

# Age-related Deficits in Episodic Memory May Result from Decreased Responsiveness of Hippocampal Place Cells to Changes in Context

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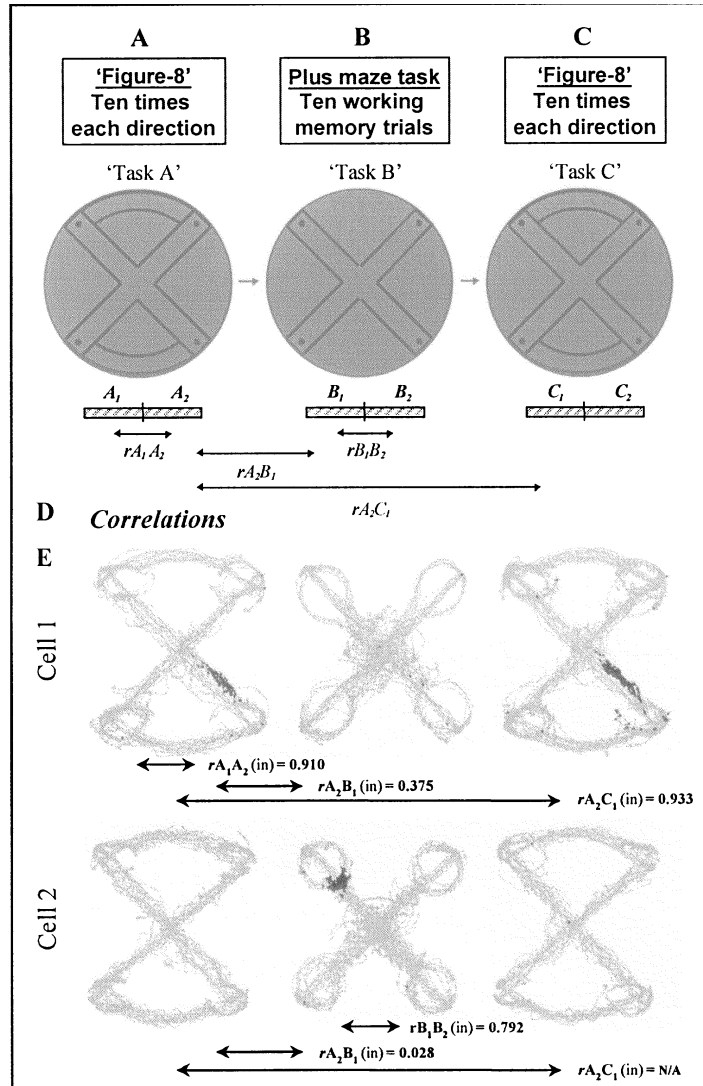
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The hippocampal formation (HF) is a vital processing stage for episodic memory<sup>1</sup> and for the performance of spatial memory tasks.<sup>2,3</sup> Aging has been shown to impair episodic memory in humans,<sup>4</sup> as well as behavioral performance on spatial tasks in rats.<sup>5,6</sup> These behavioral findings, taken together with anatomical and physiological changes, indicate impaired hippocampal function during aging. The principal cells of the rodent HF display location-dependent activity,<sup>7–9</sup> and these “place cells” may form a cognitive map of the animal’s environment.<sup>10</sup> Furthermore, the fact that the HF can change its representation of the environment in response to behavioral manipulations may form the basis for episodic memory processing.<sup>11</sup> The present study was designed to examine the effects of altering *behavioral demands* on hippocampal place cell activity in middle-aged and old rats, while the testing environment remained relatively stable, and the animals were not removed from the apparatus. The results suggest that age-related memory deficits associated with a loss of normal hippocampal function result from decreased sensitivity of the hippocampal network to respond to meaningful changes in the environment.

## METHODS

Five middle-aged (12–16 months) and six old (24–28 months) F-344 male rats were trained to run in both directions on a “figure-8” track in order to receive a food reward (see FIG. 1A). The track consisted of four arms forming a symmetrical “+”, with two removable arcs connecting the top and bottom of the figure-8. A few chocolate sprinkles were placed in small food cups at the four corners of the track, and the rats were consistently rewarded each time they reached a corner (task A). With the connecting arcs removed, the track was transformed into a traditional four-arm plus maze with identical, symmetrical arms, each with a food cup at the end (task B, see FIG. 1B). This permitted recording cells as the animal sampled the same locations under two different behavioral conditions. During task B, the baiting procedure was also changed to create a working memory task. The experiment was designed so there would be sufficient sampling of the track arms, in both directions, between task

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**FIGURE 1.** Training/recording procedure. (A) Configuration of the behavioral apparatus during task A. The rats were trained to run five laps in one direction, 10 laps in the reverse direction, and five additional laps in the original direction ( $5 \times 10 \times 5$  procedure). The animals were consistently rewarded with a few chocolate sprinkles at each corner. (B) At the end of task A, 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. (B) Following the 10th working memory trial, the arcs were returned and the food cups rebaited. The animals again performed the  $5 \times 10 \times 5$  procedure, receiving a food reward each time a corner was reached. (C) Correlation analysis. The correlation of firing-rate maps between the two halves of a behavioral task

A and task B. At the end of task B, the experimenter replaced the connecting arcs and rebaited the food cups, and the animal again ran the figure-8 task (task C; see FIG. 1C).

The animals were surgically implanted with microelectrodes for single-unit recording from the dorsal hippocampus. The recording environment was divided up into a  $64 \times 64$  bin array and smoothed firing-rate maps were constructed for each cell.<sup>12</sup> 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. To compare changes in place fields between tasks, rate map correlations within and between the different tasks were calculated (see FIG. 1D). To statistically analyze changes in place fields between behavioral tasks, several relative scores were calculated for each place cell. The following formula was used to calculate the relative score:

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

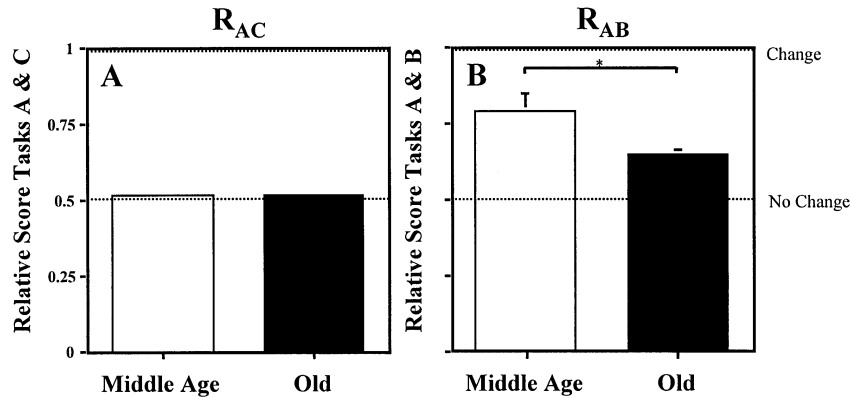
Where “ $r$  within task” is the correlation between the first and second half of a given task, and “ $r$  between tasks” is the correlation between the second half of one task and the first half of the other task. Thus, a relative score of 0.5 indicates no change in place fields across the two tasks because the within-task correlation is equal to the between-tasks correlation. A relative score closer to 1.0 indicates a change in spatial firing across tasks because the between-tasks correlation is smaller than the within-task correlation (see Oler and Markus<sup>17</sup>).

## RESULTS

A total of 187 complex spike cells were recorded as the animals performed the full sequence of tasks (A→B→C). An analysis of variance, by animal, of the middle-aged and old rats showed no effect of age on the basic spatial firing properties of the cells (all,  $p > 0.1$ ). Place fields were unchanged between tasks A and C, with the average  $R_{AC}$  score for both age groups almost exactly 0.5 (FIG. 2A). This indicates a high degree of consistency in the representation of the environment under similar behavioral circumstances. However, a substantial proportion of place fields from both middle-aged and old animals displayed “re-mapping” in response to changing the task. As can be seen in the examples in FIGURE 1E, some place fields were strongly affected. The average  $R_{AB}$  scores were significantly different from 0.5 for both the middle-aged and old rats (FIG. 2B). These relative scores denote smaller between-task correlations ( $r_{A_2B_1}$ ) than within-task correlations ( $r_{A_1A_2}$ ), indicating dissimilar

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(“within-task” correlations;  $r_{A_1A_2}$ ,  $r_{B_1B_2}$ ) were compared to the correlation of firing-rate maps between the second half of task A and the first half of the tasks B and C (“between-tasks” correlations;  $r_{A_2B_1}$ ,  $r_{A_2C_1}$ , respectively). (E) Hippocampal place cell responses to a change in task. Two examples of the spatial firing of single hippocampal neurons, recorded from different animals, during the entire sequence of the change in behavioral task, and rate map correlations. Grey depicts the position of the animal and black a spike from the neuron. *Cell 1*, A place field on the southeast arm only during the figure-8 track (task A and task C). *Cell 2*, Place field that appeared only during task B.



**FIGURE 2.** Relative scores. **A**, Task A ↔ Task C. The relative score ( $R_{AC}$ ) was calculated as the ratio of within-task correlation ( $r_{A_1A_2}$ ) over the sum of the within-task correlation and the between-tasks correlation ( $r_{A_1A_2} + r_{A_2C_1}$ ). Therefore, a score of 0.5 indicates that the within-task correlation is equal to the between-tasks correlation, whereas a score closer to 1.0 denotes a change in spatial firing across tasks. Note that for both age groups the mean  $R_{AC}$  was almost exactly 0.5, indicating that place fields represented tasks A and C in a highly similar fashion. Additionally, these relative scores are evidence for electrode stability during recording sessions. **(B)** Task A ↔ Task B. The relative score ( $R_{AB}$ ) was calculated as the ratio of within task correlation ( $r_{A_1A_2}$ ) over the sum of the within task correlation and the between tasks correlation ( $r_{A_1A_2} + r_{A_2B_1}$ ). Note that the mean  $R_{AB}$  for both age groups (middle aged:  $0.773 \pm 0.04$ ; old:  $0.648 \pm 0.03$ , mean and SEM, respectively) was significantly greater than 0.5 ( $t$ -tests,  $p < 0.01$ ), indicating that place fields represented tasks A and B differently. Additionally, the change in representation across behavioral tasks was greater for the middle-aged than for old animals (\* $p < 0.05$ ).

hippocampal representations of the environment between tasks A and B. It was found that this change in representation was greater for middle-aged than for old animals.

## DISCUSSION

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. These data support and extend previous reports that hippocampal units do not simply encode for location, but rather for location within a given reference frame or context.<sup>13</sup> Consequently, the hippocampus can represent many different environments, as well as provide multiple representations of a given environment. Each representation could therefore be encoding a significant event in a given environment—a mechanism well suited to underlie episodic memory.

In both the middle-aged and old animals, the hippocampus showed a reliable representation of a given situation/task. However, the hippocampus of the aged rats showed less of a distinction between two different tasks within the same environ-

ment. A number of studies have shown age-related differences in the manner with which a stable or changed environment is represented by the hippocampus.<sup>14–16</sup> In those studies the animals were taken out of the environment before subsequent reintroduction, and the aged animals may have been affected by this manipulation. The current findings indicate that even when the animal remains within the environment, and must only encode a change in task demands, aging effects are found. Failure of the aged hippocampal system to form distinct representations of significant events in a given environment may give rise to episodic memory impairments in the elderly.

### ACKNOWLEDGMENTS

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