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Hippocampal map realignment and spatial learning

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The spatial selectivity of hippocampal neurons suggests that they contribute to an internal representation of current location. The activity of hippocampal pyramidal cells was recorded while adult (10–13 months old) and aged (24–28 months old) rats performed a task in which two spatial reference frames were put in conflict. Rats attempted to find an unmarked goal whose position was fixed relative to only one of the two reference frames. The ability of a rat's hippocampus to adjust to the conflicting information and use the 'correct' position estimate (hippocampal map 'realignment') was correlated with the rat's ability to find the hidden goal. In addition, aged rats were impaired relative to adult rats in both goal-finding accuracy and map realignment. Thus, changes in the effectiveness with which the hippocampal spatial representation is updated on the basis of external cues may contribute to both within-age-group spatial learning variability and age-related spatial learning deficits.

Principal cells in the rat hippocampus fire preferentially when the rat occupies certain areas of a given environment[1]. The region of increased firing is called the cell's 'place field', and the activity of ensembles of these 'place cells' can be used to reconstruct a rat's trajectory through an environment[2]. Because of the spatial correlates of place-cell activity, it has been suggested that the rat hippocampus may act as or generate a cognitive map, providing the animal with an internal representation of its current location and the spatial organization of the environment[3]. If this is the case, then changes in hippocampal pyramidal cell activity should correlate with predictable changes in behavior during spatial learning tasks. Indirect support for this idea comes from studies in which experimental manipulations that disrupt place fields disrupt spatial learning in both rats[4–9] and mice[10,11] (but see refs. 12,13). Further support comes from studies in which a rat's incorrect choices of goal location corresponded with alterations of place-cell firing[14,15]. Little is known, however, about the relationship between an animal's ability to dynamically update its internal map during locomotion and the accuracy with which it can locate spatial goals.

We therefore recorded place-cell activity while rats performed a task in which two spatial reference frames were in conflict. Rats attempted to find an unmarked goal whose position was fixed relative to only one of the two conflicting sources of position information. The ability of the hippocampus to adjust to the conflicting information and use the correct position estimate (hippocampal map realignment) was correlated with the ability of individual animals to find the hidden goal.

In addition, we compared hippocampal map realignment in aged and adult rats. Because aged animals of various species show spatial-learning impairments[16,17], many previous studies have searched for age-related impairments of hippocampal function that might contribute to these deficits[18]. One important finding is that aged rats show impairments of long-term potentiation[18,19] (LTP), a form of synaptic weight change that may underlie some types of learning[20–23]. According to some models of hippocampal function[24–28], LTP deficits would interfere with the association of external cues with locations on the map, which could cause impairments in the hippocampal map realignment measured here. The correlation between hippocampal map realignment and goal-finding accuracy reported here suggests that such impairments could contribute to spatial learning deficits in aged rats.

RESULTS

Behavior

Aged and adult rats ran back and forth on a linear track for both food rewards and brain-stimulation rewards (**Fig. 1**). The start box and the track were moved between trials, but the barrier at the end of the track remained at one position in the room from trial to trial. During the journey from the start box to the barrier (the 'outbound journey'), rats earned a brain-stimulation reward by pausing in an unmarked goal zone that also remained at a constant position in the room. Because the start box and track had an inconsistent relationship to the position of the goal zone, rats had to locate the goal zone relative to the barrier and/or the distal cues in the room (hereafter referred to as the 'room cues').

Each rat was considered to have learned the location of the goal if, during outbound journeys, that rat showed a reduction in speed near the goal zone relative to a 'control' zone at a different location (**Fig. 2**). All five of the adult rats and two of the aged rats moved significantly more slowly in the goal zone than in the control zone (one-tailed t-test, $P = 0.01$), indicating that these rats had some knowledge of the location of the goal.

In addition, learning of the goal location was quantified by calculating the difference between the mean normalized speeds in the goal

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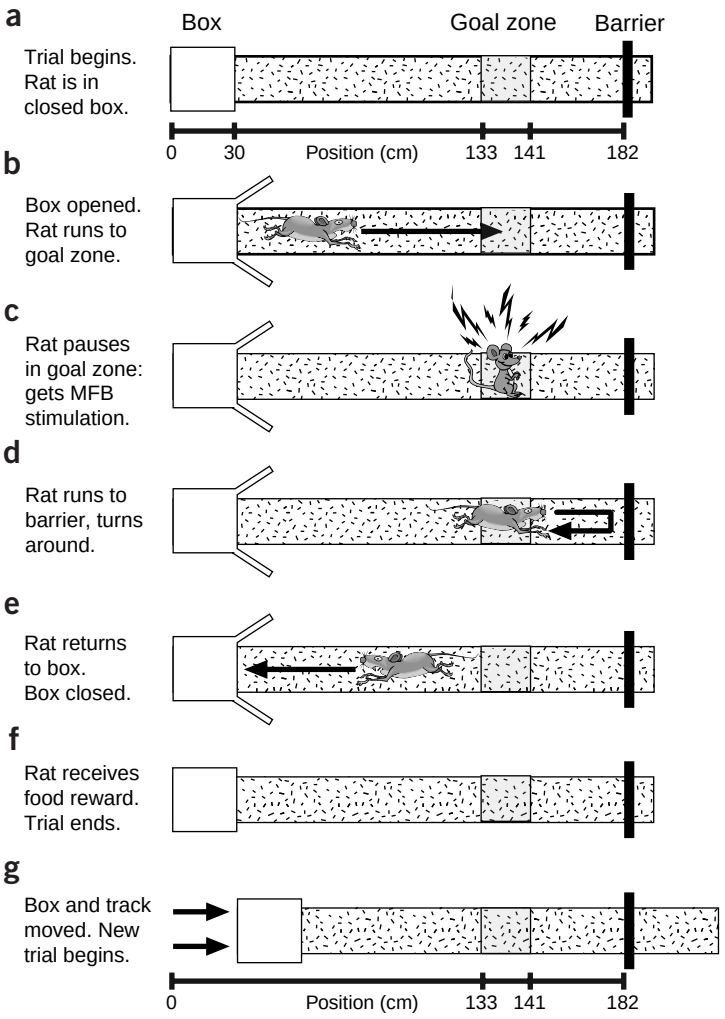

Figure 1 The linear track task. (**a**) The apparatus consisted of an elevated, linear track (182 × 16 cm) covered with thin, gray carpet. The start box, unmarked goal zone and barrier were positioned as marked (drawing not to scale). Each trial began with the animal in the closed box. (**b**) The box was opened, and the animal left the box. (**c**) If the animal paused within the goal zone for longer than the minimum delay (variable by day from 0.5–1.5 s), he received medial forebrain bundle (MFB) stimulation. Animals could earn only one stimulation per outbound journey. (**d**) After crossing the threshold, animals turned around and returned to the box (see ref. 37 for complete details of the return journey). (**e**, **f**) When the animal returned to the box, the box was closed, and the animal received a small food reward. This marked the end of the trial. (**g**) The box and track were moved (as a unit) along the long axis of the track before the beginning of the next trial. Because the goal zone remained constant in room coordinates, local and self-motion cues provided no information about the goal zone location.

zone and the control zone. One rat, for example, had a mean speed difference of 1.15 standard deviations (s.d.), whereas another had a mean speed difference of 0.54 s.d. We infer from this result that both rats learned the location of the goal, but the performance of the first rat was more accurate than that of the second rat. Using this measure, we found that aged rats, as a group, did not slow down in the goal zone as much as the adult rats (aged, 0.1 ± 0.2 σ (normalized speed); adult, 0.9 ± 0.2 σ; $t_8 = 3.03$ (one-tailed), $P = 0.008$). Furthermore, although aged rats showed a tendency toward a speed decrease in the goal zone (**Fig. 3a**), this was non-significant for the group (goal zone, –0.39 ± 0.41 σ; control zone, –0.29 ± 0.26 σ; $t_8 = 0.24$ (one-tailed), $P = 0.41$). In contrast, adult rats showed a significant speed decrease in the goal zone (**Fig. 3b**; goal zone, –0.75 ± 0.28 σ; control zone, 0.17 ± 0.22 σ; $t_8 = 2.91$ (one-tailed), $P = 0.01$). This suggests that the aged rats were impaired relative to adult rats in learning the location of the goal.

Place fields and place-field realignment

We recorded the electrophysiological activity of ensembles of hippocampal pyramidal cells while rats performed the linear track task, and then we examined these spike trains for place fields. In total, there were 1,223 acceptable place fields on the outbound journeys (aged: 95, 117, 162, 187 and 104 fields for a total of 665; adult: 164, 59, 111, 148 and 76 fields for a total of 558; see Methods for place-field criteria).

Place-cell firing is influenced by both visual cues[14,29–31] and sensory information regarding the animal's movements[30,32–36]. The mobile start box in this experiment created a mismatch between self-motion information and room-cue information (**Fig. 4**). In this situation, some place fields move with the start box, whereas other fields remain at a consistent position in the room[32,33,37] (**Fig. 5**). The field alignment varies systematically with the distance of the field from the start box: box-aligned fields tend to occur near the start box, whereas room-aligned fields tend to occur near the end of the track[32,33,37]. This suggests that rats begin each journey with a box-aligned hippocampal map, and at some point during the journey, hippocampal activity realigns to room coordinates.

For each rat, the average position of realignment across all sessions, or the 'transition point,' was estimated by quantifying the alignment of each place field (field slope[32]; **Fig. 5**), and then plotting the slope of each field versus the position of the field in the room (**Fig. 6**). The transition point was defined as the point at which the 2nd-order polynomial least-squares curve through the data dropped below 0.5. Results similar to those described herein were obtained using an alternate method that does not rely on curve-fitting (Methods).

We calculated both the distribution of transition points and the within-age-group mean field slope at each position in the room (**Fig. 7**). Note that the mean field slope of the aged animals drops into the room-aligned range farther along the track than does that of the adult rats. Transition points were significantly closer to the end of the track in aged rats (149.2 ± 4.3 cm) than they were in adult rats (139.2 ± 2.9 cm; $t_8 = 2.14$ (one-tailed), $P = 0.03$).

Correlation of electrophysiology with behavior

Because the goal was at a fixed location in the room, a box-aligned hippocampal map could provide little information regarding the location of the goal. If the hippocampal map must be properly

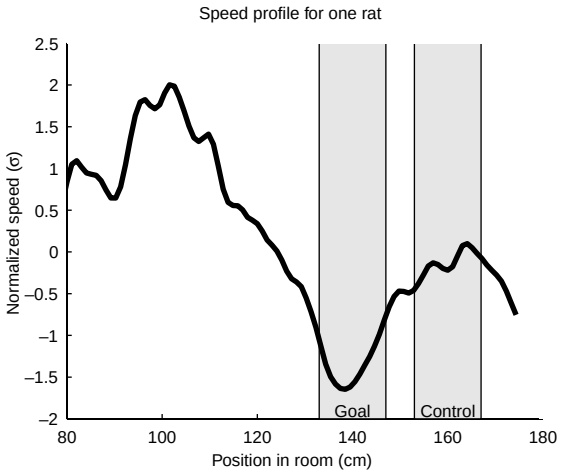

Figure 2 Estimation of task learning from the speed profile of one rat. Plot shows the mean normalized speed of a single adult animal at each position in the room (Methods). Approximate location of the goal zone is indicated by gray shading labeled 'goal'; location of the control zone is indicated by gray shading labeled 'control'. This animal moved more slowly in the goal zone than in the control zone, indicating that the rat had some knowledge of the goal location.

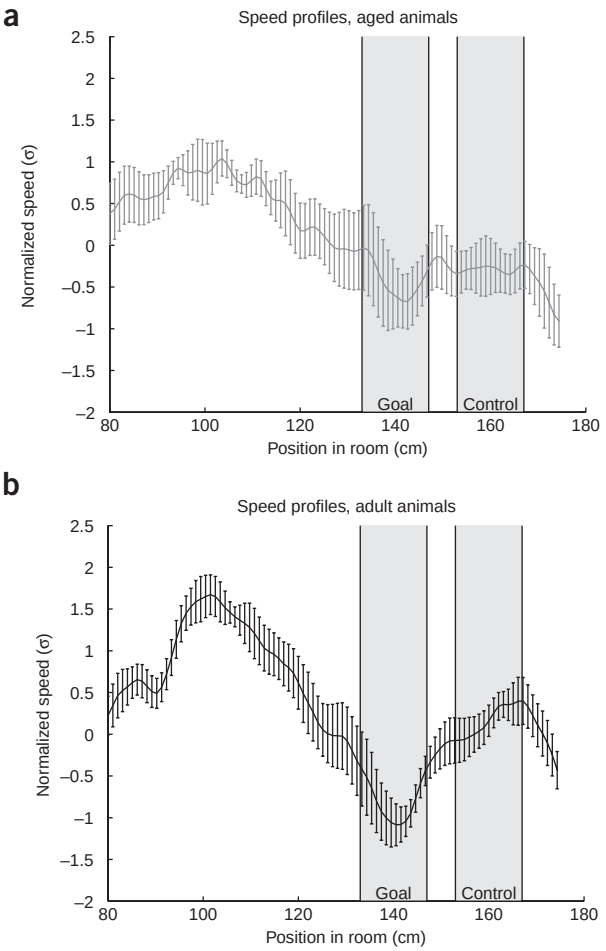

Figure 3 Aged rats did not learn the location of the goal as well as did adult rats. Conventions and axes as in **Fig. 2**; error bars indicate standard error of the mean (s.e.m.). (**a**) Although aged rats showed a tendency toward a speed decrease in the goal zone, this was non-significant for the group. (**b**) In contrast, adult rats showed a significant speed decrease in the goal zone. Note that, because speed has been normalized for each animal, the lack of significant speed change in aged rats is not an artifact of their slower running speeds.

aligned in order to encode the goal location, learning of the goal location would require realignment of the hippocampal map (to room coordinates) by the time the animal reached the goal zone. We predicted that animals whose hippocampal activity, on average, had not realigned by the time the rat reached the goal would have more difficulty learning the location of the goal.

The behavioral and electrophysiological data were therefore examined for correlations between the position of the transition point and the accuracy of learning of the goal location. Age-group differences in both variables were factored out by subtracting the appropriate age-group mean from the value of each data point (Methods). Realignment nearer to the end of the track was correlated with poorer learning of the goal location ($r^2 = 0.64$; ANOVA, $F_{1,8} = 14.443$, $P = 0.005$), regardless of the age of the animal (**Fig. 8**).

DISCUSSION

There are two main findings in the present study: (i) an age-independent correlation between hippocampal processing capabilities and goal-finding behavior and (ii) age-related deficits in both of these characteristics. The first finding is that the ability of a rat's hippocampus to align its activity with room cues was correlated with the ability of the rat to locate a hidden goal whose position was fixed relative to those cues. This suggests that when hippocampal activity was not aligned to the room cues when a rat reached the goal zone, the rat was unable to associate the goal zone with a particular location. This interpretation is based on (and supports) the idea that hippocampal activity provides a rat with information regarding its current position[3]. Alternatively, it is possible that rats that learned the location of the goal zone used it as an additional room-aligned cue, thus hastening hippocampal map realignment. Future studies are needed to determine whether hippocampal map realignment affects the ability of rats to find a hidden goal, or vice versa.

The second finding of the current study is that the ability to correct a position estimate based on room cues declines with age. That is, hippocampal map realignment occurred nearer to the end of the track in aged rats than it did in adult rats. This result is consistent with observations of a decreased influence of cue configuration on place-cell activity patterns in aged rats[38–40]. When considered in concert with the age-independent correlation between realignment and spatial learning, this result suggests that delays in hippocampal map realignment could contribute to age-related spatial learning deficits[16,17].

There are at least three potential sources of the variability in hippocampal map realignment (note that the relative contributions of these sources of variability may differ between the within- and across-age-group cases). First, some animals may poorly attend to room cues. Second, some animals may have impairments in the speed or accuracy of sensory processing. These first two possibilities would degrade the room-cue information, or prevent or delay the delivery of that information to the hippocampus. A third possibility, which was the motivation for this study, is that animals with LTP deficits (aged rats, for example[18,19]), may show impaired association of cues and landmarks with locations on the hippocampal map[24–28]. To determine the contri-

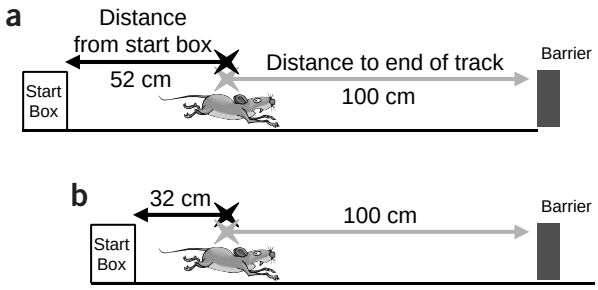

Figure 4 Mismatch of position information from self-motion and room cues during outbound journeys. (**a**) On a long track configuration, the rat gets position estimates from both self-motion information (black star) and room-cue information (gray star). In this example, 100 cm from the end of the track is equivalent to 52 cm from the start box. (**b**) On a shorter track configuration, the position estimates do not match up in the same way, as 100 cm from the end of the track is now equivalent to 32 cm from the start box. Thus the position estimates do not match up consistently from lap to lap.

butions of each of these variables to hippocampal map realignment, future studies will need to measure LTP and realignment in the same animals, and, eventually, assess the content of input to the hippocampus. In any case, the present results provide insight into possible neural bases for individual differences in navigation skills and spatial learning.

METHODS

Subjects. Ten male Fischer-344 rats were used in this study. Five were adults (10–13 months old) and five were aged (24–28 months old). Animals were food-deprived and maintained at 80% of *ad-libitum* feeding weight. All experiments were conducted in accordance with the guidelines of the University of Arizona Institutional Animal Care and Use Committee.

Behavioral task pretraining. Animals were trained to shuttle back and forth on a linear track (182 × 16 cm; **Fig. 1**). Distal visual cues were available around the walls of the room (~2 m away; large blocks of white and black curtains and small white and black posters). The rat left a 30-cm-long start box at one end of the track, ran to a barrier at the other end of the track, and returned to the box. After returning to the box, the animal received a food reward, the box was closed, and the box and track were moved (as a unit) along the direction of the long axis of the track. Twenty-four different track configurations, each separated by 2.5 cm, were used pseudo-randomly. In the longest and shortest configurations, respectively, the barrier was 152 cm and 91 cm from the front edge of the start box. Reward was never given at the far end of the track.

Animals were then implanted with a hyperdrive (a microdrive allowing individual manipulations of 12 tetrodes and 2 single electrodes[2,41,42]) above the right hippocampus. Simultaneously, stimulation electrodes were implanted in the medial forebrain bundle (for details, see ref. 37). Before surgery, animals received *ad-libitum* food and no training for 2–5 d. After surgery, animals were allowed an additional 2–5 d to recover. For another 3–5 d, rats ran for food reward around a rectangular track in a different room. Finally, to allow the rats to adapt to the weight of the headstage, cable and implanted hyperdrive, the rats received 5–7 d of additional pretraining using the protocol described above.

Linear track task. The linear track task was performed on the same apparatus and with the same cues as the pretraining shuttle task (Fig. 1). The behavioral protocol also remained the same, except for the addition of an unmarked goal zone on the track (8 cm long, 133–141 cm from the beginning of the track in its longest configuration). If the animal paused in the goal zone for a sufficient period of time, he received medial forebrain bundle stimulation reward. The required duration of the pause in the goal zone varied from day to day (0.5–1.5 s), gradually increasing as animals learned the task. The animal could receive a maximum of one reward before reaching the end of the track. As part of another study, animals could also receive another reward on the return journey to the start box (for details, see ref. 37; return journeys and their associated rewards are not considered in this paper). Although the box and track were moved after each trial, the goal zone remained at a constant position within the room throughout the task. In the longest and shortest configurations, respectively, the center of the goal zone was 107 cm and 46 cm from the front edge of the start box. Animals received two 30-min sessions on the linear track task per day, separated by a 20-min rest period in a small box adjacent to the track. Old rats ran significantly fewer laps on average than did adult rats (15.5 ± 2.6 and 27.3 ± 2.2 laps, respectively; $t_8 = 3.82$ (two-tailed), $P = 0.005$). In addition, old rats tended to run more slowly than did adult rats (19.7 ± 1.5 and 24.5 ± 1.3 cm/s, respectively; $t_8 = 2.69$ (two-tailed), $P = 0.03$).

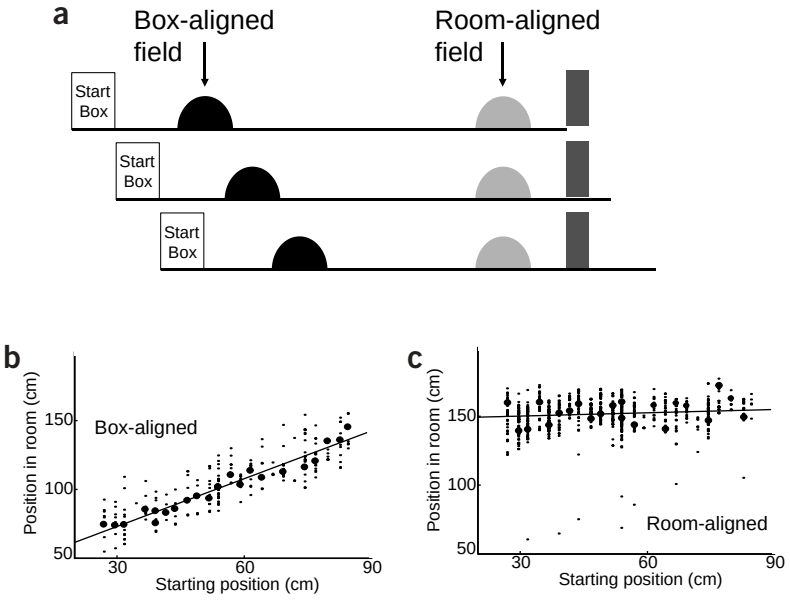

Figure 5 Place fields can be aligned to the room or to the start box (or they may show intermediate alignment; see **Fig. 6**.) (**a**) The mismatch of position information from self-motion and room cues (**Fig. 4**) causes some fields to move with the start box from trial to trial, whereas other fields stay fixed regardless of the start box position. (**b**, **c**) Example fields and calculation of field slope. Small data points represent single spikes recorded from the cell; large data points represent field centers-of-mass (centroids) from each journey. Both are plotted according to the position of the rat and the starting position of the particular journey. Least-squares lines, calculated from the field centroids, indicate the dependence of firing position on the position of the start box. (**b**) A box-aligned field, with a slope of approximately 1. (**c**) A room-aligned field, with a slope of approximately 0. Note that some journeys produced insufficient firing for place-field analysis and hence do not have a centroid marked. Multiple centroids at the same starting position are taken from multiple laps at that starting position. (**b**, **c**) adapted from ref. 37.

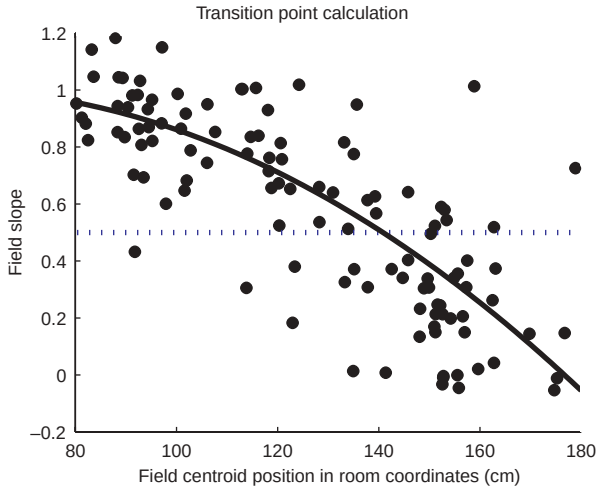

Figure 6 Calculation of the transition point. All place fields of one adult rat are shown. The *x*-axis is the position in the room of each field's centroid. The *y*-axis is the slope of each place field. Black line is the 2nd-order least squares curve. Transition point is the point at which the line crosses 0.5 (at 141 cm for this example).

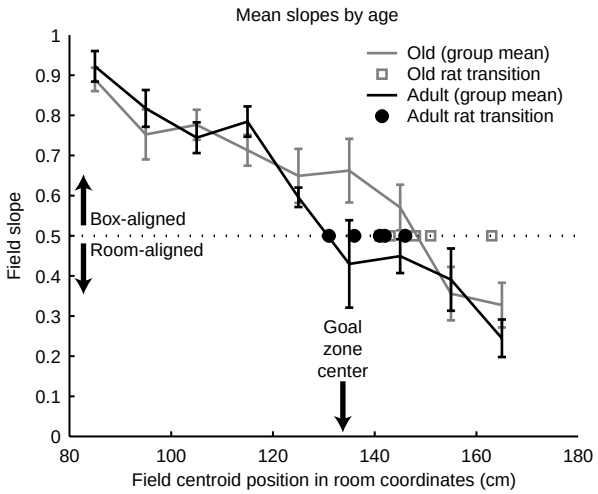

Figure 7 Mean field slopes at each position (10-cm bins) in aged and adult rats. The upper half of the plot represents box-aligned fields; the lower half represents room-aligned fields. Note that the mean field slope of the aged animals drops into the room-aligned range farther along the track than does that of the adult rats. The center of the goal zone and transition points of individual rats are also shown.

Position analysis. The two-dimensional position of the rat on the video image was projected onto a line stretching along the length of the track (measured from the center of the back of the box to the center of the barrier). This produced a one-dimensional measure of position in the room used for all analyses. Only data from the track were analyzed; data obtained while the animal was in the box were not included. In addition, only data recorded during outbound journeys (from the start box to the end of the track) are included in this report. It is important to note that the outbound journeys did not consist of only outbound motion; animals occasionally turned around to retrace part of a path and then continued in the outbound direction.

Using speed to estimate learning of goal zone. Learning of the hidden goal location was estimated using a method that may be independent of actual success in obtaining reward. The analysis examined the possibility that, even if a rat did not always remain motionless in the goal zone for a sufficient period of time to receive a reward, the rat might have slowed down in the correct location.

For each session, mean running speed during outbound journeys was calculated for each point on the track. Because rats generally remained motionless for up to a few seconds after receiving stimulation reward, data taken between the time of stimulation and the end of a journey were omitted from these calculations. The resultant values were averaged over all sessions recorded from a given rat. To prevent bias due to the different mean running speeds of old and adult rats, the values were normalized according to the animal's mean running speed. That is, speed was expressed as standard deviations from the mean running speed of the rat.

The mean speed of the rat near the goal zone (133–147 cm) was then compared with its mean speed in a 'control' zone of equivalent size (**Fig. 2**). The control zone (153–167 cm) was located between the goal zone and the end of the track. This location, rather than one between the start box and the goal zone, was chosen to prevent interpretational ambiguity: a rat approaching the goal zone might slow down because he knew the location of the goal zone or because he was approaching the end of the track. A higher speed in a zone beyond the goal zone, however, would indicate that the rat increased its speed after passing the goal zone, and therefore knew the approximate location of the goal.

It should be noted that a speed change of zero does not represent the worst possible performance of the task. Because rats slow down while approaching the end of the track, and because the control zone was near to the end of the track, an animal that had not learned the task at all would actually show a negative speed change. That is, the animal would run more quickly in the goal zone than in the control zone. This was true for one of the aged rats.

Place cell isolation. Because a tetrode consists of four closely-spaced wires, spikes from different cells produce differentiable patterns on the four channels[2,43,44]. Spikes from different cells were separated subjectively using in-house software (*XClust* by M. Wilson, *MClust* by A.D.R. and *BubbleClust* by P. Lipa; Arizona Research Laboratories) based on previously developed algorithms[43,45]. Cells were classified as pyramidal cells or interneurons based on waveform shape, inter-spike interval histograms and average firing rate. Only

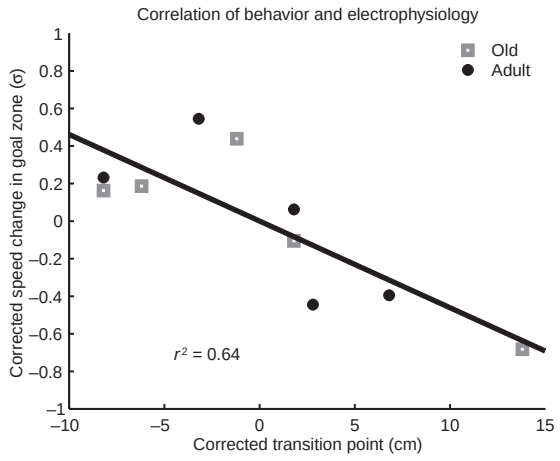

Figure 8 Learning of the goal location was correlated with the position of map realignment. Behavioral accuracy, as reflected in each rat's tendency to slow down in the goal zone, is plotted versus the rat's transition point. Differences between age groups, along both *x*- and *y*-axes, have been factored out by subtracting the appropriate age-group mean from the value of each data point (Methods). The behavioral and electrophysiological measurements are significantly correlated.

pyramidal cells were included in analyses[31,46–48]. All cells were required to have no inter-spike intervals shorter than 2 ms, a physiologically plausible refractory period for a single unit[46,48]. The data presented here may include multiple recordings from the same cells, as electrodes were not always moved between recording sessions.

Place field determination. After action potentials had been assigned to a particular cell, the correlation between the rat's location and the activity of each cell (the 'place field' of the cell) was computed. First, we removed spikes that were recorded either while the animal was in the start box or on the inbound journey, or while the animal was not moving (speed <7 cm/s). The latter step minimized the contamination of the data with the nonspatial firing observed during a hippocampal state called 'large irregular activity'[49]. We also removed spikes that did not occur within 5,000 ms of any other spike from the same cell. This reduced the noise in the data because place cells tend to fire multiple spikes at ~10 Hz when the rat is in the cell's field. Cells were then checked to see that the preceding steps did not bring their spike counts below 50, and there was no difference between age groups in the percentage of cells that met this criterion (adult, 61 ± 5%; aged, 51 ± 3%; $t_8 = 1.70$ (two-tailed), $P = 0.13$). Spikes of the remaining cells were then assigned to one of 64 spatial bins (2.4 cm each) according to the position the rat occupied when the spike was fired. Resultant values of spikes per bin were divided by the time the rat spent in each bin, giving an average firing rate for each bin. Finally, field boundaries were determined according to established criteria[50], and the center of mass, or centroid, of the place field was calculated.

Field slope. The field slope[32] was used to quantify the preferred alignment of each place field. First, the centroid of the field on each lap was calculated. The single-lap centroids were then plotted versus the position of the start box on each lap (**Fig. 5**). The field slope was defined as the slope of the least-squares line fit to this plot. Thus, for a box-aligned place field, the centroid of the field moved with the start box, and the least-squares line had a slope of 1. For a room-aligned place field, the centroid position was stable, regardless of the position of the start box, and the least-squares line had a slope of 0.

At this stage, fields were tested for lap-to-lap field variability. If the mean-squared error (MSE) of the residuals of the least-squares line was greater than 20 cm per data point, the field was considered unreliable and was removed from further analyses. MSE was calculated as $\sqrt{[(\Sigma R^2)/(n-2)]}$, where n is the number of data points and R is the residuals from the least-squares line. There was no age-group difference in the percentage of fields that met this criterion (adult, 63 ± 6%; aged, 68 ± 3%; $t_8 = 0.847$ (two-tailed), $P = 0.42$).

Transition point determination. For each rat, fields from outbound journeys from all sessions were used to estimate the transition point. The slope of each field was plotted versus the position of the field in the room, and a 2nd-order polynomial least-squares curve was fit to the data (**Fig. 6**). The transition point for each rat was the position at which this curve dropped below 0.5 (that is, into the 'room-aligned' range).

Alternate method of transition point determination. The mean field slope on the latter portion of the track (120–180 cm) provides a curve-fitting–independent estimate of the relative position of the reference-frame transition point. Because this portion of the track straddles the approximate position of the transition, a high mean field slope indicates a late transition, whereas a low mean field slope indicates an early transition. Use of this method replicated the results already described, including both the age-group difference in the position of the transition point ($t_8 = 2.02$ (one-tailed), $P = 0.04$) and the correlation between learning of the goal location and the transition point ($r^2 = 0.52$; ANOVA, $F_{1,8} = 8.761$, $P = 0.02$).

Factoring out of age-dependent effects. Before the correlation of map realignment and behavioral accuracy was calculated (**Fig. 8**), age-group differences in both variables were factored out. For each rat, the raw value of each variable was converted to a value relative to the mean value of that variable for the entire age group. One aged rat, for example, had a transition point of 141 cm. Because this value is 8.2 cm less than the mean transition point of the aged rats (149.2 cm), the corrected transition point for this rat is –8.2 cm (**Fig. 8**). This correction is similar to a z-score calculation, but is less dependent on the assumption of normally-distributed data.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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