, a 2×14 repeated measures ANOVA found main effects for training session [$F(13, 221) = 3.23, p < 0.001$] and surgery [$F(1, 17) = 6.12, p < 0.05$] (Fig. 2d). In the reference memory component, main effects were found for training session [$F(13, 221) = 3.28, p < 0.001$] and surgery [$F(1, 17) = 6.64, p < 0.01$] as well as a training session by surgery interaction [$F(13, 221) = 1.89, p < 0.05$] (Fig. 2e). In the repeated-reference memory component, main effects were found for training session [$F(13, 221) = 3.03, p < 0.001$] and surgery [$F(1, 17) = 13.14, p < 0.01$] (Fig. 2f).

3.3. Age effects

To investigate general aging effects on maze performance, sham rats from each age group were compared using 2×14 repeated measures ANOVAs. In the working memory component of the task, main effects were found for training session [$F(13, 286) = 5.73, p < 0.001$] and age [$F(1, 22) = 5.46, p < 0.05$]. In the reference memory component, main effects were found for training session [$F(13, 286) = 10.98, p < 0.001$] and age [$F(1, 22) = 6.18, p < 0.05$]. Finally, in the repeated-reference memory component, main effects were found for training session [$F(13, 286) = 13.15, p < 0.001$] but not for age [$F(1, 22) = .42, p > 0.10$].

3.4. Sessions to criterion

Performance on radial-arm maze tasks was also indexed by the number of training sessions each rat required to reach a predetermined criterion (2 error-free sessions out of 3 consecutive sessions). If a rat never reached this criterion, their number of sessions to criterion was coded as 16 (see Table 2).

A one-way ANOVA revealed a main effect for surgery for middle-aged rats on working memory sessions to criterion [$F(1, 20) = 6.30, p < 0.05$], but not for reference [$F(1, 20) = 2.05, p > 0.10$] or repeated-reference [$F(1, 20) = 1.49, p > 0.10$]. No surgery effects were found for aged rats on working [$F(1, 16) = .83, p > 0.10$], reference [$F(1, 16) = 3.24, p > 0.10$], or repeated-reference memory errors [$F(1, 16) = .79, p > 0.10$]. Likewise, no age effects were found between middle-aged and aged sham rats for working

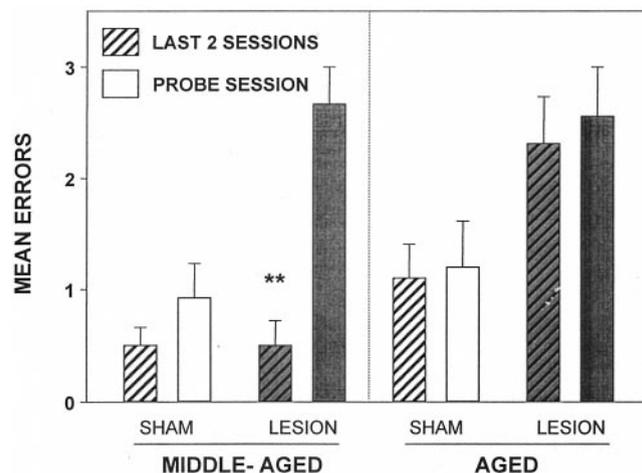


Fig. 3. The probe session. The mean number of reference memory errors on the last two training sessions compared with mean errors during the probe session. Only middle-aged lesioned rats were affected by the cue rotation as indicated by the large increase in errors after the cues were rotated in the probe session. **, $p < 0.01$.

[$F(1, 21) = 1.56, p > 0.10$], reference [$F(1, 21) = .296, p > 0.10$], or repeated-reference memory errors [$F(1, 21) = .12, p > 0.10$].

3.5. Probe session

The local cue rotation allowed an examination of which stimuli the animals employed to solve the reference memory task. For each rat, reference memory errors for the probe session were compared with mean reference errors on the previous two sessions. Middle-aged rats with hippocampal lesions committed more errors during the probe session [paired $t(4) = 5.73, p < 0.01$]. All other groups were unaffected by the cue rotation [paired t -tests all $p > 0.10$] (Fig. 3).

3.6. Relationship between degree of hippocampal damage and behavioral ability

Each hemisphere was assigned a value indicating the extent of hippocampal damage: 4 = complete ablation of all Cornus Ammon (CA) fields and the dentate gyrus, 3 = extensive damage to the CA1 and 3 fields, 2 = partial damage to the CA fields, 1 = minor damage to the CA fields. Furthermore, extraneous damage to the thalamus and the cortex overlying the hippocampus was indexed from 0 (no damage) to 2 (extensive damage).

The extent of hippocampal damage (the sum of the ablation value for each hemisphere) for lesioned rats was directly related to the mean number of errors on the radial-arm maze for working memory [$r(22) = .439, p < 0.05$], and repeated-reference memory [$r(22) = .625, p < 0.01$], however there was no correlation with reference memory [$r(22) = .378, p > 0.05$], (Fig. 4). Notably, no such corre-

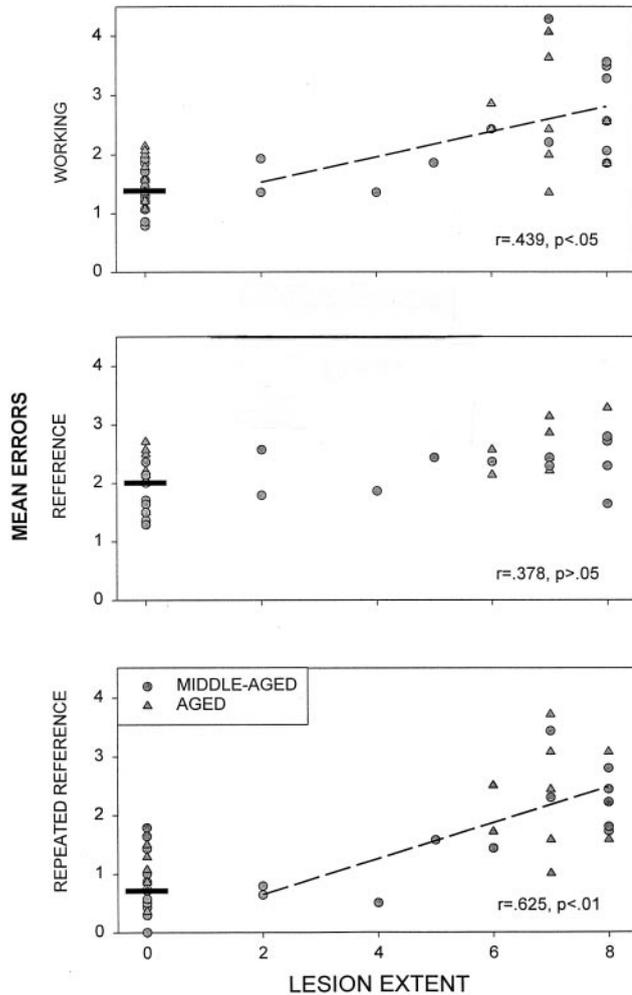


Fig. 4. Relationship between maze performance and lesion size. The mean errors committed on the memory tasks as a function of lesion size. The thick bar in the sham rats' (i.e., lesion extent zero) data indicates the median of their errors. The dotted line and r -value indicate the regression of lesioned rats only. Significant correlations were found between working memory errors and lesion extent, as well as repeated-reference memory errors and lesion extent. The similarity of the sham rats' median errors and partially lesioned rats' errors suggests a threshold for damage necessary to produce a deficit.

lation was found between any of the behavioral tasks and the degree of cortical or thalamic damage (all $p > 0.10$).

3.7. Comparing fear conditioning and radial-maze behavior

The relative contextual freezing values for individual rats from the 1- and 7-day interval groups of the previous article were compared to the *same animal's* performance on the radial-arm maze. Rats with more relative contextual freezing showed fewer working [$r(40) = -0.368, p < 0.05$] and repeated-reference memory errors [$r(40) = -0.566, p < 0.001$], however no correlation with reference memory errors was found [$r(40) = -0.220, p > 0.10$] (Fig. 5). Con-

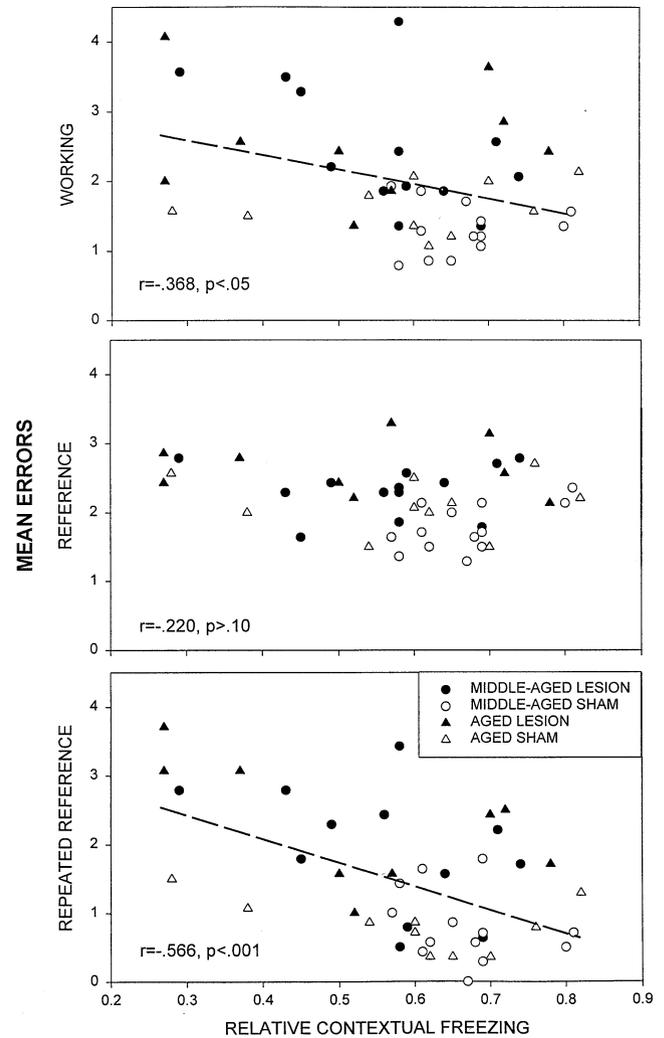


Fig. 5. Relationship between maze performance and fear conditioning. The mean errors committed on the memory tasks as a function of the relative freezing during contextual retention in Ward et al. [30]. A significant negative relationship was found between hippocampus-dependent working memory errors and relative contextual freezing as well as repeated reference memory errors and relative contextual freezing.

versely, relative freezing to the tone, that is hippocampus independent, did not correlate with maze performance (all three types of errors, $p > 0.10$).

4. Discussion

Dorsal hippocampus lesions caused an increase in the number of errors per session on the working, reference, and repeated-reference memory tasks for both middle-aged and aged rats. Moreover, an examination of the sham animals revealed an age-related deficiency on both the working and reference memory components. The additive deficits produced by lesion and age suggest that the hippocampus continues to process spatial information during senescence.

4.1. Lesion effects on aged rats

The present study is one of the first to employ aged rats with dorsal hippocampal lesions on tests of learning and memory. Comparing sham-operated and lesioned aged rats' performance in this way allows the examination of the hippocampus's contribution to age-related changes in learning and memory. For all three types of memory errors, removing the aged rats' hippocampus disrupted memory performance beyond the age-related decline. The implication of this effect is that, although its functioning has degraded, the hippocampus still plays a role in encoding memories in aged rats.

4.2. Reference memory task

Both aged and hippocampus lesioned animals showed impairments on the reference memory task. Unlike spatial working memory performance, locally cued reference memory performance is usually unaffected by either hippocampal lesions [10] or age [18]. In previous radial-arm maze studies, however, the reference memory task has been cued with textured inserts at the beginning of the arms closest to the central platform [10,18,19]. In contrast, the reference cues in the present study were relatively small and located at the ends of the arms such that the cues were visible but provided no tactile information. Thus, the effect of the hippocampal lesions could be attributed either to (a) the location of the reference cues at the ends of the arms or (b) the fact that the reference cues were visual rather than tactile. Such factors may have caused the sham rats to encode the reference memory component of the task spatially, in which case a lesion effect would be predicted [11,30].

These interpretations can be examined further through the results of the probe session. As can be seen in Fig. 2B, middle-aged lesioned rats were slower to learn the cued-reference memory task, but after extensive training reached a similar level of performance to intact animals. An examination of the probe session reveals that, although rats with and without a hippocampus show an equivalent number of reference memory errors at asymptote, different cues were used to solve the task. When the local cues were rotated to provide conflicting spatial and local information, intact middle-aged rats ignored the local reference cues whereas rats with hippocampal lesions tended to use the local reference cues more than the distal/spatial cues.

Though the lesioned middle-aged rats learned to utilize the visual reference cues at the ends of the arms, the aged lesioned rats never learned to perform the task efficiently, as indicated by the high number of errors in the last two sessions preceding the probe (see Fig. 2e, 3). Seemingly in contrast with recent electrophysiological results [27], the aged rats seemed to have had difficulty using the visual reference cues at the ends of the arms. This inability may reflect a non-hippocampal age-related deficit such as a gen-

eral reduction in visual ability; however, unpublished results from our lab find no differences in brightness discrimination between middle-aged and aged rats. Alternatively, these results may indicate an age-related change in the utilization of landmarks (i.e., a landmark at the end of an arm may be used as a local cue for middle-aged animals but a distal-spatial cue in the aged).

A number of different factors play a role in whether a stimulus is treated as a spatial landmark or a local cue. These include the stimulus's salience, stability, size, and distance from the horizon. Presumably, the distance between the stimulus and the organism could also have an impact on whether an object is treated as a spatial landmark. The possibility of an age-related change in the effect of distance on cue utilization needs to be examined further.

4.3. A comparison of performance measures

Dorsal hippocampus lesions caused an increase in errors per session on the working, reference, and repeated-reference memory tasks for both middle-aged and aged rats. An examination of sessions to criterion showed a similar trend, although only the middle-aged animals' lesion effects on the spatial working memory task reached significance. Thus in the current study, the errors per session measure was more sensitive to the effects of age and surgery whereas the number of sessions to criterion measure only revealed the strongest effect.

4.4. Extent of lesion and maze performance

Incomplete damage to the dorsal hippocampus did not have a substantial effect on the animals' maze learning ability. Although only a small number of animals received incomplete lesions, and the spatial working memory task was a relatively simple one, the data suggest a step function or a threshold of damage the hippocampus can sustain before behavioral deficits occur. The current effects on radial-arm maze performance are similar to the reported data for spatial navigation in the water maze [16] and for learning spatial alternation on the T-maze [28]. Moser et al. [16] systematically varied the volume of dorsal hippocampus lesion size and found that small amounts of damage (20% volume) had no effect, whereas larger volumes of damage were directly related to escape latency.

4.5. Relationship between hippocampal tasks

Rats that made few spatial working memory or repeated-reference memory maze errors showed high levels of relative contextual freezing (details of the task and results are in the previous article, [29]). The correlations between spatial working memory errors, repeated-reference memory errors, and contextual retention suggest that all three tasks are dependent on hippocampal memory processes [18]. The selectivity of these correlations suggests a genuine relation-

ship, rather than a general effect such as stress, with the fear-conditioning study. Despite the fact that, as a group, lesioned and aged animals were deficient on both types of hippocampal tasks, within a group individual rat's performance on the fear-conditioning task was not predictive of its maze ability. Though age-related deficits are found on many spatial tasks, the performance of an individual aged rat on one spatial task does not predict performance on other spatial tasks, such as the circular platform, water-maze, and radial-arm maze [6,13,24,36]. The lack of individual correlation may indicate that optimal performance on these 'hippocampus-dependent tasks' relies on many 'hippocampus-independent' variables [9]. Aging is characterized by a multitude of neurobiological changes: such as alterations in visual ability [20,23], thermoregulation [4,12] and motor ability [21,33]. Individual differences in any one of these 'non-hippocampal' variables could lead to differential behavior on different 'hippocampal' tasks.

Alternatively, the lack of correlation could indicate that different hippocampal-dependent tasks rely on different aspects of hippocampal function. For example, synaptic changes in the hippocampus [34,35] may cause a deficit in hippocampal aversive tasks, while producing no change or even an improvement in performance on hippocampal appetitive tasks [5,14].

4.6. Hippocampal dysfunction during aging

The current and preceding articles both examined functional changes in hippocampal processing. The data indicate that the aged hippocampus continues to contribute to animals' learning and memory abilities. This continued contribution is notable given the findings of a reduction in hippocampal processing ability. The present studies indicate this reduction through the age-related hippocampal deficits found on the radial-arm maze, context retention, and acquisition of contextual fear. Furthermore, the disparate consolidation gradients suggest that, in addition to impairment in hippocampal function, aging results in a reduced flow of information from the hippocampus to the rest of the brain.

In middle-aged animals, hippocampal ablation resulted in a modification of interaction with the environmental stimuli. This modification was especially apparent during the probe session: local visual cues which were normally ignored were utilized as reference landmarks. Conversely, neither the sham aged nor the lesioned aged rats showed this plasticity and did not compensate for hippocampal impairment by a change in cue utilization. Thus, an inability to change navigation strategy resulted in increased dependence on aged rats' hippocampal functioning.

Aged rats' lack of ability to compensate for hippocampal dysfunction may be related to findings of increased perseveration and impaired discrimination reversal in aged animals [15,31,32]. When reference cues are very salient aged rats will adopt a cue-strategy over a spatial-strategy [18]. When the cues are weak, such as those in the present study,

or the task is difficult, this age-related deficit in cue use becomes apparent.

The current findings indicate that the normal aging process results in a reduced ability to shift between alternative learning strategies and an increased dependence on a dysfunctional hippocampus. These results underscore the importance of continued research into understanding the mechanisms leading the age-related hippocampal impairment.

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