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Hippocampal dysfunction during aging I: Deficits in memory consolidation☆

Mattison T. Ward, Jonathan A. Oler, Etan J. Markus*

Behavioral Neuroscience Division, Department of Psychology, University of Connecticut, 406 Babbidge Road, Box U-20, Storrs, CT 06269, USA

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Abstract

Numerous ablation studies indicate a critical role for the hippocampal system in establishing or consolidating certain types of memory. Normal aging manifests by selective neurobiological changes in the hippocampal formation and on performance of tasks that require a functional hippocampus, including retention of contextual fear conditioning. To determine if impairments in the consolidation process contribute to memory dysfunction in aging, middle-aged and aged rats were fear conditioned and subsequently received dorsal hippocampal lesions or sham surgery after a 1, 7, 14, or 28-day interval. During retention tests, middle-aged rats exhibited a temporally graded retrograde amnesia of contextual fear conditioning, whereas aged rats manifested contextual memory impairments at all intervals. We postulate that the lack of consolidation in aged animals relates to previous findings of age-related changes in neuroanatomy and neurophysiological plasticity. The present findings suggest that impaired hippocampal consolidation contributes to age-related learning and memory deficits.

Keywords: Aging; Memory consolidation; Retrograde amnesia; Fear conditioning; Hippocampus; Lesion; Learning

1. Introduction

Selective changes in learning and memory abilities occur during the natural course of aging in humans [13] and other mammals. For example, aged rats perform well on tasks requiring simple discriminations [6], but poorly on tasks requiring the integration of a large amount of spatial information [4,16,29,33]. Rats' age-related deficits in learning and memory are remarkably similar to the deficits found after hippocampal damage [16]. For example, in a recent study [27] aged rats were tested on a battery of spatial and nonspatial tasks. Similarly to young rats with hippocampal lesions, aged rats performed poorly on the spatial tasks. Aged rats, however, performed equivalently with young intact rats on the nonspatial tasks.

Ablation to certain portions of the hippocampal system interferes with retention of events that occurred in the days preceding the removal, yet usually leaves older memories unaffected [2,11,23,40]. The resilience of previously learned behaviors after hippocampal damage indicates a transient involvement of the hippocampus in memory retention. This transience suggests that a hippocampal-neocortical dialogue strengthens the neocortical memory trace over time, making the hippocampus irrelevant by the end of the process [10]. The mechanisms by which memory traces are strengthened, and whether the strengthened traces are distributed across both the hippocampus and neocortex [25] or transferred from the hippocampus to the neocortex [15,24, 36] are still a subject of debate. Regardless, the behavioral findings taken together with neurophysiological evidence of a hippocampal-neocortical dialogue [12,24,32] underscore the importance of the hippocampus in retrograde amnesia.

To examine the effects of aging on memory consolidation, the present study employed the dissociable simple and contextual learning that occurs during fear conditioning. Previous studies have found that hippocampal lesions disrupted rats' recognition of the background context, whereas recognition of an explicit stimulus (such as a conditioned tone) remained unaffected [2,30,31]. Furthermore, memory for the conditioning context shows hippocampus-related consolidation. If ablation of the dorsal hippocampus occurs one day after fear conditioning, a young rat will not display

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* Corresponding author. Tel.: +1-860-486-4588; fax: +1-860-486-2760.

E-mail address: markus@psych.psy.uconn.edu (E.J. Markus)

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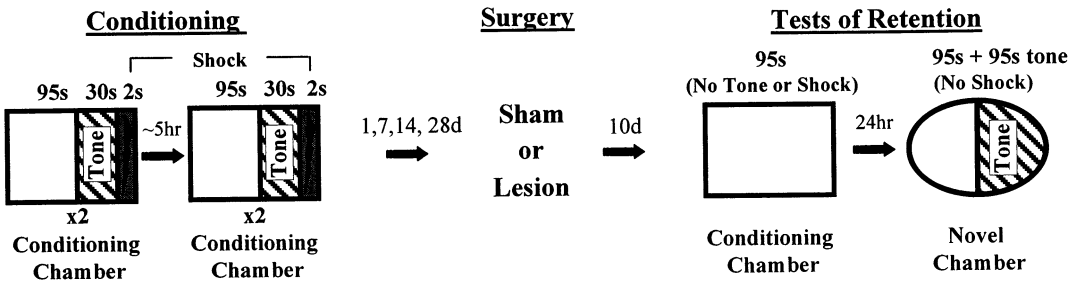

Fig. 1. Experimental procedure. Rats received two sessions of two tone-shock pairings separated by about 5 h; 1, 7, 14, or 28 days after conditioning, middle-aged and aged animals received sham or lesion surgery. Ten days later, a context retention test was conducted in the conditioning chamber. The following day the rats were tested for freezing in response to a novel chamber and to the conditioned tone.

a fear response when returned to the conditioning chamber. If, however, the hippocampus is ablated 14, 28, or 50 days after conditioning, the rat will remember the chamber and display a fear response when subsequently placed in the conditioning chamber [2,23].

Aged rats show deficits in contextual fear conditioning [9,21,27,38]. In a previous study from our laboratory [27], young, middle-aged, and aged rats were fear conditioned in a distinctive context. The animals were tested for retention both 10 and 52 days after conditioning. Between the two tests of retention, young rats' contextual fear responses increased or remained stable, whereas almost all aged rats showed a decline in levels of freezing. These data suggest that an age-related decrease in the duration and/or efficiency of hippocampal consolidation could impede proper memory formation. Due to the within-subject design of the previous study, however, these data are merely suggestive. To determine if age-related memory deficits on complex configurational/spatial tasks could be related to deficits in memory consolidation, the effect of dorsal hippocampal lesions on aged and middle-aged rats' memory retention was explicitly evaluated in the present study.

2. Materials and method

2.1. Subjects

Seventy-three aged (22 month) and sixty-four middle-aged (9–10 month) F344 male retired breeders (Harlan Sprague–Dawley, Indianapolis, IN) were individually housed in transparent plastic cages and maintained on a 12-h light/dark cycle with lights off at 19:00. Both water and food were available ad lib.

2.2. Fear conditioning

To familiarize the animals with the experimental procedure, each animal received three adaptation sessions over a period of six days. Each session consisted of placing the rat in a novel chamber within a novel room for 2.5–4 min.

On the day of conditioning, rats were placed in the shock chamber (28 × 21 × 21 cm, Med Associates, East Fairfield, VT) for a 95-s exploratory period. A 35-s tone (70 dB) was then delivered, followed by a 2-s 0.4 mA shock generated by a scrambler (Lafayette Instruments, Lafayette, IN). Following another 95-s period, the tone and shock were administered again. Animals were returned to the colony room until the procedure was repeated approximately five hours later. Thus, each animal received a total of 4 tone-shock trials (see Fig. 1). The conditioning chamber was cleaned with 70% ETOH between rats. Due to the large number of animals, conditioning trials were staggered over three days.

2.3. Surgery

One, 7, 14, or 28 days after conditioning, rats received either a bilateral electrolytic dorsal hippocampal lesion or sham surgery. Animals in both groups were mounted into a stereotaxic frame under sodium pentobarbital (Nembutal) anesthesia (middle-aged = 40 mg/kg, aged = 30 mg/kg), and methoxyflurane (Metofane) if necessary, to maintain surgical anesthesia. A midline incision was made and the scalp retracted. Two holes, 1–2 mm in diameter, were drilled in the skull of all animals. Electrodes were lowered into the dorsal hippocampus of each rat in the lesion group in 2 locations bilaterally (−3.1 mm posterior to Bregma, ±3.0 mm lateral, −3.6 mm ventral to the surface of the brain, and −3.1 mm posterior, ±1.5 mm lateral, −3.3 mm ventral). A 1.0 mA anodal DC current was passed for 15 s through each electrode (Grass Instruments Lesion Maker). The stainless steel electrodes (0.33-mm diam.) were insulated with Epoxylite except for 0.5 mm at the tip. Electrodes were not lowered into the brains of sham-operated rats.

Both skull holes were filled with bone wax and the incision was closed with wound clips. Postoperatively, the animals were kept on heating pads and monitored until ambulatory, then administered acetaminophen (Infantaire) and returned to the colony room.

2.4. Retention

After a ten-day recovery period, context retention was examined by returning each rat to the original conditioning chamber for a period of 95 s with no tone or shock administered. The following day, the animals were placed into a different chamber in a novel room. The animals' activity was monitored in the novel context for 95 s, after which the conditioned tone was delivered for an additional 95 s (see Fig. 1). To ensure novelty of the context, a chamber of comparable size (30 × 22 × 20 cm) made of a different material (clear Plexiglas not metallic), with a different shape (oval rather than rectangular) and odor (cleaned with soap and water instead of alcohol) was used.

The first five seconds of data for the context retention, novel context, and tone retention were dropped to eliminate motion data unrelated to the fear response such as movement or postural changes in response to placement in the chamber. Freezing, defined here as the suppression of non-respiratory-related movement, was used as a measure of fear. Rats emit this species-specific fear response when subjected to inescapable shock [7,8]. Using a microwave motion detection security system (Radio Shack, Fort Worth, TX) supplemented by video recordings; the rats' movements were evaluated at 3-Hz. The degree of motion detection sensitivity was adjusted to record small movements but not the animals' heartbeat or respiration. The advantages of fear conditioning in aging studies have been discussed previously [29].

2.5. Histology

After the retention tests, the rats were deeply anesthetized with sodium pentobarbital (120 mg/kg) and perfused with phosphate buffered EDTA solution followed by 3.7% of buffered formalin. Brains were postfixed in buffered formalin then transferred to buffered sucrose solution, frozen, and sliced into 30-μm sections in a cryostat. Every fifth section was mounted on a gelatin-coated slide and stained with cresyl violet to assist in evaluation of the lesions. Each hemisphere was assigned a value indicating the extent of dorsal hippocampal damage: 4 = complete ablation of all Cornus Ammon (CA) fields and the dentate gyrus, 3 = extensive damage to both the CA1 and CA3 fields, 2 = partial damage to the CA fields, 1 = minor damage to the CA fields. The score for each hemisphere was combined yielding a total value with a possible range of 0–8. Only data from rats with lesion values of 6 or higher were analyzed.

2.6. Shock sensitivity

Different levels of shock responsivity among groups could cause disparate levels of freezing [19]. Accordingly, the rats were evaluated for possible effects of age or surgery on shock sensitivity. After the tone retention test, rats were placed individually into the conditioning chamber and the current was slowly raised until a flinch was observed by an experimenter blind to the level of current. Because of the variable nature of this behavior, the test was repeated five times and the median value was used as an index of each animal's shock sensitivity.

All data were analyzed with the SPSS 8.0 statistical package

3. Results

Ablations for the two rats with the greatest and smallest extent of acceptable dorsal hippocampal damage are presented in Fig. 2. Most rats received extensive damage to the entire dorsal hippocampus and some showed damage to the overlying cortex. Four aged and six middle-aged rats were dropped from the study because the CA1 and CA3 fields were not bilaterally ablated. The lesion size of rats with bilateral ablation to CA1 and CA3 was compared for the different groups to ensure that lesion extent did not influence the results. A 2 × 4 ANOVA found no effects on lesion size of age [$F(1, 42) = .60$, $p > 0.10$], conditioning-surgery-interval [$F(3, 42) = .54$, $p > 0.10$], nor age by conditioning-surgery-interval interaction [$F(3, 42) = .63$, $p > 0.10$].

Three aged and six middle-aged rats were dropped from the study because they did not respond to all episodes of shock administration. Five aged rats and one middle-aged rat died of natural causes between conditioning and retention. To ensure that sickness did not influence performance, the data from any rat that died within 2 weeks of testing were not included in analysis. Table 1 presents the number of rats retained in each group and included in the statistical analysis.

3.1. Shock sensitivity

Equivalent shock sensitivity was found for all groups (see Fig. 3). A 2 × 2 ANOVA found no differences for age [$F(1, 99) = .06$, $p > 0.10$], surgery [$F(1, 99) = 2.22$, $p > 0.10$], nor age by surgery interaction [$F(1, 99) = .39$, $p > 0.10$].

3.2. Conditioning

There were no age-related differences in activity levels during the initial 95 s before the tone or shock presentation (Fig. 4A, context conditioning trial 1). The data were analyzed with a 2 × 4 repeated measures ANOVA that revealed that during conditioning middle-aged rats froze more to the context than aged rats [$F(1, 106) = 17.09$, $p < 0.001$]. Furthermore, a significant age by trial interaction was found (Fig. 4A): [$F(3, 318) = 118.6$, $p < 0.001$]. Conversely, in response to the tone middle-aged rats froze less than aged rats [$F(1, 106) = 16.89$, $p < 0.001$] with an age by trial interaction [$F(3, 318) = 12.48$, $p < 0.001$] (Fig. 4B).

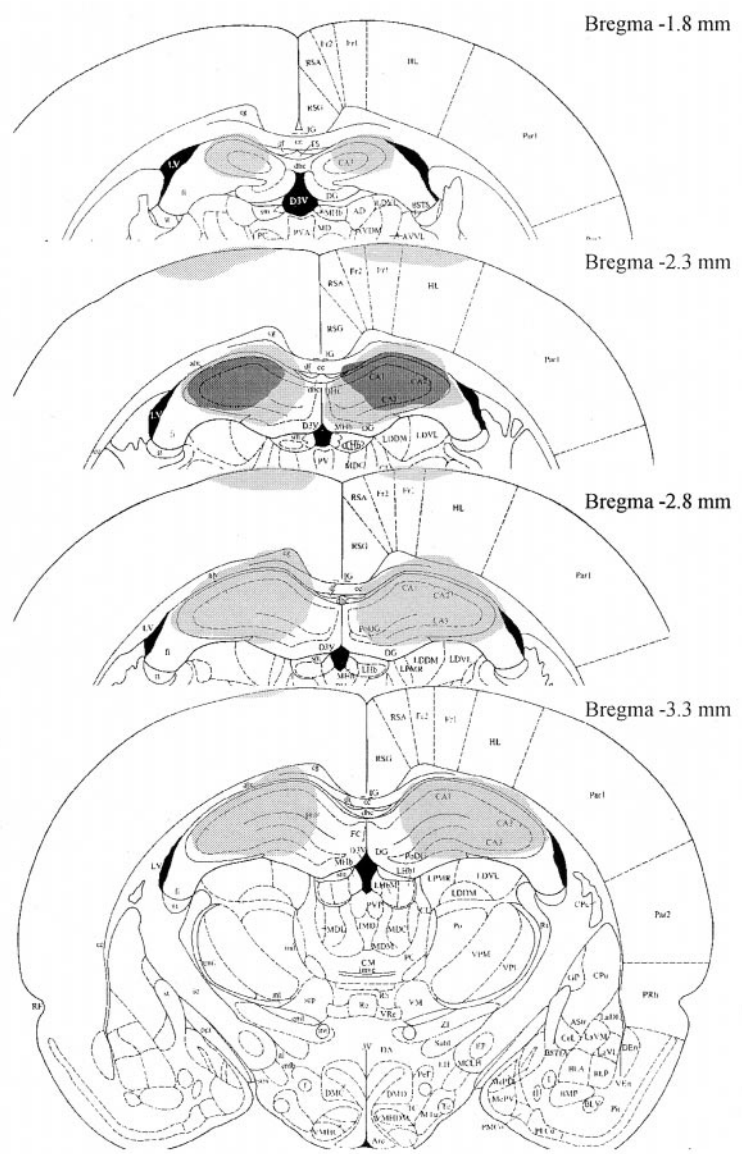

Fig. 2. Coronal sections illustrate the dorsal hippocampus lesions. Lesion extent for the rats with the largest and smallest acceptable amount of hippocampal damage are shaded lightly and darkly, respectively, and superimposed on the corresponding coronal schematic [28]. Rats without bilateral damage to CA1 and CA3 were not included in the behavioral analysis.

3.3. Retention

3.3.1. Lesion effects—middle-aged rats

A 2 × 4 ANOVA of contextual freezing revealed a main effect for surgery [$F(1, 43) = 25.24$, $p < 0.001$], conditioning-surgery-interval [$F(3, 43) = 6.89$, $p < 0.01$], and a surgery by conditioning-surgery-interval interaction [$F(3, 43) = 4.43$, $p < 0.01$]. Middle-aged rats with hippocampal lesions froze less than sham-operated animals. Hippocampal lesions resulted in lower levels of freezing at the 1- and 7-day conditioning-surgery-intervals, but not at the 14- and 28-day conditioning-surgery-intervals (see Fig. 5a).

In the novel context, lesioned and sham middle-aged rats froze equivalently [$F(1, 43) = 2.91$, $p > 0.10$], and both showed higher levels of freezing at longer conditioning-surgery-intervals [$F(3, 43) = 8.38$, $p < 0.001$] (Fig. 6a). For tone retention, a main effect was found for surgery [$F(1, 43) = 38.15$, $p < 0.001$], conditioning-surgery-interval [$F(3, 43) = 7.48$, $p < 0.001$], and surgery by conditioning-surgery-interval interaction [$F(3, 43) = 5.82$, $p < 0.01$]. Middle-aged lesioned rats froze less than shams at all con-

Table 1
The number of rats in each group

	Lesion				Sham			
Consolidation Interval	1	7	14	28	1	7	14	28
Middle-aged	3	7	4	7	8	8	7	7
Aged	6	9	8	6	8	8	8	8

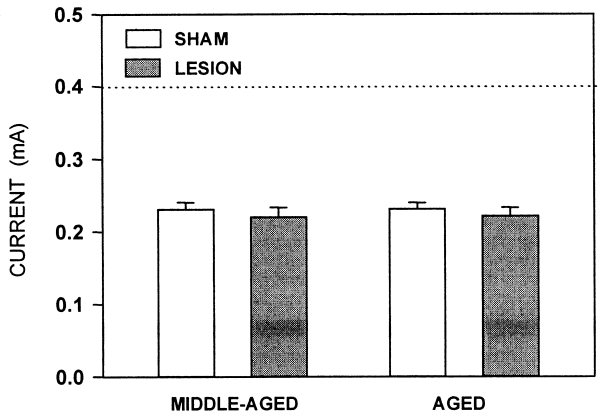

Fig. 3. Levels of shock sensitivity by condition. Middle-aged and aged rats with and without hippocampal lesions displayed equivalent levels of shock responsivity. The dotted line at 0.4 mA indicates the level of shock employed during conditioning.

ditioning-surgery intervals with the exception of the 14-day interval [$t(9) = 0.87$, $p > 0.10$] (Fig. 6b).

3.3.2. Lesion effects—aged rats

Aged lesioned rats froze less in the conditioning context than controls [$F(1, 53) = 8.15$, $p < 0.01$] regardless of the conditioning-surgery-interval [$F(3, 53) = .299$, $p > 0.10$] (Fig. 5b). Neither hippocampal lesions [$F(1, 53) = 1.74$, $p > 0.10$] nor length of conditioning-surgery-interval [$F(3, 53) = 1.97$, $p > 0.10$] had any effect on freezing in the novel context (Fig. 6c). During the tone retention test, aged lesioned rats froze less than controls [$F(1, 53) = 5.58$, $p < 0.05$] (Fig. 6d).

3.3.3. Age effects

To investigate general aging effects on retention, middle-aged and aged sham rats from each age group were compared with a 2 × 4 ANOVA. Aged rats showed less contextual freezing [$F(1, 54) = 45.68$, $p < 0.001$] and less freezing in the novel context [$F(1, 54) = 12.67$, $p < 0.01$]. Additionally, an age by conditioning-surgery-interval interaction showed that middle-aged rats froze more to the novel context at the longer conditioning-surgery-intervals whereas aged rats showed low freezing at all intervals [$F(3, 54) = 3.44$, $p < 0.05$]. Freezing to the conditioned tone, however, was equivalent for both age groups [$F(1, 54) = .66$, $p > 0.10$].

3.3.4. Relative freezing

Middle-aged animals froze more as the interval between conditioning and placement in the novel chamber increased (see Fig. 6a), possibly because of an increase in generalized fear (discussed below). This general increase in levels of freezing was corrected for by calculating the relative amount of freezing to the context and tone for *each rat*. Relative contextual freezing was calculated for *each animal* by dividing contextual freezing by the sum of contextual and novel-chamber freezing. In the same way, relative tone freezing was calculated for each animal by dividing tone freezing by the sum of tone and novel-context freezing. Consequently, a relative freezing value of 0.5 indicates equal freezing, or a lack of discrimination, between the conditioning chamber and the novel chamber, 0.66 equals 2 times more freezing, and 0.75 equals 3 times more freezing in the conditioning context than in the novel context.

The relative freezing values were analyzed with 2 × 4

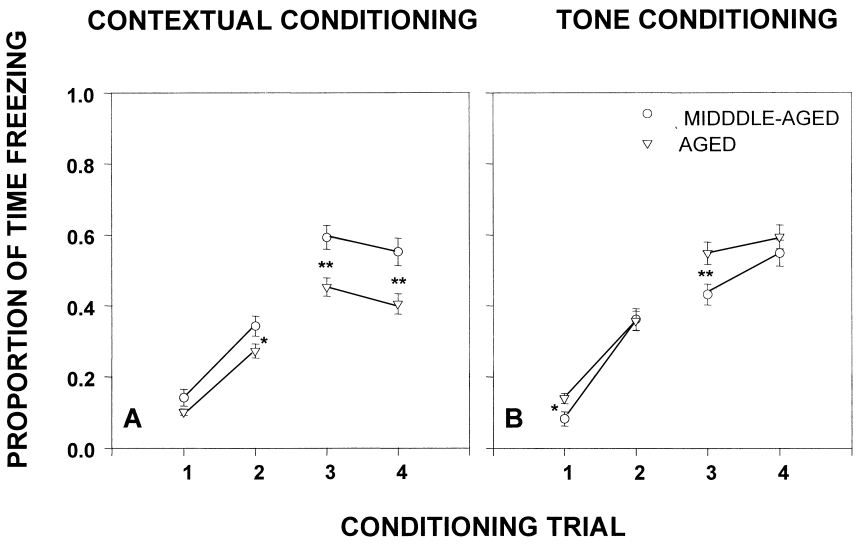

Fig. 4. Proportion of time spent freezing to the tone and context before each shock administration. (a) Overall, middle-aged rats froze more during the 95-s context exposures than aged rats. (b) Aged rats froze more during the 30-s tone presentations than middle-aged rats. The gap between the second and third tone-shock pairing represents the five-hour interval that elapsed (see Fig. 1). One or two asterisks indicate two-tailed *t*-test (*) $p < 0.05$ or (**) $p < 0.01$, respectively.

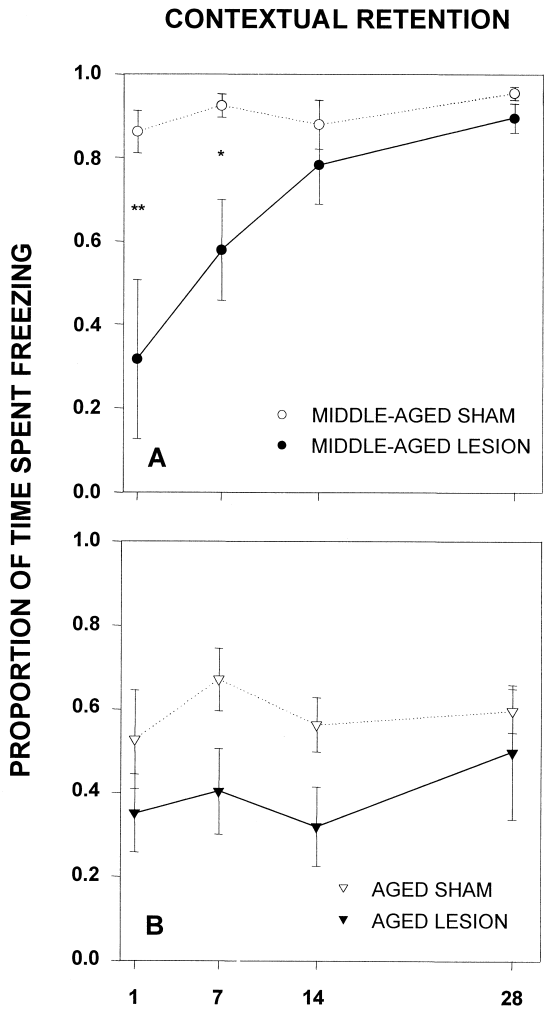

Fig. 5. Proportion of time spent freezing during contextual retention tests for rats with different conditioning-surgery intervals. (a) Middle-aged lesioned rats froze less than middle-aged sham operated rats at 1 and 7 days but equivalently at 14 and 28 days. (b) Aged lesioned rats froze less than sham operated rats. One or two asterisks indicate two-tailed *t*-test (*) $p < 0.05$ or (**) $p < 0.01$, respectively.

ANOVAs. For middle-aged rats' relative contextual freezing, a main effect was revealed for surgery [$F(1, 43) = 5.53$, $p < 0.05$] and a trend toward significance was found for the surgery by conditioning-surgery-interval interaction [$F(3, 43) = 2.68$, $p = 0.059$] (see Fig. 7a). A surgery effect was found for aged rats' relative contextual freezing [$F(1, 53) = 4.36$, $p < 0.05$] with no surgery by conditioning-surgery-interval interaction [$F(3, 53) = .37$, $p > 0.10$] (see Fig. 7b). As shown in Fig. 7, middle-aged lesioned rats with a conditioning-surgery-interval of 1 or 7 days did not distinguish between the conditioning and novel chambers. After 14 or 28 days of consolidation, however, high levels of relative contextual freezing suggest that middle-aged lesioned rats did differentiate between the conditioning and novel chambers quite well. Conversely, aged lesioned animals did not discriminate between the novel and conditioning context regardless of the conditioning-surgery-interval. Neither age nor surgery affected the amount of relative freezing to the conditioned tone (see Fig. 7c and 7d).

4. Discussion

4.1. Contextual fear conditioning trials and aging

During the conditioning trials, aged rats developed a fear response to the context more slowly than middle-aged rats, but froze to the tone more quickly. Such unequal levels of conditioning may be the source of the age-related retention deficits reported after a 24-h delay [38]. Conversely, other studies using a different conditioning procedure have found that aged and young rats show equal levels of contextual fear conditioning after a 7- or 10-day delay [9,27]. The predictiveness/contingency values of the context and conditioned stimulus influence the strength of conditioning to each [34,35]. In both studies with age-related deficits in conditioning to the context (present study, 38), the tone was a far better predictor of the shock than the context. In contrast, the difference between the predictiveness of the tone and context were smaller in the two studies where no age-related deficits were found [9,27]. In both of these studies, the animals received an equal ratio of placements (in the conditioning chamber) and tones (i.e., after each shock administration the animal was removed from the conditioning context). Taken together, these findings may indicate that context conditioning in aged rats varies directly with the relative salience and predictiveness of the contextual conditioning procedure employed.

4.2. Contextual retention

In the present study, aged rats with dorsal hippocampus lesions showed a deficit in contextual retention, however they did not display the retrograde temporal gradient typically exhibited by young animals. Instead, lesions produced a general deficit in contextual retention regardless of the conditioning-surgery-interval for aged rats. Conversely, middle-aged rats manifested a consolidation gradient similar to previous studies [23]. Hippocampus lesions 1 or 7 days after conditioning caused deficits in contextual retention whereas lesions after 14 and 28 days had no effect.

4.3. Generalized fear

Middle-aged rats displayed only a mild fear response to the novel environment when tested soon after the day of conditioning; however, as the interval increased middle-aged animals displayed freezing to the novel environment at levels approaching their fear response to the conditioning context. Aged rats, regardless of the interval length, showed only slightly lower levels of freezing to the novel environ-

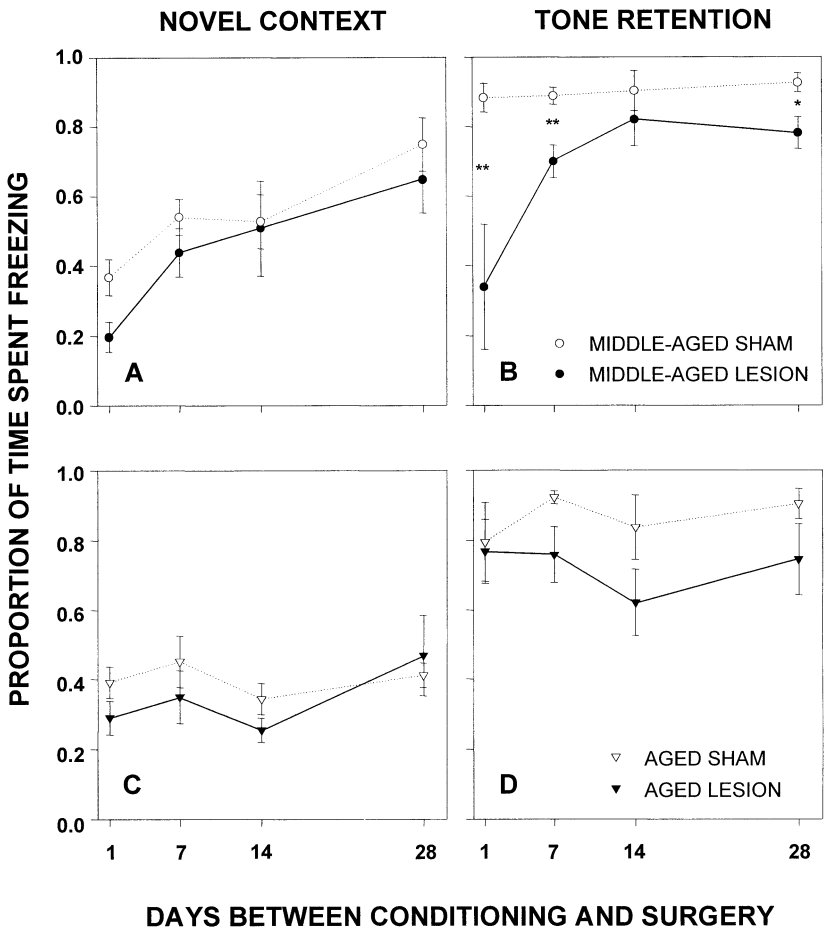

Fig. 6. Proportion of time spent freezing during novel context and tone retention tests for rats with different conditioning-surgery-intervals. (a) During the novel context tests, middle-aged lesioned and sham rats froze equivalently at all intervals, and levels of freezing increased at longer intervals. (b) During the tone retention, middle-aged lesioned rats froze less than middle-aged shams at 1, 7, and 28 days. (c) During the novel context tests, aged lesion and sham rats both showed similar low levels of freezing. (d) During tone retention, aged lesioned rats froze less than sham operated rats. One or two asterisks indicate two-tailed *t*-test (*) $p < 0.05$ or (**) $p < 0.01$, respectively.

ment and conditioning context. The middle-aged rats' increase in generalized fear response is similar to previous findings (compare Figs. 5a and 7a in ref. 27; see also 20).

There are several possible explanations for this phenomenon. Because the shorter intervals are closer to the actual aversive conditioning event, the middle-aged rats may more easily discriminate between the conditioning context and a novel context, producing low levels of freezing in the novel context. At the longer intervals, they may have lost their ability to discriminate between the conditioning chamber and the novel chamber, and thus show a high level of fear to both environments. Conversely, the aged rats had difficulty distinguishing between the conditioning and novel environments at even the short time intervals.

A similar study [23] reported little freezing in the novel environment regardless of the time interval from conditioning. A possible source of these conflicting results is the age of the animals, 3–3.5 months vs. approximately 10 months old in the current study. In addition, both the procedure and the method by which freezing was evaluated differed. For example, the previous study [23] employed a blind observer who sampled movement every eight seconds. The present study employed computer controlled motion detectors that sampled movement three times per second. Whereas control rats in the previous study [23] were recorded as freezing to the conditioning context about 50% of the time, the present controls were recorded as freezing about 90% of the time. The greater sensitivity of the present procedure may have revealed effects that were overlooked by a human observer. When corrected for this generalized fear effect by factoring out freezing in the novel chamber with our relative freezing index, middle-aged lesioned rats display a consolidation effect only for the hippocampus-dependent context, whereas aged lesioned rats manifested a consistent deficit remembering the conditioning context at most intervals.

4.4. Tone retention

Hippocampal lesions produce less freezing during tone retention for middle-aged and aged rats, and middle-aged

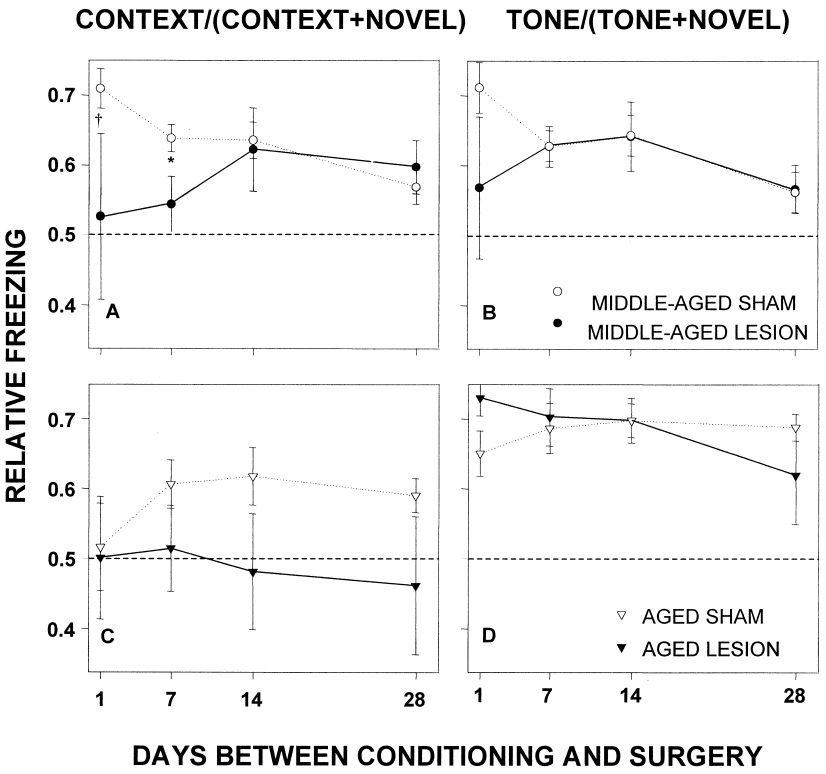

Fig. 7. Relative freezing to the context and tone at the different conditioning-surgery-intervals. Relative contextual freezing was calculated by dividing freezing to the context by the sum of freezing to the conditioning context and freezing in the novel context. Relative tone freezing was calculated in a similar manner. The dashed line at 0.5 indicates equal freezing to the conditioned stimulus and to a novel environment, i.e. no discrimination between the two situations. (a) Middle-aged lesioned rats froze less to the context than shams at 1 and 7 days between conditioning and surgery but not at 14 and 28 days. (b) Middle-aged lesioned and sham rats froze equivalently to the tone. (c) Aged lesioned rats froze less to the context than sham rats. (d) Aged lesioned and sham rats froze equivalently to the tone. Symbols indicate two-tailed *t*-test (†) $p < 0.06$, (*) $p < 0.05$, or (**) $p < 0.01$, respectively.

rats displayed a larger lesion effect at 1 day than at the longer intervals. All of these lesion effects, however, were eliminated once the amount of freezing in the novel chamber was taken into account (i.e., the relative freezing score for tone showed no effect of the lesion).

4.5. Changes in consolidation over the lifespan

The present study employed 10-month-old rats whereas a previous study [23] employed 3 to 3½-month-old rats. In both studies, a similar consolidation function was found. This similarity suggests that through middle age the consolidation process remains largely stable, with changes occurring only during old age. Providing indirect support for this hypothesis, a previous study [27] found no differences in contextual fear retention or working memory errors between young (4 month) and middle-aged (10 month) rats, whereas aged rats (24 month) showed deficits on both when compared to the younger rats.

4.6. Consolidation and aging

The lack of temporally graded retrograde amnesia for the aged rats' hippocampal-dependent retention suggests an impaired consolidation process. This impairment may result from morphological changes in the hippocampal formation during aging that could lead to an impoverished hippocampal-cortical dialogue. The number of perforant path fibers from the entorhinal cortex to the dentate gyrus decreases during aging [17,18]. These axons are the primary source of cortical input to the hippocampus [1]. Therefore, a reduction in this pathway would inevitably decrease the richness and/or variety of cortical information flowing into the hippocampus. An age-related decline in the quality of the inputs could lead to a higher probability of new sensory information 'resetting', or replacing previously stored hippocampal representations.

Synaptic plasticity also decreases in the aged hippocampus. For example, aged rats exhibit reduced frequency potentiation in the dentate gyrus [14] and CA1 [3,14,22]. Furthermore, synaptic changes in the hippocampus are less persistent in aged rats: Long Term Depression is more easily induced [26], Long Term Potentiation dissipates more rapidly [5,26], and animals with the fastest decay show the largest spatial memory impairments [5]. Together, these findings suggest that aging reduces the ability of the hippocampus to store and retain memories.

The findings of a temporally graded retrograde amnesia

after hippocampal damage have been interpreted in a number of different ways. One approach posits a transient role for the hippocampus in establishing the memory trace in the neocortex through changes in synaptic strength [15,24,37]. The results of the present study would suggest that the ability of the hippocampus to transfer the memory trace to the cortex diminishes with age. An alternative approach of memory formation views consolidation as a strengthening of the joint neocortical-hippocampal memory trace with each reactivation of the memory [25]. Based on this approach, the present results could be interpreted to indicate that age-related deficits in memory stem from a reduction in the efficacy of reinstatement or that, in aged animals, even limited hippocampal damage is enough to completely disrupt memory retrieval regardless of the length of consolidation.

The present experiments are the first, to our knowledge, that explicitly investigate memory consolidation in aged rats. Whereas middle-aged rats exhibited the temporally graded retrograde amnesia associated with consolidation, aged rats with hippocampal lesions manifested no such effect. This difference in hippocampal consolidation may underlie human memory deficits in normal aging and in Alzheimer's disease.

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