HIPPOCAMPUS 10:338–350 (2000)

Age-Related Deficits in the Ability to Encode Contextual Change: A Place Cell Analysis

Jonathan A. Oler and Etan J. Markus*

Behavioral Neuroscience Division, Department of Psychology, University of Connecticut, Storrs, Connecticut

ABSTRACT: Aging is known to impair the formation of episodic memory, a process dependent upon the integrity of the hippocampal region. To investigate this issue, hippocampal place cells were recorded from middle-aged and old F-344 male rats while running on a "figure-8" track. The top and bottom arcs of the track were removed, converting it into a plus maze, and the animals were required to conduct a working memory task. Following this change in task, the arcs were replaced and the animals again ran the figure-8 task. Analysis of place fields across the recording session demonstrated that both middle-aged and old rats had reliable representations of the figure-8 task. A comparison of place fields between different behavioral tasks (figure-8 and plus maze) demonstrated a change in the hippocampal representation of the environment in both age groups, despite the fact that the animals remained on the maze throughout the recording session. Notably, place cells in old animals were less affected by the change in task than those in middle-aged animals. The results suggest that hippocampal neurons reflect significant behavioral events within a given environment. Furthermore, the data indicate that age-related episodic memory deficits may result from decreased sensitivity of the hippocampal network to respond to meaningful changes in the environment. ***Hippocampus 2000;10:338–350.*** **© 2000 Wiley-Liss, Inc.**

KEY WORDS: aging; episodic memory; navigation; spatial learning; rats

INTRODUCTION

Investigation into the role of the hippocampus in learning and memory has led to the finding that the structure is crucial in the formation of episodic memory (Tulving, 1983; see Scoville and Milner, 1957; Gaffan, 1991; Squire, 1992; Cohen and Eichenbaum, 1994). Additionally, a considerable body of evidence demonstrates a clear hippocampal role in the performance of spatial and/or configural memory tasks in mammals (e.g., Olton and Samuelson, 1976; Morris et al., 1982, 1999; Parkinson et al., 1988; Sutherland and Rudy, 1989; Phillips and LeDoux, 1992; Jarrard, 1993). The principal cells of the rodent hippocampus display location-dependent activity, or "place fields" (O'Keefe and Dostrovsky, 1971; Ranck, 1973), and it has been suggested that the activity of these cells forms the basic element of a cognitive map (O'Keefe and Nadel, 1978). Previous research has shown that the hippocampus supports multiple representations of an environment (e.g., Gothard et al., 1996; Barnes, 1998; Skaggs and McNaughton, 1998), functions in concert with directional systems (Knierim et al., 1995), and can exhibit "remapping" in response to environmental and behavioral manipulations (e.g., Markus et al., 1995; Shapiro et al., 1997). Nevertheless, few studies have examined the effects of a cognitive, rather than a cue-based, manipulation on the hippocampal place code. The experiment described here was conceived with the intention of observing changes in the hippocampal representation of the environment in response to altering behavioral task demands while the testing environment, reward locations, and running trajectories remained relatively stable.

The process of aging has been shown to impair episodic memory in humans (e.g., Light et al., 1986; Uttl and Graf, 1993), as well as behavioral performance on hippocampus-dependent memory tasks in rats (e.g., Barnes, 1979; Gallagher and Burwell, 1989; Oler and Markus, 1998). These findings have led to the proposal that the selective learning and memory deficits observed in aged mammals directly reflect changes in hippocampal processing (see Landfield, 1988; Barnes, 1994; Geinisman et al., 1995). Tanila et al. (1997a,b) found that the place fields of aged rats often maintained similar firing patterns despite changes of landmark cues in the environment, while in young animals there was a greater tendency to display new firing patterns. However, Barnes et al. (1997) found that when rats were removed from the environment between recording sessions, old rats had less consistent hippocampal representations when returned to the same environment.

In the above studies, the animals were removed from the testing apparatus during the course of the experiment and/or subjected to disorientation before being reintroduced to the environment. Thus, age-related differences in visual ability, stress response, and/or susceptibility to disorientation could have contributed to these findings.

Grant sponsor: National Institute on Aging; Grant number: R29-A613941-01A1; Grant sponsor: University of Connecticut Research Foundation; Grant number: 441713; Grant sponsor: Claude Pepper Research Development Core, University of Connecticut Health Center.
*Correspondence to: Etan J. Markus, Behavioral Neuroscience Division, Department of Psychology, University of Connecticut, 406 Babbidge Rd., Box U-20, Storrs, CT 06269. Fax: 860-486-2760.
E-mail: markus@psych.psy.uconn.edu
Accepted for publication 1 March 2000

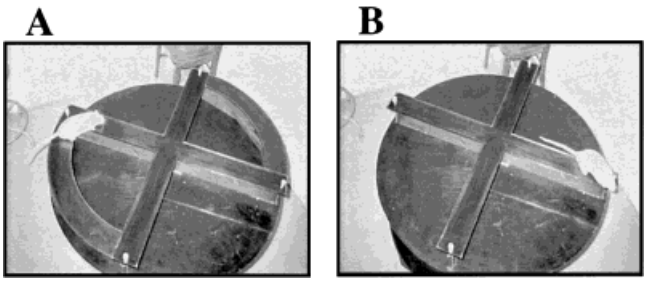

FIGURE 1. Apparatus. A: Photograph of the training apparatus configured for the figure-8 portion of the task. B: Photograph of the training apparatus configured for the plus maze portion of the task. The connecting arcs could be easily detached without removing the animal from the environment.

Therefore, the present study used a paradigm in which the animals remained on the apparatus throughout the recording session. Consequently, any age-related differences in the hippocampal response to a change in behavioral task would indicate a decline in the ability of the hippocampus to differentiate among discrete situations within a given environment.

MATERIALS AND METHODS

Subjects and General Procedures

Five middle-aged (12–16 months) and six old (24–28 months) Fischer-344 male retired breeders served as subjects (Harlan Sprague-Dawley, Indianapolis, IN). Rats were individually housed in tubs, maintained on a 12 h light/dark cycle (lights-on 7:00 AM), and food-deprived to approximately 85% of ad libitum body weight throughout the experiment. Animal care and surgical procedures were conducted according to National Institutes of Health guidelines. Rats were acclimated to eat chocolate sprinkles and trained to sit on a holding platform. The testing environment was a small room (2.1 × 2.1 m) containing several visual cues along the walls, dimly lit through an open door by hallway lights, with a track in the center. The track consisted of four black Plexiglas arms (10.5 × 51cm) forming a symmetrical "+", with two black Plexiglas arcs connecting the top and bottom of a "figure 8" (Fig. 1A). In order to decrease the visual salience of the black Plexiglas track, the entire track was elevated 12 cm from a black circular base (133 cm in diameter), which was raised 70 cm off the floor. Following acclimation, animals were trained to run in a single direction on the figure-8 track in order to receive a food reward. A few chocolate sprinkles were placed in small food cups at the four corners of the track, and rats were consistently rewarded with food each time they reached a corner. After several days of running the figure-8 track, animals were trained to reverse direction. As the rat approached the center, a small wooden barrier was placed on the track. This directed the animal to turn left onto the adjacent arm. In order to attain equal sampling in both directions, subsequent training sessions included five laps in one direction, 10 laps in the reverse direction, and five additional laps in the original direction (5×10×5). Once animals were proficient at running this task, they were surgically implanted with microelectrodes for recording.

Surgery

Animals were anesthetized with an intraperitoneal (i.p.) injection of sodium pentobarbital (Nembutal, 30 mg/kg for old and 40 mg/kg for middle-aged; Abbott, North Chicago, IL) supplemented with methoxyflurane (Metofane) when necessary and placed in a stereotaxic apparatus (ASI Instruments, Warren, MI). An incision was made in the scalp, and several small anchor screws, one of which functioned as the electrical ground, were fastened to the skull. Craniotomies were made bilaterally over the dorsal hippocampi at coordinates 3.5 mm posterior to bregma and 2.2 mm lateral from the midline (Paxinos and Watson, 1986). With the dura excised, a microdrive with six independently movable tetrodes (Recce and O'Keefe, 1989; Wilson and McNaughton, 1993) was lowered into the brain approximately 1.5 to 1.8 mm below the pial surface. Tetrodes were constructed from four twisted, polyamide-insulated, 14 μm nichrome wires (H.P. Ried, Palm Coast, FL). The tips of the tetrodes had an overall diameter of approximately 40 μm and were gold-plated to a final impedance of approximately 300 to 500 KΩ at 1 kHz. The rat was sutured if necessary and postoperatively administered acetaminophen (children's Tylenol; McNeil Consumer Products, Fort Washington, PA). Animals were given several days to recover from surgery prior to retraining and recording sessions.

Recording

After recovery, animals were retrained on the 5×10× 5 figure-8 procedure while wearing a head stage. The head stage consisted of a microchip (Multichannel Concepts, Gaithersburg, MD) containing 25 unity gain field effect transistor amplifiers and two arrays of infrared and light-emitting diodes, for tracking the animals' position and head direction. XY position coordinates of both diode arrays were sampled at 60 Hz with an overhead video tracking system (Dragon Tracker SA-3; Boulder, CO), providing data on location and heading on the track.

A multiwire cable was mounted to a pulley system in the ceiling to counterbalance the weight of the wire and head stage (approximately 16 g). Signals from the head stage were carried by the cable to a set of rack-mounted amplifiers (Assembly Hunter; Neuralynx, Tucson, AZ), amplified 5,000 times, filtered between 300 Hz and 6 kHz, and sent to a PC-based analog-to-digital signal-capture board (Data Translation, Marlboro, MA). Whenever spike amplitude exceeded a preset threshold, a 1.0 ms sample of data was acquired at a rate of 25 kHz, with a channel from one of the other tetrodes used as a reference. Neuronal and position data were sampled concurrently, and the time was stamped using a synchronization clock board (ComputerBoards, Mansfield, MA). Electrodes were slowly advanced into the cell body layers of the dorsal hippocampus until clear signals from individual units could be established.

An effort was made to reduce duplicate analysis of the same cell by either advancing the electrodes after the recording session (20 to 40 μm) and/or comparing cluster profiles (see below, Data Anal-

ysis) between sessions. If the same cell was thought to have been recorded in more than one session, only one session was used in the analysis. This decision was based on the following criterion: if the cluster boundaries and place fields on successive recordings were similar, the cell with the higher place field reliability was chosen. However, if two cells were thought to be the same but the behavioral correlates (place fields) were different, both data points were kept. The final position of the electrodes was estimated based on physiological criteria (i.e., sharp waves, or "ripples") and the distance the electrodes were advanced, followed by a histological analysis (see below).

Once the recordings appeared stable (at least 0.5 h after moving an electrode), a baseline period of approximately 10 min was recorded while the animal sat on a holder in the recording room. Following this baseline period, the animal was placed on the figure-8 track and run on the 5×10×5 procedure as during training (task A).

Change of Task

A unique feature of this figure-8 track was that the top and bottom arcs were removable. With the arcs removed, the track is transformed into a traditional four-arm plus maze with identical, symmetrical arms, each with a food cup at the end (Fig. 1B). This permits recording cells as the animal samples the same locations under two different behavioral conditions. During the twentieth lap around the track, the experimenter quietly removed the top and bottom arcs after the rat had traversed them. The beginning of task B was designated when the animal finished eating at the end of the arm. During task B, the baiting procedure was also changed. Once the rat ate from an arm, the chocolate was not replaced. After the rat ate from all four arms, a fifth food cup was placed at the center of the maze while the four arms were rebaited. This procedure was repeated 10 times so that if a rat were to perform this task without error, there would be equal sampling of the track arms, in both directions, between task A and task B. As the rat ate in the center of the maze following the tenth working memory trial, the experimenter replaced the top and bottom arcs and rebaited the food cups. When the animal had finished eating in the maze center, it was again run on the 5×10×5 figure-8 procedure (task C). Following the last lap, the animal was placed on the holder for a second baseline period of at least 10 min, to ensure that the electrodes had not drifted during recording. Following the recording session, the animal was returned to the colony room.

Histology

After the last recording session, the animal was put down with CO_2 and perfused intracardially with a 10% formalin solution. Electrodes were withdrawn, and the brain was removed and placed in formalin for at least 24 h. Coronal sections (40 μm) were cut using a cryostat and mounted on a gelatin-coated slide. The tissue was stained using cresyl violet and examined microscopically for electrode tracks.

Data Analysis

Individual units were isolated off-line using a spike parameter cluster separation method (Markus et al., 1994, 1995) on a SPARCstation 20 computer (Sun Systems, Mountain View, CA) workstation. Data collection and unit cluster identification were performed using custom interactive software written by M. Wilson and L. Frank (MIT, Cambridge, MA). Data analysis was performed using software written by W. E. Skaggs (University of Pittsburgh, Pittsburgh, PA).

The recording environment was divided up into a 64 × 64 bin array consisting of 0.6 × 0.6 cm squares. Firing rate maps were constructed for each cell using an adaptive smoothing method (see Skaggs and McNaughton, 1998). Place fields were defined as an area of at least 15 bins sharing adjacent edges, with a firing rate per bin greater than two standard deviations above the mean firing rate of the cell on the entire apparatus. A velocity filter was used to ensure that all data recorded while the animal was moving slower than 2.4 cm/s were excluded from analysis. This was done to ensure that data used for analysis of place fields were taken when the rat was moving (i.e., in theta) and not in a sharp wave state (see Chrobak and Buzsáki, 1998). Only those cells with a mean firing rate ≥0.1 Hz were included in the analysis. High-rate theta cells, putative inhibitory interneurons classified by a mean firing rate ≥2.5 Hz (Markus et al., 1994) on all three tasks, were excluded from the analysis.

Three measures were used to quantify the spatial tuning of recorded cells: reliability, specificity, and selectivity. Place field reliability was calculated by measuring the correlation between the firing rate maps of a cell for the two halves of a task. Specificity was calculated in terms of the spatial information content (in bits) that a single spike conveyed about the animal's location. Spatial information content of spike discharge was calculated using the following formula:

$$\text{information content} = \sum P_i(R_i/R)\log_2(R_i/R)$$

where i is the bin number, P_i is the probability for occupancy of bin i, R_i is the mean firing rate for bin i, and R is the overall mean firing rate (Skaggs et al., 1993). The selectivity of firing in the field (ratio of maximal signal to noise) was calculated by dividing the firing rate of the cell in the bin with the maximum average rate by its mean firing over the entire apparatus.

Changes in place fields between behavioral tasks were measured by dividing the recording time for each task into two halves (A_1 and A_2 for task A, B_1 and B_2 for task B, C_1 and C_2 for task C) and then constructing separate firing rate maps for each epoch. The different rate maps were then compared using Pearson correlation coefficients, computed on a bin by bin basis. Within-task correlations for a place cell were found by comparing the firing rate maps between the two halves of a task (i.e., rA_1A_2 and rB_1B_2). These were contrasted with the between-task correlations, found by comparing the firing rate maps of the second half of task A to the first half of task B (rA_2B_1) and the second half of task A to the first half of task C (rA_2C_1). Figure 2 is a diagram of the rate map correlations performed. Only reliable place fields exhibiting a within-task cor-

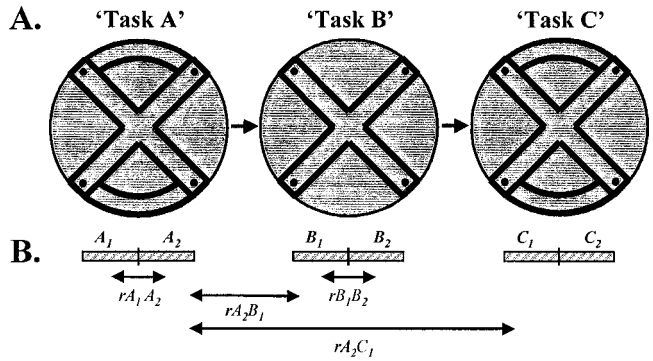

FIGURE 2. A: Behavioral procedure. The configuration of the behavioral apparatus during the full sequence of tasks (A→B→C). Task A: Rats were trained to run five laps in one direction, 10 laps in the reverse direction, and five additional laps in the original direction (5×10×5). Animals were consistently rewarded with a few chocolate sprinkles at each corner. Task B: The top and bottom arcs of the track were removed. With the apparatus in this configuration, the corners were rebaited only after the rat ate from all four arms. This working-memory procedure was repeated for 10 trials. Task C: Following the tenth trial on the plus maze, the arcs were returned and the food cups rebaited. Animals were again run on the 5×10×5 figure-8 procedure, receiving a food reward each time a corner was reached. B: Correlation analysis. A firing rate map was calculated for each place cell during the first and second halves of each task (e.g., A_1–A_2). To analyze changes in place field location across tasks, the correlation of firing rate maps between the two halves of a behavioral task (within-task correlations; rA_1A_2, rB_1B_2) were compared to the correlation of firing rate maps between the second half of task A and the first half of tasks B and C (between-task correlations; rA_2B_1, rA_2C_1, respectively).

relation ≥0.2 were included in the relative score analyses (described below).

Place cells are directionally selective on linear track mazes (Markus et al., 1995). Accordingly, comparisons of place fields across behavioral tasks were performed separately for inward and outward headings and only on those regions of the apparatus sampled in both tasks, defined by at least three visits to a location at a minimum speed of 2.4 cm/s in each task. A prerequisite for performing a rate map correlation was a minimum of one place field (based on the criteria above) during at least one of the two segments being compared. In addition, if a cell had only one place field in task A, the centeroid of the field had to be within the four arms of the track, to ensure that only those areas traversed in both tasks were compared.

To quantify and statistically compare changes in place fields between behavioral tasks, three relative scores were calculated for each place cell (R_{AC}, R_{AB}, R_{BA}). The following formula was used to calculate the relative score:

$$R = \frac{(r \text{ within task})}{(r \text{ within task} + r \text{ between tasks})}$$

where "r within task" is the correlation between the first and second halves of a given task, and "r between tasks" is the correlation between the second half of one task and the first half of the other task. Thus, a relative score of 0.5 indicates no change in place fields across the two tasks because the within-task correlation is equal to the between-task correlation. A relative score closer to 1.0 indicates a change in spatial firing across tasks because the between-task correlation is smaller than the within-task correlation. R_{AC} is the relative score comparing the second half of task A and the first half of task C (both the figure-8 task). R_{AB} is the relative score comparing the second half of task A and the first half of task B. Some cells which were silent during task A had place fields during task B (Fig. 3, Cell 2). Because of their low firing rates, these cells would not have had an rA_1A_2 score (correlation within task A) and would not have been included in the R_{AB} analysis. Therefore, R_{BA} was calculated as the relative score for comparing the second half of task A and the first half of task B in relation to the rate map correlation within task B.

Behavioral Assessment

Performance on task B (plus maze task) was assessed in two ways. First, the number of errors within a trial was recorded and an average was taken of the 10 trials. An error was counted when an animal returned to an arm already visited during a given trial, and

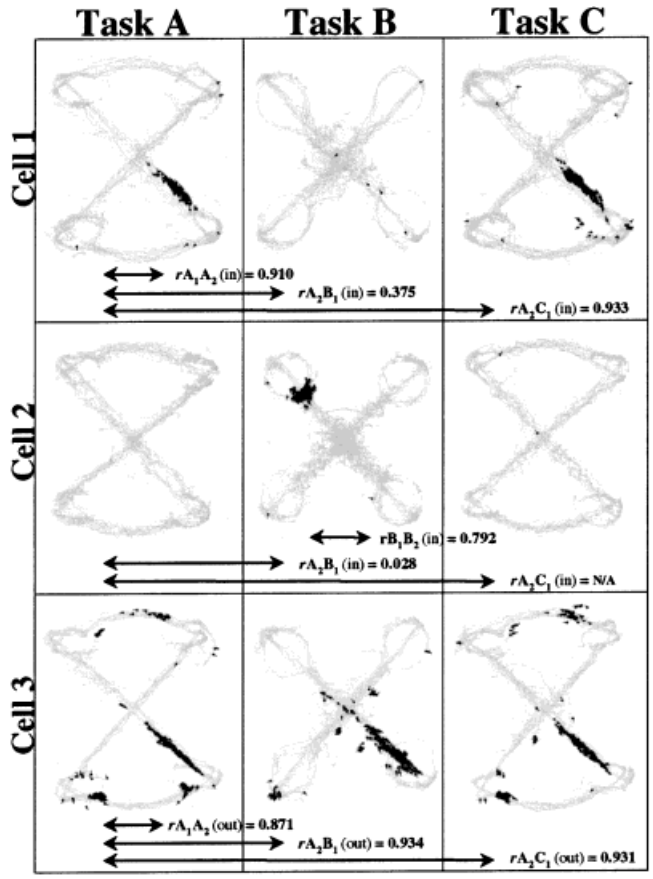

FIGURE 3. Three examples of the spatial firing of single hippocampal neurons, recorded from different animals, and their corresponding map correlations, during the entire sequence of the change in behavioral task and rate map correlations. Gray depicts the position of the animal and black, a spike from the neuron. Cell 1: A place field on the southeast arm of the figure-8 track (tasks A and C). Cell 2: Place field that appeared on the northeast arm only during task B. The rA_1A_2 and rA_2C_1 rate map correlations for this type of field could not be calculated because there were too few spikes during tasks A and C. Cell 3: Unchanged place field across tasks.

TABLE 1.

Age of Rats During Recording, Number of Recording Sessions and Cells From Each Individual Animal, and Total Cells Per Age Group

Rat number	Group	Age (months)	Recording sessions	Place cells	Total cells
329	M-aged	14	3	16	
570	M-aged	16	3	8	
582	M-aged	15	3	10	
586	M-aged	16	6	27	
876	M-aged	12	3	16	77
295	Old	24	4	21	
296	Old	25	3	16	
620	Old	28	2	8	
872	Old	24	5	23	
873	Old	25	2	21	
874	Old	25	4	21	110

Average ages: middle-aged = 14.4 months, old = 25.2 months.

a maximum of five errors were allowed before the animal was directed to the correct arm. In addition to the errors, the time it took for an animal to complete the task was noted.

RESULTS

All analyses of variance (ANOVA) were performed based on the mean scores per animal. This was done in order not to inflate the sample size and to prevent disproportionate sampling from a single animal to bias the data. This also reduces the potential impact of variability in recording electrode quality. Thus, any differences reflect group differences rather than individual differences. A total of 187 complex spike cells were recorded from 11 animals as they did the full sequence of tasks (A→B→C, Table 1). Data from the session in which the animals learned task B were not included in the analysis due to the large variability in behavior during this session.

Effects of Recording Site

Based on histological and/or physiological landmarks, place cells were identified as recorded from either the CA1 or CA3-DG (dentate gyrus) region of the hippocampus. Electrode position data were not always clearly discernible, and in these cases the lamina of the recorded place cells was considered unidentified. Of the 77 complex spike cells recorded from middle-aged animals, 33 were from CA1 and 44 were from CA3-DG. Of the 110 recorded from old animals, 22 were CA1, 52 were CA3-DG, and 36 were unidentified. The mean and standard error of maximum spike amplitude, mean firing rate, and relative scores are shown separately for cells identified as CA1 or CA3-DG in Table 2. There were no significant differences in maximum spike amplitude between cells identified as CA1 or CA3-DG for either age group (ANOVA, both $P > 0.1$) or in the mean firing rate during any of the tasks (all $P > 0.1$). A two-way ANOVA (age × lamina) of the response to the change in task (relative score R_{AB}) detected no effects of age or lamina, nor were any age by lamina interactions observed (all $P > 0.1$). Consequently, the data from cells identified as CA1 or CA3-DG or those with unidentified lamina were combined for the analysis of age differences in response to the change in task.

TABLE 2.

Mean and Standard Error for Spike Amplitude, Mean Firing Rate, and Relative Scores of CA1 and CA3-DG Cells Recorded From Middle-Aged and Old Rats

	Middle-aged (n = 6)			Old (n = 11)		
Spike amplitude (mV)						
CA1	0.65 ± 0.01			0.63 ± 0.02		
CA3-DG	0.64 ± 0.03			0.65 ± 0.02		
	Task			Task		
	A	B	C	A	B	C
Firing rate (Hz)						
CA1	0.43 ± 0.19	0.50 ± 0.19	0.46 ± 0.20	0.59 ± 0.14	0.79 ± 0.18	0.69 ± 0.16
CA3-DG	0.57 ± 0.05	0.49 ± 0.07	0.57 ± 0.04	0.57 ± 0.17	0.54 ± 0.21	0.60 ± 0.20
	R_{AC}	R_{AB}	R_{BA}	R_{AC}	R_{AB}	R_{BA}
Relative score						
CA1	0.51 ± 0.02	0.85 ± 0.14	0.69 ± 0.06	0.49 ± 0.02	0.63 ± 0.04	0.61 ± 0.02
CA3-DG	0.52 ± 0.02	0.77 ± 0.02	0.72 ± 0.02	0.55 ± 0.06	0.71 ± 0.11	0.57 ± 0.04

TABLE 3.

Mean and Standard Error for Relative Scores, Firing Properties, and Place Field Characteristics of Cells Recorded From Middle-Aged and Old Rats

	Middle-aged (N = 5)			Old (N = 6)		
R_{AC}	0.51 ± 0.02			0.52 ± 0.02		
R_{AB}	0.77 ± 0.04			0.65 ± 0.03		
R_{BA}	0.71 ± 0.03			0.61 ± 0.01		
Spike amplitude (mV)	0.65 ± 0.02			0.65 ± 0.01		
	Task			Task		
	A	B	C	A	B	C
Firing rate (Hz)	0.52 ± 0.08	0.50 ± 0.10	0.54 ± 0.10	0.51 ± 0.07	0.62 ± 0.09	0.58 ± 0.07
Reliability	0.63 ± 0.03	0.65 ± 0.04	0.71 ± 0.01	0.64 ± 0.04	0.59 ± 0.04	0.66 ± 0.03
Specificity[a]	0.99 ± 0.41	0.88 ± 0.04	1.05 ± 0.10	0.87 ± 0.08	0.76 ± 0.08	0.85 ± 0.07
Selectivity[b]	51.9 ± 8.7	37.0 ± 3.7	46.1 ± 7.5	44.8 ± 5.7	35.0 ± 4.4	38.3 ± 2.1

[a] Information (in bits) that a single spike conveys about the animal's location.
[b] Maximal firing rate/mean firing rate.

Except for spike amplitude, all physiological characteristics and place field indices were calculated separately for the three behavioral tasks (Table 3). An ANOVA, by animal, of middle-aged and old rats showed no effect of age on spike amplitude ($P > 0.1$) or on the mean firing rate for any of the tasks (all $P > 0.1$). Similarly, no age differences were found during any of the tasks on measures of reliability (all $P > 0.1$), specificity (all $P > 0.1$), or selectivity (all $P > 0.1$) of the place fields.

Effects of Behavioral Task on Place Field Location

As can be seen in Figure 3, some place fields were strongly affected by the change in behavioral task. Figure 4 depicts the relationships among the correlation of spatial firing within task A (rA_1A_2) and the correlation of spatial firing between the second half of task A and the first half of tasks B and C (rA_2B_1 and rA_2C_1, respectively). Data from middle-aged (Fig. 4A,C) and old (Fig. 4B,D) animals are presented separately. Although there is some variability, note the clustering of points around the 45-degree line in Figure 4A and B, indicating that most place cells represented tasks A and C in a similar fashion. Figure 4C and D depicts the relationship between the figure-8 and plus maze tasks. Note that a large proportion of the points are off the 45-degree line for both middle-aged and old animals, indicating that these cells represent tasks A and B differently.

Statistical analysis of the relative score R_{AC} (Fig. 5A) revealed that neither middle-aged nor old animals were significantly different from a relative score of 0.5 (middle-aged $t_{(4)} = 0.72$, $P > 0.1$; old $t_{(5)} = 1.44$, $P > 0.1$) and that the age groups were not different from one another (ANOVA, $P > 0.1$). Analysis of the relative score R_{AB} (Fig. 5B) revealed that both middle-aged and old animals were significantly different from a relative score of 0.5 (middle-aged $t_{(4)} = 7.52$, $P < 0.01$; old $t_{(5)} = 4.40$, $P < 0.01$). Furthermore, there was a significant difference between age groups on the relative score R_{AB} (ANOVA, $F_{(1,9)} = 6.35$, $P < 0.05$), indicating that old rats were less affected by the change in task than middle-aged rats.

In order to include cells that began to fire only during task B (Fig. 3, Cell 2), the correlation of spatial firing within task B (rB_1B_2) was compared to the correlation of spatial firing between the second half of task A and the first half of task B (rA_2B_1). Statistical analysis of the relative score R_{BA} revealed that both middle-aged and old animals were significantly different from a relative score of 0.5 (middle-aged $t_{(4)} = 6.51$, $P < 0.01$; old $t_{(5)} = 11.07$, $P > 0.001$). Again, there was a significant difference between age groups (ANOVA, $F_{(1,9)} = 9.63$, $P < 0.05$), with middle-aged animals more affected by the change in task than old animals.

Figure 6 presents the frequency distributions of the within-task (rA_1A_2) and between-task (rA_2B_1) directional rate map correlations for all cells from middle-aged and old animals. Both middle-aged and old animals displayed unimodal frequency distributions for rA_1A_2, indicating high within-task reliability for place fields recorded from both age groups (Fig. 6A,B). Nonparametric analysis of the rA_1A_2 frequency distributions revealed that the within-task place field correlations from middle-aged and old rats were not statistically different from one another (Mann-Whitney $U = 5885.0$, $P > 0.1$). The between-task (rA_2B_1) frequency distribution for middle-aged animals again appears unimodal but has shifted to the left (Fig. 6C), indicating a low degree of correlation between the hippocampal representation of the two tasks. The rA_2B_1 frequency distribution for old animals also shifted to the left but reflected a bimodal distribution, indicating a higher proportion of place fields unaffected by the change in task (Fig. 6D). Analysis of the rA_2B_1 frequency distributions revealed that the between-task place field correlations from middle-aged and old rats statistically differed from one another (Mann-Whitney $U = 7562.5$, $P < 0.05$).

Figure 7 shows pie charts depicting the percentages of place fields affected by the change in task. If a cell had a place field during

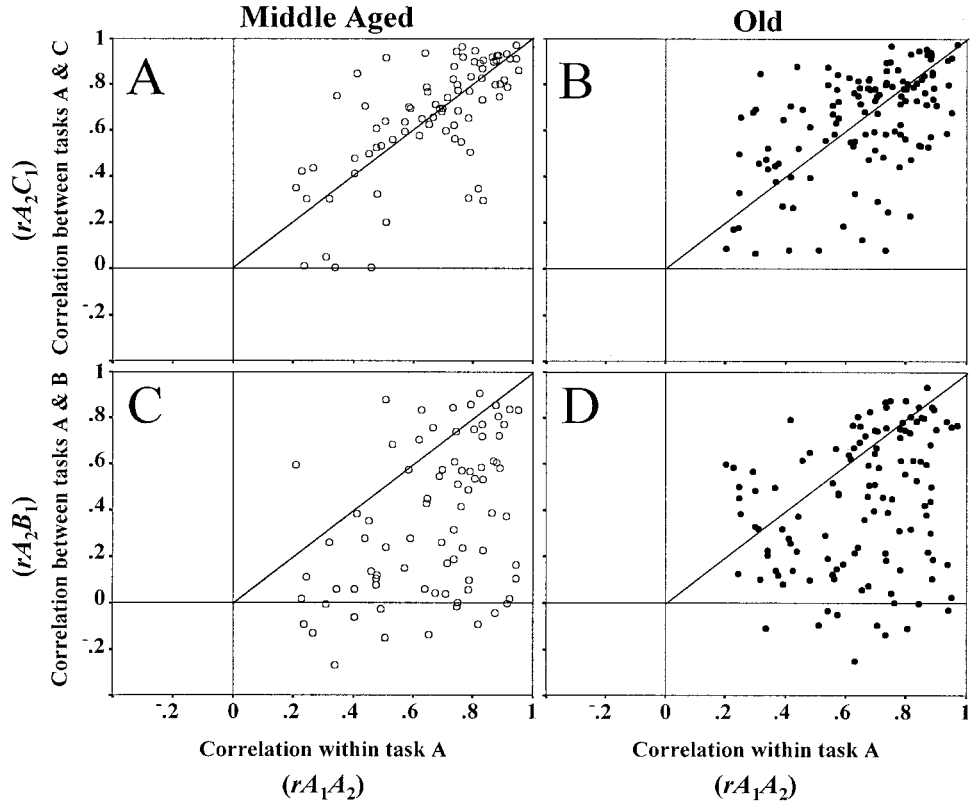

FIGURE 4. Comparison of spatial firing across tasks. A and B: Scatterplots depicting the correlation of firing rate maps across behavioral tasks of the same type (rA_2C_1) in relation to the correlation of firing rate maps within task A (rA_1A_2). For both age groups, most of the cells displaying place fields in task A were equally reliable across tasks A and C (cluster around 45-degree line). C and D: Scatterplots depicting the correlation of firing rate maps across different behavioral tasks (rA_2B_1) in relation to the correlation of firing rate maps within task A (rA_1A_2). For many of the cells, the correlation within task A was substantially higher than the correlation between tasks A and B (below the 45-degree line). Cells recorded from middle-aged and old animals are presented separately, and only those cells exhibiting within-task reliability ≥0.2 were analyzed.

task A (based on size and firing rate, see criteria in Materials and Methods) but none during task B, the place field was designated as "disappeared" (e.g., Fig. 3, Cell 1). If a cell had no place field during task A but developed one during task B, the place field was designated as "appeared" (Fig. 3, Cell 2). If a cell had a place field in both tasks, the field's relative score across both tasks was examined. An arbitrary cut-off (decided upon prior to data analysis) of $R_{AB} = 0.70$ was used to differentiate between changed and unchanged place fields. While almost two-thirds of the place fields of middle-aged rats were affected by the change in task, only about half in the old rats were affected.

A detailed analysis of the place field response to the change in task was conducted to examine whether the changed representation was concentrated at a specific region of the maze. Analyses restricted to the inner, middle, and outer thirds of the maze revealed a similar trend to that found for the entire maze (Fig. 8A). A two-way ANOVA (age × field location) of R_{AB} detected a significant effect of age (ANOVA, $F_{(1,27)} = 6.45$, $P < 0.05$) with no significant effect of field location ($F_{(2,27)} = 3.14$, $P = 0.06$) and no age × field location interactions ($P > 0.1$). While not significant, there was a tendency for a greater change in representation at the center of the maze and the end of the arms. This was true for both age groups (Fig. 8B).

Behavioral Performance

Assessment of behavioral performance on the plus maze portion of the recording session (task B) revealed no differences between middle-aged and old animals either on errors (middle-aged 2.10 ± 0.26 errors/trial, old 2.11 ± 0.09 errors/trial, mean ± s.e.m., respectively; ANOVA, $P > 0.1$) or the time it took to complete the task (middle-aged 1,396 ± 220 s, old 1,394 ± 199 s; $P > 0.1$). In addition, there was no improvement from day to day in performance of this task (Fig. 9). The extent to which the hippocampal representation changed in response to the new task (as measured by R_{AB} and R_{BA}) was not predictive of behavioral performance on the memory task (both $P > 0.1$).

DISCUSSION

Place fields were virtually unchanged between tasks A and C, indicating a high degree of consistency in the representation of the environment under similar behavioral circumstances. This also

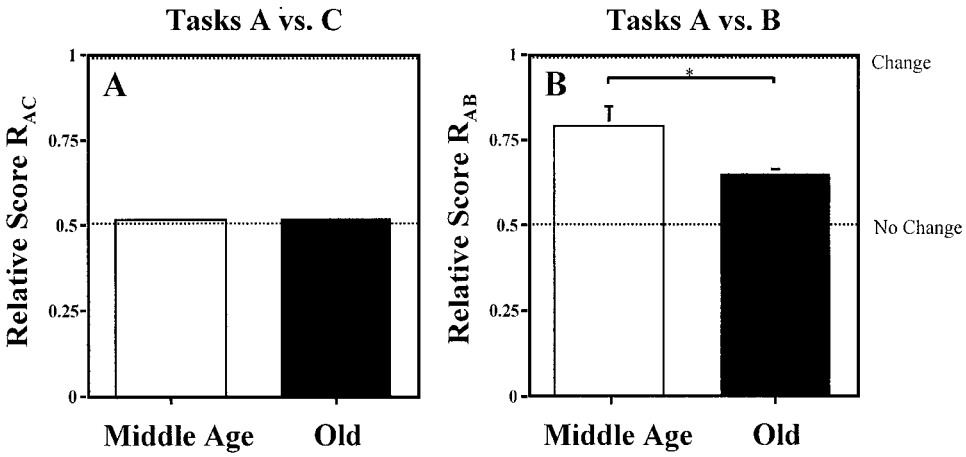

FIGURE 5. Relative scores. A: Between tasks A and C. The relative score (R_{AC}) was calculated as the ratio of within-task correlation (rA_1A_2) over the sum of the within-task correlation and the between-task correlation ($rA_1A_2 + rA_2C_1$). A score of 0.5 indicates no change across tasks relative to within task A, while a score closer to 1.0 denotes a change in spatial firing across tasks (see Materials and Methods). For both age groups, the mean R_{AC} (middle-aged 0.511 ± 0.02; old 0.523 ± 0.02; mean ± SEM) was almost exactly 0.5, indicating that place cells represented tasks A and C in a highly similar fashion. Additionally, these relative scores are evidence for electrode stability during recording sessions. B: Between tasks A and B. The relative score (R_{AB}) was calculated as the ratio of the within-task correlation (rA_1A_2) over the sum of the within-task correlation and the between-task correlation ($rA_1A_2 + rA_2B_1$). The mean R_{AB} for both age groups (middle-aged 0.773 ± 0.04; old 0.648 ± 0.03, mean ± SEM) was significantly greater than 0.5, indicating that place cells represented tasks A and B differently. The change in representation between behavioral tasks was greater for middle-aged than for old animals ($^*P < 0.05$). Only those cells exhibiting within-task reliability ≥0.2 were included in the analysis.

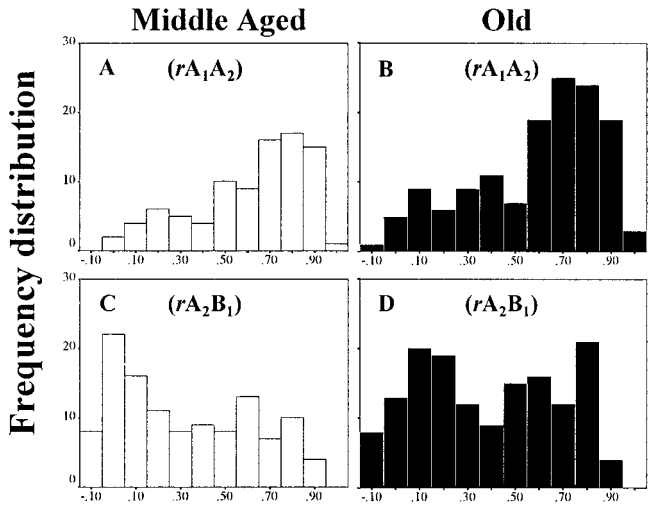

FIGURE 6. Frequency distributions of the within- and between-task correlation coefficients. A and B: Histograms of within-task directional rate map correlations (rA_1A_2) for all place cells. The peak is around 0.7 to 0.8, indicating reliable place fields in task A. This was found in both middle-aged (A) and old (B) animals ($U = 5885.0$, $P > 0.1$). C: Histogram of between task rate map correlations (rA_2B_1) for cells recorded from middle-aged animals. The peak is around 0, indicating many cells with low reliability of place fields across behavioral tasks. D: Histogram of between task rate map correlations (rA_2B_1) for cells recorded from old animals. There are two peaks, one around 0 and another around 0.8, indicating that while there were some place fields with a low correlation across behavioral tasks, others remained unchanged. Nonparametric tests indicate that the between-task frequency distributions of middle-aged and old rats significantly differed ($U = 7562.5$, $P < 0.05$). The total number of place cells recorded was greater in the aged group, affecting absolute frequencies but not the pattern of distribution.

demonstrates the stability of the recording electrodes throughout the recording session. In response to changing the behavioral task, a substantial proportion of place fields displayed remapping. This change in hippocampal representation occurred despite the fact that the surrounding environment was unchanged and rats were not removed from the apparatus.

Differences Between Lamina

In agreement with previous reports, there were no differences in how cells identified as CA1 or CA3-DG neurons responded to a change in context (Markus et al., 1995; Tanila et al., 1997a,b). Although no differences were found between cell layers, this experiment was not designed specifically to detect such differences. There are reports of some differences between CA1 and CA3-DG neurons (Mizumori et al., 1996), and the possibility remains that there are subtle variations between CA1 and CA3 cells in the way they respond to changes in context.

Hippocampal Place Cells Encode Contextual, Task-Related Information

Previous studies have shown that hippocampal place cell firing may be modulated by behavioral and task-related factors (McNaughton et al., 1983; Wible et al., 1986; Eichenbaum et al., 1987; Muller and Kubie, 1987; Breese et al., 1989; Wiener et al., 1989; Fukuda et al., 1992; Markus et al., 1995; Deadwyler et al., 1996; Gothard et al., 1996; Kobayashi et al., 1997; Matsumura et al., 1999; Sharp, 1999). Reorganization of the hippocampal representation could be induced by changes in the sensory environment, reinforcement location, reinforcement contingencies, the animal's planned trajectories, or frame of reference used by the animal.

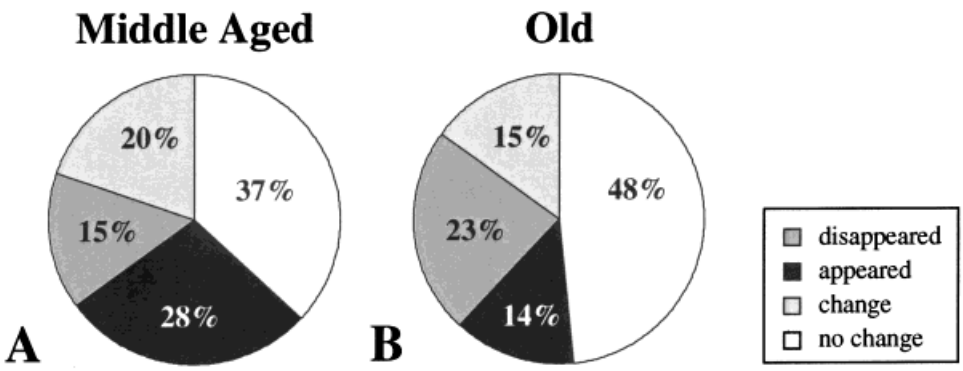

FIGURE 7. Proportion of place fields affected by the change in behavioral context between tasks A and B. For a cell to be included in this breakdown, its mean firing rate must have reached 0.1 Hz and it must have displayed at least one statistical place field in an area traversed in both tasks. If a cell had a place field during task A but none during task B, the place field was designated as "disappeared." If a cell had no place field during task A but developed one during task B, the place field was designated as "appeared." If a place field did not fall into the first two categories, its relative score across both tasks was examined (see Materials and Methods). An arbitrary cut-off of R_{AB} = 0.70 was used to differentiate between changed and unchanged place fields. While almost two-thirds of the place fields of middle-aged rats were affected by the change in task, only about half in old rats were affected. A: Percentages for middle-aged rats. B: Percentages for old rats.

In the present study, the environment was relatively stable across tasks, with the only sensory changes occurring at the arm ends (removal of the arcs), yet place fields were affected by the change in task throughout the maze, rather than being concentrated only at the end of the arms (Fig. 8). Previous work has shown that removal or rotation of a subset of cues has only minimal effects on place cell firing (e.g., O'Keefe and Speakman, 1987; Cressant et al., 1997). Furthermore, Markus et al. (1995) showed remapping despite the fact that the sensory environment remained unchanged across tasks. Thus, it is unlikely that the minor visual change in the apparatus between tasks is the source of the change in representation in the present study.

In many remapping studies, reinforcement locations and/or contingencies change between tasks. For example, Markus et al. (1995) found that requiring young rats to change from a random search for food to a directed search was sufficient to cause a change in hippocampal place fields. This manipulation resulted in changes in locomotor behavior, reinforcement locations, and trajectory planning. In the present study, remapping was found despite the fact that reward locations were kept constant and animals ran along the same runway in both tasks. On the plus maze task, the reward location provided reinforcement only on the first visit to an arm during a given trial (since arms were not rebaited). If the change in representation reflects changed reinforcement contingencies, then one might predict that place fields would persist during the initial departures from baited arms while remapping when the animal departed from the arm on subsequent visits (when the arm was

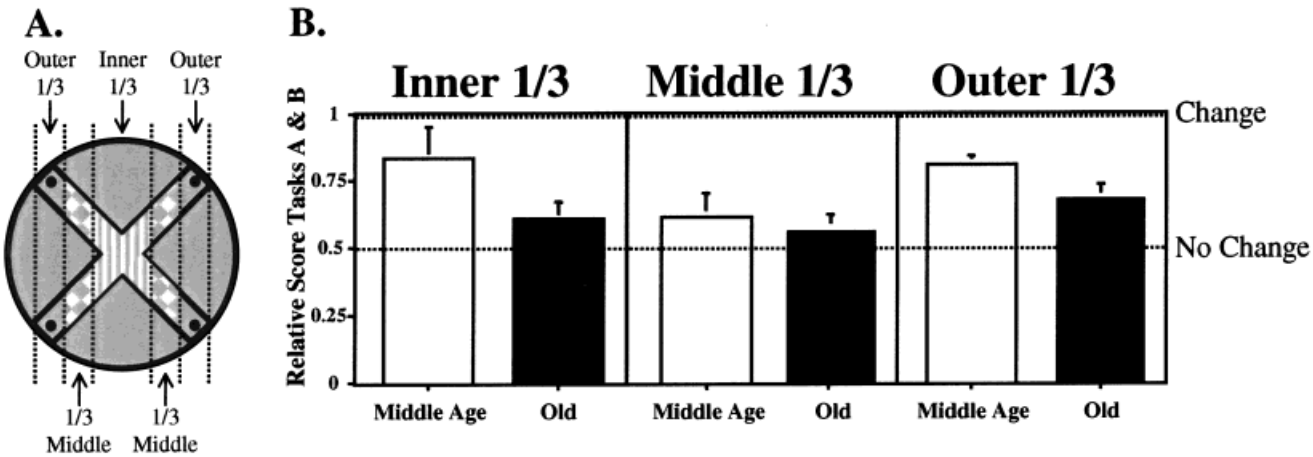

FIGURE 8. Analysis of the change in representation between behavioral tasks in relation to place field location on the maze. A: Diagram illustrating the portions of the apparatus included in each analysis. B: Examinations of R_{AB} restricted to the inner, middle, and outer thirds of the maze. While there was a trend for changed fields to be localized to the inner and outer thirds of the maze, this was not significant. Thus, place fields affected by the behavioral change were distributed across the apparatus, rather than concentrated at the spot where there was a physical change in the apparatus. Also, in each third of the maze, middle-aged animals were more affected by the change in task than old animals.

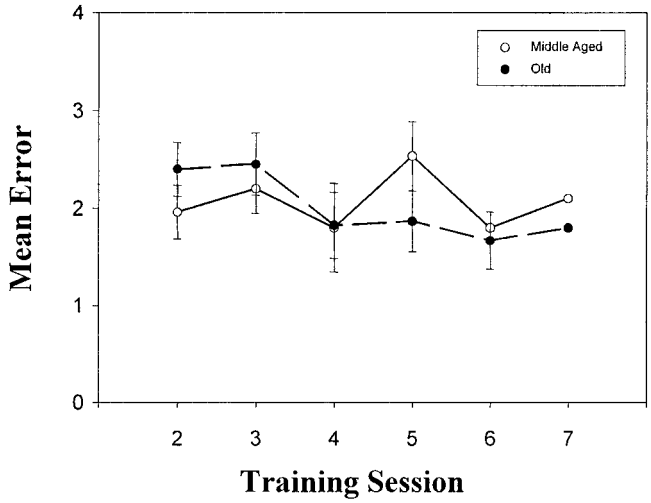

FIGURE 9. Behavioral performance on the plus maze task over training sessions. The average number of errors per each 10 trial recording session was calculated for each age group. An error was counted when an animal returned to an arm already visited during a given trial. A maximum of five errors were allowed on a given trial before the animal was directed to the correct arm. As can be seen, neither age group displayed improvement on the task with repeated training.

unbaited). As can be seen in Figure 10, this was not the case since the new place field appears in task B prior to any change in reinforcement. Consequently, rather than overt changes in the sensory environment or reward contingencies, the reorganization found in hippocampal representation between tasks A and B in the present study appears to be due to changes in search strategy and/or trajectory planning. This conclusion is further supported by recent preliminary reports showing that place cells respond differentially, dependent on the trajectory to be executed (Frank and Wilson, 1999; Wood et al., 1999).

The present data support the hypothesis that hippocampal units encode location within a given reference frame or context (Redish and Touretzky, 1997; Redish, 1999). Consequently, in addition to representing many different environments, the hippocampus can provide multiple representations of a given environment, a mechanism well suited to underlie episodic memory.

Behavioral Performance

Average errors as well as the average time it took to complete the plus maze task were strikingly similar for both age groups. This lack of deficit in aged animals and the fact that there was no learning curve for either age group (Fig. 9) suggest that the plus maze was not treated as a standard working memory task. Presumably, the fact that the animals had to solve the plus maze 10 times in a row, with no intertrial interval, resulted in a severe degree of proactive interference and increased the task difficulty. Subsequently, we have found that simply adding a 30 s delay between trials eliminates the interference (unpublished observations).

Having no age-related behavioral differences on the plus maze is both fortunate and unfortunate. On the one hand, because the plus maze task is not treated as a spatial working memory task, this task cannot be seen as purely hippocampus-dependent. However, since behavioral performance was identical, it is unlikely that the age-related electrophysiological effects observed were due to overt differences in running velocity, motor ability, response to hunger, stressfulness of the task, or the reaction to making errors. Consequently, the age differences found in place cell response to the change in task seem to be cognitive in nature and reflect differences in hippocampal information processing.

Age-Related Changes in Hippocampal Representation

In agreement with the findings from several previous studies, there were no major differences in the basic firing properties or spatial tuning of place cells in old rats (see Barnes, 1998; note, however, Mizumori et al., 1996; Shen et al., 1997). While it is known that there is a loss of neurons in many brain regions during aging (see Flood and Coleman, 1988), hippocampal neurons are unaffected (e.g., West, 1993; Rapp and Gallagher, 1996). Furthermore, the debate over whether there is any loss of CA1 synapses

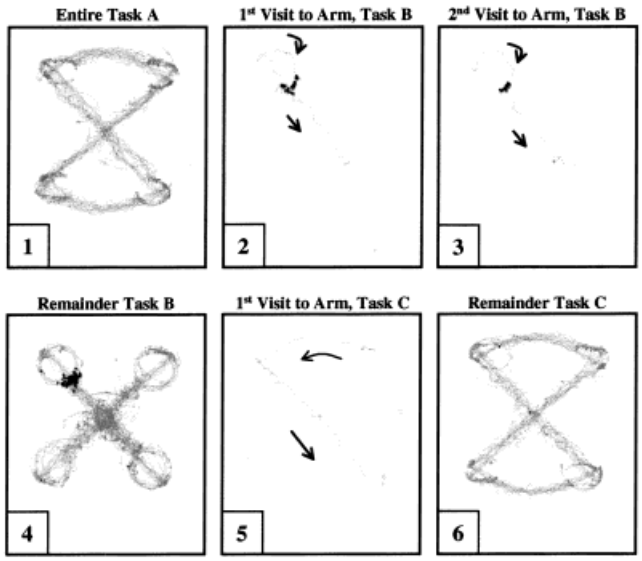

FIGURE 10. Dynamics of place field change. A detailed breakdown of the place field example presented in Figure 3, Cell 2. Gray lines represent the position of the animal, arrows depict the animal's heading, and a spike is represented by a single black dot. 1: Task A (0–993 s). The cell is silent during the figure-8 task. 2: First visit to the northeast arm following removal of the connecting arcs of the figure-8 track (task B). The cell fires robustly after the rat has turned around following food reinforcement. 3: Second visit to the northeast arm during task B. Again, the cell fires in the field when the rat is returning toward the center of the maze. On this visit, the animal did not receive food at the end of the arm (working-memory error), indicating that the occurrence of spatial firing in this cell is not related to the presence or absence of reward (panels 2 and 3 are each 15 s epochs). 4: Remainder of task B (60–1,273 s). 5: First visit to northeast arm during the subsequent figure-8 trial (task C, 20 s epoch). The first time the animal passes through the place field during task C, the cell does not fire. 6: Remainder of task C (40–896 s). Just as it had during task A, the place cell no longer displays a field. This example demonstrates that the shift in representation between tasks happens abruptly and precedes the change in reinforcement contingencies.

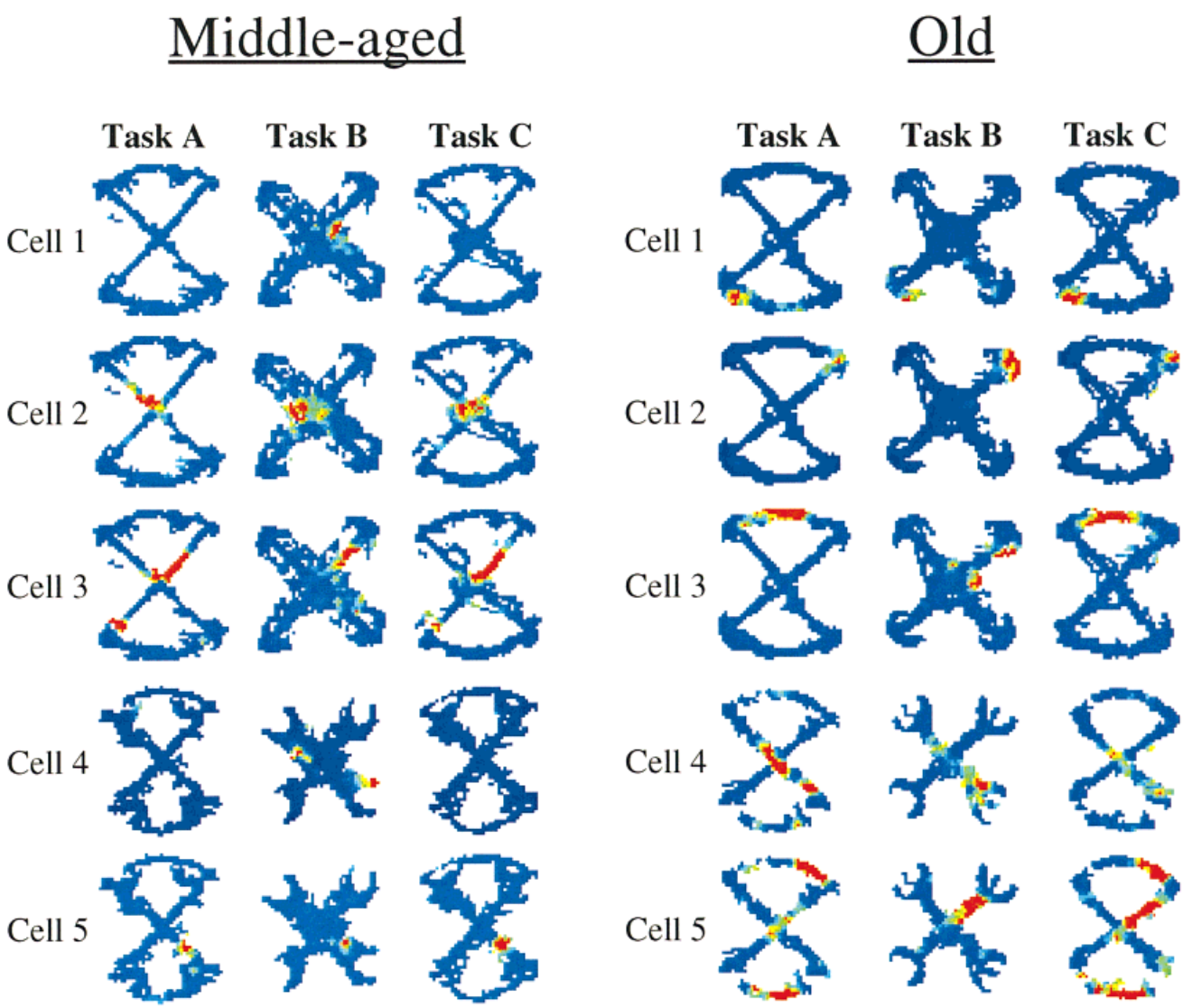

FIGURE 11. Representative example of the changes found in middle-age and old animals. Five simultaneously recorded place cells from a middle-aged and an old rat during the change in task. Firing rate maps were directional and constructed according to whether the rat was facing toward (inward) or away from (outward) the center of the maze. For a given cell, only one set of directional rate maps is shown (i.e., inward or outward). Cells 1–3 from both animals are examples of outward rate maps; cells 4 and 5 are inward rate maps. The firing rate scale was held constant for each cell across the different tasks. Maximum firing rate is indicated by red and occupancy with no firing, by dark blue. For middle-aged rats, three of the five cells displayed different firing patterns during the plus maze task relative to the figure-8 task (cell 1 middle of maze, cell 3 southwest field, cell 4 northwest arm), while only one of the five cells from the old rat was affected by the change in task (cell 3 middle of maze). Red: middle-aged cell 1 = 5 Hz, cell 2 = 18 Hz, cell 3 = 8 Hz, cell 4 = 7 Hz, cell 5 = 5 Hz; old cell 1 = 7 Hz, cell 2 = 8 Hz, cell 3 = 8 Hz, cell 4 = 16 Hz, cell 5 = 10 Hz.

with aging underscores the idea that if there is any change, it is relatively small (Scheff et al., 1985; see Geinisman, 1999 for a recent discussion). Thus, the basic machinery remains intact, and hippocampal place cells continue to show robust spatial tuning even into old age.

Previous data from our laboratory (Oler and Markus, 1998; Ward et al., 1999a,b) and others indicate that aged rats show selective learning and memory deficits related to changes in hippocampal function. Tanila et al. (1997a) reported that when the relationships among environmental cues (visual and tactile/olfactory) are changed between sessions, the majority of place fields from memory-impaired aged rats were yoked to distal visual cues. Conversely, in young rats, a large proportion of cells displayed new uncorrelated fields (i.e., remapped). The present experiment extends upon these findings by showing that without overt manipulations of the cue configuration in the environment (i.e., when only task demands are changed), the aged hippocampal representation is less responsive than that of younger animals (Fig. 11).

Aged animals exhibit a large degree of variability in cognitive abilities (e.g., Gallagher and Burwell, 1989; Markowska et al., 1989). In the present study, old animals were not screened for hippocampal function. Presumably, if only memory-impaired rats had been examined or the comparison made to young rather than middle-aged animals, a larger effect would have been found. These issues should be explored further in the future.

Notably, the young animals used in the studies of Tanila et al. (1997a,b) were between 4 and 6 months of age, whereas the younger group in the present study was between 12 and 16 months. Behavioral studies employing young, middle-aged, and old animals have shown that age-related deficits in hippocampal processing tend to be specific to the aged cohort (Oler and Markus, 1998). The present data, taken together with the findings of Tanila et al. (1997a,b), suggest that the diminished hippocampal response to contextual change is also specific to old age, rather than reflecting a lifelong decrease in plasticity.

Barnes et al. (1997) found that within a recording session, place field representation was equally reliable for both young and old rats. In other words, once the animals had selected a map, the hippocampal representation remained constant for both age groups. The present result of equivalent reliability within a given task for both middle-aged and old rats corroborates that finding. In addition, Barnes et al. (1997) found that when rats were removed from the environment between recording sessions, old rats had less consistent hippocampal representations when returned to the same environment. In the present study, animals remained on the behavioral apparatus for the duration of the recording, and therefore, this phenomenon could not be examined.

That aged animals are less affected by significant changes in the environment is suggestive of decreased synaptic plasticity. Numerous studies demonstrate age-related alterations in the neurophysiology of the hippocampal formation (e.g., Barnes and McNaughton, 1985; de Toledo-Morrell et al., 1988; Mizumori et al., 1992; Foster and Norris, 1997; Shen et al., 1997). Furthermore, there is a substantial age-related decrease in the number of perforant path synapses in the dentate gyrus (Geinisman et al., 1977), the primary source of cortical afferents to the hippocampus (Amaral and Witter, 1989). While the diversity/efficacy of the cortical input may decrease, once the representation of an environment is established within the network, the aged hippocampus is able to sustain it reliably. However, the representation is less adaptable to important changes within a given environment, as demonstrated by the lack of responsiveness to the change in task. Failure of the aged hippocampal system to form distinct representations of significant events in the environment may give rise to episodic memory impairments in the elderly.

Acknowledgments

We thank Dr. Bill Skaggs for help with statistical analyses; Joel Brown for technical assistance; Melissa Cunningham, Carl Stoelzel, Jennifer Tropp, and Mattison Ward for assistance with behavioral training and recording; and Amy Sternberg for editorial assistance. Preliminary data from this research were presented at the 1999 Meeting of the Society for Neuroscience (Oler and Markus, 1999), and at a 1999 meeting of the New York Academy of Science (Oler and Markus, in press).

REFERENCES

Amaral DG, Witter MP. 1989. The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience 31:571–591.

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

Barnes CA. 1994. Normal aging: regionally specific changes in hippocampal synaptic transmission. Trends Neurosci 17:13–18.

Barnes CA. 1998. Spatial cognition and functional alterations of aged rat hippocampus. In: Wang E, Snyder DS, editors. Handbook of the aging brain. New York: Academic Press.

Barnes CA, McNaughton BL. 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 CA, Suster MS, Shen J, McNaughton BL. 1997. Multistability of cognitive maps in the hippocampus of aged rats. Nature 388:272–275.

Breese CR, Hampson RE, Deadwyler SA. 1989. Hippocampal place cells: stereotypy and plasticity. J Neurosci 9:1097–1111.

Chrobak JJ, Buzsáki G. 1998. Operational dynamics in the hippocampal–entorhinal axis. Neurosci Biobehav Rev 22:303–310.

Cohen NJ, Eichenbaum H. 1994. Memory, amnesia, and the hippocampal system. Cambridge, MA: MIT Press.

Cressant A, Muller RU, Poucet B. 1997. Failure of centrally placed objects to control the firing fields of hippocampal place cells. J Neurosci 17: 2531–2542.

de Toledo-Morrell L, Geinisman Y, Morrell F. 1988. Age-dependent alterations in hippocampal synaptic plasticity: relation to memory disorders. Neurobiol Aging 9:581–590.

Deadwyler SA, Bunn T, Hampson RE. 1996. Hippocampal ensemble activity during spatial delayed-nonmatch-to-sample performance in rats. J Neurosci 16:354–372.

Eichenbaum H, Kuperstein M, Fagan A, Nagode J. 1987. Cue-sampling and goal-approach correlates of hippocampal unit activity in rats performing an odor-discrimination task. J Neurosci 7:716–732.

Flood DG, Coleman PD. 1988. Neuron numbers and sizes in aging brain: comparisons of human, monkey, and rodent data. Neurobiol Aging 9:453–463.

Foster TC, Norris CM. 1997. Age-associated changes in Ca^{2+}-dependent processes: relation to hippocampal synaptic plasticity. Hippocampus 7:602–612.

Frank L, Wilson F. 1999. A comparison of the firing properties of simultaneously recorded units in CA1 and the entorhinal cortex. Soc Neurosci Abstr 25:1382.

Fukuda M, Kobayashi T, Ono T, Tamura R. 1992. Effects of learning place significance in rat hippocampal place cells. Soc Neurosci Abstr 18:1462.

Gaffan D. 1991. Spatial organization of episodic memory. Hippocampus 3:262–264.

Gallagher M, Burwell RD. 1989. Relationship of age-related decline across several behavioral domains. Neurobiol Aging 10:691–708.

Geinisman Y. 1999. Age-related decline in memory function: is it associated with a loss of synapses? Neurobiol Aging 20:353–356.

Geinisman Y, Bondareff W, Dodge JT. 1977. Partial deafferentation of neurons in the dentate gyrus of the senescent rat. Brain Res 134:541–545.

Geinisman Y, de Toledo-Morrell L, Morrell F, Heller RE. 1995. Hippocampal markers of age-related memory dysfunction: behavioral, electrophysiological and morphological perspectives. Prog Neurobiol 47:223–252.

Gothard KM, Skaggs WE, Moore KM, McNaughton BL. 1996. Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. J Neurosci 16:823–835.

Jarrard LE. 1993. On the role of the hippocampus in learning and memory in the rat. Behav Neural Biol 60:9–26.

Knierim JJ, Kudrimoti HS, McNaughton BL. 1995. Place cells, head direction cells and the learning of landmark stability. J Neurosci 15: 1648–1659.

Kobayashi T, Nishijo H, Fukuda M, Bures J, Ono T. 1997. Task-dependent representations in rat hippocampal place neurons. J Neurophysiol 78:597–613.

Landfield PW. 1988. Hippocampal neurobiological mechanisms of age-related memory dysfunction. Neurobiol Aging 9:571–579.

Light LL, Singh A, Capps JL. 1986. Dissociation of memory and awareness in young and older adults. J Clin Exp Neuropsychol 8:62–74.

Markowska AL, Stone WS, Ingram DK, Reynolds J, Gold PE, Conti LH, Pontecorvo MJ, Wenk GL, Olton DS. 1989. Individual differences in aging: behavioral and neurobiological correlates. Neurobiol Aging 10: 31–43.

Markus EJ, Barnes CA, McNaughton BL, Gladden V, Skagga WE. 1994. Spatial information content and reliability of hippocampal CA1 neurons: effects of visual input. Hippocampus 4:410–421.

Markus EJ, Qin Y, Barnes CA, McNaughton BL. 1995. Interactions between location and task affect the spatial and directional firing of hippocampal neurons. J Neurosci 15:7079–7094.

Matsumura N, Nishijo H, Tamura R, Eifuku S, Endo S, Ono T. 1999. Spatial- and task-dependent neuronal responses during real and virtual translocation in the monkey hippocampal formation. J Neurosci 19: 2381–2393.

McNaughton BL, Barnes CA, O'Keefe J. 1983. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. Exp Brain Res 52:41–49.

Mizumori SJY, Barnes CA, McNaughton BL. 1992. Differential effects of age on subpopulations of hippocampal theta cells. Neurobiol Aging 13:673–679.

Mizumori SJY, Lavoie AM, Kalyani A. 1996. Redistribution of spatial representation in the hippocampus of aged rats performing a spatial memory task. Behav Neurosci 110:1006–1016.

Morris RGM, Garrud P, Rawlins JNP, O'Keefe J. 1982. Place navigation impaired in rats with hippocampal lesions. Nature 297:681–683.

Morris RG, Nunn JA, Abrahams S, Feigenbaum JD, Recce M. 1999. The hippocampus and spatial memory in humans. In: Burgess N, Jeffery KJ, O'Keefe J, editors. The hippocampal and parietal foundations of spatial cognition. Oxford: Oxford University Press, p 259–289.

Muller RU, Kubie JL. 1987. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J Neurosci 7:1951–1968.

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. 1978. The hippocampus as a cognitive map. Oxford: Clarendon Press.

O'Keefe J, Speakman A. 1987. Single unit activity in the rat hippocampus during a spatial memory task. Exp Brain Res 68:1–27.

Oler JA, Markus EJ. 1998. Age-related deficits on the radial maze and in fear conditioning: hippocampal processing and consolidation. Hippocampus 8:402–415.

Oler JA, Markus EJ. 1999. Hippocampal place cells are less responsive to changes in task demands in aged rats. Soc Neurosci Abstr 25:1627.

Oler JA, Markus EJ. In press. Age-related deficits in episodic memory may result from decreased responsiveness of hippocampal place cells to changes in context. In: Scharfman HE, Witter M, Schwarcz R, editors. The parahippocampal region: Implications for neurological and psychiatric diseases. New York, NY: NYAS.

Olton DS, Samuelson RJ. 1976. Remembrance of places passed: spatial memory in rats. J Exp Psychol Anim Behav Process 2:97–116.

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

Paxinos G, Watson C. 1986. The rat brain in stereotaxic coordinates, 2nd ed. New York: Academic Press.

Phillips RG, LeDoux JE. 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106:274–285.

Ranck JB Jr. 1973. Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. Part 1. Behavioral correlates and firing repertoires. Exp Neurol 41:461–531.

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

Recce ML, O'Keefe J. 1989. The tetrode: an improved technique for multi-unit extracellular recording. Soc Neurosci Abstr 15:1250.

Redish AD. 1999. Beyond the cognitive map: from place cells to episodic memory. Cambridge, MA: MIT Press.

Redish AD, Touretzky DS. 1997. Cognitive maps beyond the hippocampus. Hippocampus 7:15–35.

Scheff SW, Anderson KJ, DeKosky ST. 1985. Strain comparison of synaptic density in hippocampal CA1 of aged rats. Neurobiol Aging 6:29–34.

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21.

Shapiro ML, Tanila H, Eichenbaum H. 1997. Cues that hippocampal place cells encode: dynamic and hierarchical representation of local and distal stimuli. Hippocampus 7:624–642.

Sharp PE. 1999. Complimentary roles for hippocampal versus subicular/entorhinal place cells in coding space, context, and events. Hippocampus 9:432–443.

Shen J, Barnes CA, McNaughton BL, Skaggs WE, Weaver KL. 1997. The effect of aging on experience-dependent plasticity of hippocampal place cells. J Neurosci 17:6769–6782.

Skaggs WE, McNaughton BL. 1998. Spatial firing properties of hippocampal CA1 populations in an environment containing two visually identical regions. J Neurosci 18:8455–8466.

Skaggs WE, McNaughton BL, Gothard KM, Markus EJ. 1993. An information-theoretic approach to deciphering the hippocampal code. In: Hanson SJ, Cowan JD, Giles CL, editors. Advances in neural information processing 5. San Mateo, CA: Morgan Kaufmann, p 1030–1037.

Squire LR. 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys and humans. Psychol Rev 99:195–231.

Sutherland RJ, Rudy JW. 1989. Configural association theory: the role of the hippocampal formation in learning, memory, and amnesia. Psychobiology 17:129–144.

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

Tulving E. 1983. Elements of episodic memory. London: Oxford University Press.

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

Ward MT, Oler JA, Markus EJ. 1999a. Hippocampal dysfunction during aging I: deficits in memory consolidation. Neurobiol Aging 20:363–372.

Ward MT, Stoelzel CR, Markus EJ. 1999b. Hippocampal dysfunction during aging II: deficits on the radial-arm maze. Neurobiol Aging 20:373–380.

West MJ. 1993. Regionally specific loss of neurons in the aging human hippocampus. Neurobiol Aging 14:287–293.

Wible CG, Findling RL, Shapiro M, Lang EJ, Crane S, Olton DS. 1986. Mnemonic correlates of unit activity in the hippocampus. Brain Res 399:97–110.

Wiener SI, Paul CA, Eichenbaum H. 1989. Spatial and behavioral correlates of hippocampal neuronal activity. J Neurosci 9:2737–2763.

Wilson MA, McNaughton BL. 1993. Dynamics of the hippocampal ensemble code for space. Science 261:1055–1058.

Wood ER, Dudchenko PA, Eichenbaum H. 1999. Episodic determinants of hippocampal place cell activity during t-maze spatial alternation. Soc Neurosci Abstr 25:1381.