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Does the dorsal hippocampus process navigational routes or behavioral context? A single-unit analysis

Jonathan A. Oler,[1,2] Stephanie C. Penley,[1] Simona Sava[1] and Etan J. Markus[1]
[1]Behavioral Neuroscience Division, Department of Psychology, University of Connecticut, U-1020, Storrs, CT 06269, USA
[2]Laboratory for Affective Neuroscience, University of Wisconsin – Madison, Waisman Center, Madison, WI, USA

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Abstract

In humans the hippocampus plays a role in both episodic memory and spatial navigation. Similar findings have been shown in other animals including monkeys and rats. The relationship between the processing of episodic and spatial related inputs within the hippocampus remains a puzzle. One approach to understanding how the hippocampus processes information is to examine how hippocampal cell activity corresponds to environmental experience. Hippocampal pyramidal cells can alter their spatial tuning (re-map) in response to changes in task demands. The degree to which this re-mapping is related to contextual/episodic information or to changes in spatial navigation/trajectories is unclear. The current study was designed to examine cell activity under two conditions that differed in contextual information without alterations in the goal-directed trajectories taken by the animals. Adult and aged rats were trained to do an alternation task on a fixed pathway [J. A. Oler *et al.* (2005) *Neuroscience*, **131**, 1–12]. The animals ran this pathway during either 'safe' or 'unsafe' (a tone indicating a shock region) trials, with hesitation during 'unsafe' trials providing a clear behavioral measure of discrimination between these two conditions. Relatively few place cells displayed re-mapping between the two conditions. We propose that the principle source of re-mapping in the dorsal hippocampus is changes in the animal's trajectories rather than behavioral context. Possible reasons why so few cells responded to the change in context are discussed.

Introduction

Location-specific activity of hippocampal neurons during navigation, while initially discovered in the rodent (O'Keefe & Dostrovsky, 1971; Ranck, 1973), has subsequently been found in monkeys (Matsumura *et al.*, 1999) and in humans (Ekstrom *et al.*, 2003). The existence of these place cells, together with the fact that lesions of the hippocampal system cause severe impairment in spatial memory, suggests that the hippocampus acts as part of an environmental mapping system (O'Keefe & Nadel, 1978). Functional neuroimaging studies provide further links between spatial navigation and hippocampal function (Ghaem *et al.*, 1997; Maguire *et al.*, 1997, 1998; Iaria *et al.*, 2003; Kumaran & Maguire, 2005). It has also long been evident that the hippocampus plays a central role in the formation of episodic memory (Milner *et al.*, 1968; Squire, 1992; Cohen & Eichenbaum, 1994; Eichenbaum *et al.*, 1999). A critical question therefore, and one that has been debated in the literature (Nadel & Eichenbaum, 1999; Redish, 1999), is whether the activity of place cells reflects the encoding of location-related or more abstract episode-related information.

In response to manipulation of environmental cues place cells can alter their spatial tuning, an experimental effect termed re-mapping (Muller & Kubie, 1987; Bostock *et al.*, 1991; Bures *et al.*, 1997; Shapiro *et al.*, 1997; Skaggs & McNaughton, 1998; Brown & Skaggs, 2002; Cressant *et al.*, 2002; Anderson & Jeffery, 2003; Hayman *et al.*, 2003; Jeffery *et al.*, 2003; Lee *et al.*, 2004; Lenck-Santini *et al.*, 2005; Leutgeb *et al.*, 2005b). Such cue manipulation data indicate that the hippocampus can maintain multiple representations of altered environments. In addition, place cell activity is affected by where the last reward was found and where the next reward is expected (Frank *et al.*, 2000; Oler & Markus, 2000; Wood *et al.*, 2000; Ferbinteanu & Shapiro, 2003; Smith & Mizumori, 2006), and in situations where the animals alternate between two different tasks (Markus *et al.*, 1995; Oler & Markus, 2000). These data indicate that the hippocampus can maintain multiple representations of a fixed environment.

It remains unclear to what degree re-mapping in a fixed environment is a consequence of changes in navigation (trajectories) or related to the induction of a new hippocampal representation reflecting different mnemonic demands of a task (Ferbinteanu & Shapiro, 2003; Moita *et al.*, 2003, 2004; Smith & Mizumori, 2006). Any experimental situation that requires an animal to change trajectories (e.g. instead of going from location 'A to B', go from 'A to C') must rely upon mnemonic or task-related signals. The above reports of re-mapping in a fixed environment paralleled changes in the trajectories taken by the animals. However, re-mapping in these situations can also be interpreted as cells responding to changes in task demands or expectations.

While training an animal to change trajectories necessitates a change in behavioral context, not every task that incorporates a change in behavioral context necessarily includes changes in trajectories. The current study was designed to examine the effect of an overt contextual change on place fields, while holding the environment and the goal-related trajectories constant. Rats were trained on an alternation task using a fixed pathway. The animals ran this pathway during either 'safe' or 'unsafe' trials (Oler *et al.*, 2005). The aim of the present experiment was to test whether place field re-mapping can

Correspondence: Dr E. J. Markus, as above.
E-mail: etan.markus@uconn.edu

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occur as a result of contextual change alone, rather than as a result of alterations in visuospatial input or the trajectories traveled. Given previous reports of reduced re-mapping in response to task/environmental changes (Tanila *et al.*, 1997a, b; Oler & Markus, 2000; Wilson *et al.*, 2004), aged animals were also examined to see if they would show a differential place cell response to a change in context.

Materials and methods

Subjects and apparatus

All experiments were approved by the University of Connecticut animal care committee and conformed to the National Institutes of Health standards for the humane treatment of animals. All efforts were made to minimize the number of animals used. Thirteen male F-344 rats (11–28 months) were food deprived to approximately 80% of their *ad libitum* body weight throughout the experiment. The animals were trained to alternate for food reinforcement (Noyes Precision Pellets; Research Diets, New Brunswick, NJ, USA) in a high-walled, diamond-shaped runway (1 × 1.2 m) located in a dimly lit room (2.1 × 2.8 m) containing several visual cues (Fig. 1A). Two pellet dispensers (Med-Associates, St Albans, VT, USA) were located in chambers at opposite ends of the runway. The walls of the runway were made of clear Plexiglas, and the track floor connecting the chambers was composed of stainless steel rods. Sensors were placed in the runway walls at the entrance to both of the chambers. As the animal entered the chamber, a single 45-mg food pellet was dispensed into a plastic cup inside the chamber. Once a pellet had been dispensed in one chamber, the animal was required to traverse the runway and enter the opposing side to attain reinforcement in the same manner. After reaching criterion performance levels of at least 60 trials in 30 min, animals began discrimination training.

Discrimination training

During discrimination training, a section of the track at the apex was electrified during 'tone trials', which were initially presented on a 1 : 10 (tone to no-tone) ratio schedule, in a pseudo-random order. The tone (75 dB, 300–500 Hz; Radio Shack, Fort Worth, TX, USA) and the apex current (~0.15 mA, Model 82404SS Master Shocker; Lafayette Instruments, Lafayette, IN, USA) were presented together. A new trial was initiated at the time the animal entered the subsequent chamber, and a trial was defined as a traversal of the runway from one food chamber to the other. Therefore, during a tone trial the rat had to cross over the electrified region of the runway in order to attain food reinforcement. While the tone remained on for the duration of the trial, the rat only received the shock when crossing the apex of the runway. On each day of discrimination training the session was terminated when the animal reached either 80 alternation trials or 30 min had passed. Over the course of training the tone to no-tone trial ratio was slowly increased from the 1 : 10 (tone to no-tone) ratio until there were

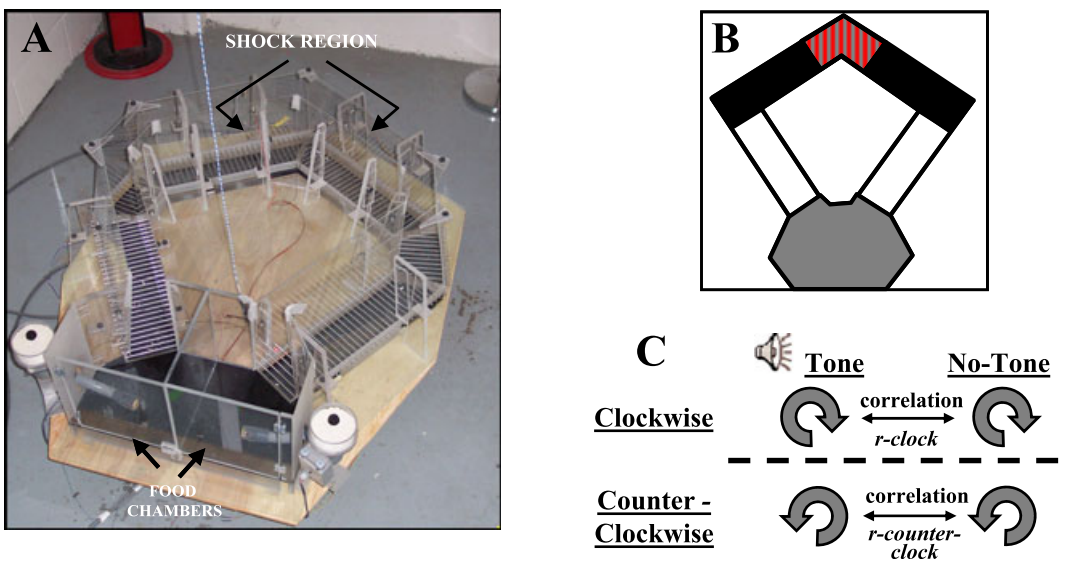

FIG. 1. Behavioral apparatus used in this study. (A) Photo of the runway used in the present study demonstrating the location of the shock region and food chambers. Refer to the text for a description of the training procedure and behavioral analysis. The track was 1 × 1.2 m from end to end, and the width of the runway arms was approximately 13 cm. The outside walls of the runway were angled inward slightly to eliminate reflections from the tracking diodes. In addition to the sensors at the entrances to the food chambers, two more recessed photocell/light-emitting diode pairs were placed opposite one another in the runway walls. These sensors were located on either side of the track apex, at the boundaries of the shock region. Therefore, during a tone trial, the shock stimulus could be initiated and terminated by the animal's entry and exit from the shock region. This feature allowed us to circumvent the potential confound produced by the large electrical field that was produced by the shock generator. (B) Diagram of the zones used to analyse the discriminatory behavior. The track was partitioned into several regions. The time spent in the different areas during each trial was recorded. The duration of the first entry per trial to each region of interest was used as the dependent variable to measure discriminative behavior. The discrimination analysis compared the hesitation response during the tone and no-tone trials in the area adjacent to the shock region (depicted in black). A videotaped example of the discrimination behavior can be seen at http://psychlops.psy.uconn.edu/Markus/DiscriminationTask.html. (C) Diagram of the correlation analysis used in the present study. The computer controlling delivery of stimuli was synchronized with the computers recording the place cell data. Using time stamps generated by the sensors in the track walls, the recording session was divided into four segments based on heading (clockwise and counter-clockwise) and trial condition (tone and no-tone). Four firing rate-maps were then constructed for each cell (i.e. clockwise/tone, counter-clockwise/tone, clockwise/no-tone, counter-clockwise/no-tone) using separate time range files containing the time stamps for each of the four segments. In order to compare the location of place fields between behavioral conditions (tone vs. no-tone), two rate-map correlation coefficients were calculated (one for each direction) using pixel-by-pixel comparisons of the firing rate-maps between the two segments of the task (i.e. '*r*-clock' and '*r*-counter-clock', see text). This analysis was performed on each recorded cell that met the criteria for inclusion in the data set (see text).

equal amounts of each trial type. When the animals were displaying significant tone/no-tone discriminative performance (see 'Behavioral data analysis') and running a minimum of 40 trials in 30 min, they were given free access to food for several days prior to surgery.

Behavioral data analysis

The location and direction of the rats' movements were recorded using a video-based tracking program (S.M.A.R.T System; Panlab, Barcelona, Spain). Behavioral tracking data were collected in tandem with the electrophysiological data (see 'Recording' below). The track was partitioned into several 'zones' (Fig. 1B). Well-trained rats stop just before the first electrified rung, and hesitate before crossing the apex only on the tone trials, this is not observed on no-tone trials (Oler *et al.*, 2005); for a short video demonstration of the behavior visit http://psychlops.psy.uconn.edu/Markus/DiscriminationTask.html.

Consequently, the duration of the first entry per trial into the runway area adjacent to the apex (while heading towards the shock region; see Fig. 1B) was used as the dependent variable to measure discriminative behavioral performance. An animal was considered to be discriminating when it spent significantly more time hesitating during tone trials than the no-tone trials in the runway area adjacent to the shock region. Only data from sessions where animals were displaying significant discriminative performance were used in the analysis.

Surgery

Animals were anesthetized either with isoflurane gas (AErrance; Baxter Pharmaceuticals, Deerfield, IL, USA) or an intramuscular (i.m.) injection of a cocktail consisting of ketamine (12.4 mg/mL), acepromazine (0.1 mg/mL) and xylazine (1.27 mg/mL). Once anesthetized, a peripheral anticholinergic (Glycopyrrolate, 0.1 mg/kg, i.m.) was administered to block parasympathetic activity. Body temperature was maintained at 37 °C with a heating pad, the eyes were coated with ophthalmic ointment and covered to prevent drying. The rat was placed in a stereotaxic device, 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 hippocampus (DH) at coordinates 3.5 mm posterior to Bregma, 2.2 mm lateral from the midline (Paxinos & Watson, 1986). With the dura excised, a miniature drive (microdrive) with eight movable microelectrodes (tetrodes) was lowered into the brain approximately 1.5–1.8 mm below the pial surface. The recording electrodes (Recce & O'Keefe, 1989; Wilson & McNaughton, 1993; Gray *et al.*, 1995; Oler & Markus, 2000) were constructed from four twisted polyamide-insulated 14-μm nichrome wires (H.P. Ried, Palm Coast, FL, USA). The rat was sutured if necessary, and postoperatively administered buprenorphine (Buprenex; Reckitt & Colman Pharmaceuticals, Richmond, VA, USA) to reduce pain and Penicillin G benzathine to prevent infection. The animals were given at least 1 week to recover from surgery prior to retraining and recording sessions.

Recording

Following recovery from tetrode implantation surgery, the animals were retrained to run the discrimination task with the microdrive attached to a head stage. The head stage cable was mounted to a pulley system in the ceiling to counterbalance the weight of the head stage (approximately 16 g). The head stage consisted of two microchips (Dr Matt Wilson, MIT, Cambridge, MA, USA) 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 (Tracker SA-3; Dragon, Boulder, CO, USA), providing data on the rats' location and heading while on the track. The signals from the head stage were carried by a cable to a set of rack-mounted amplifiers (Neuralynx, Tucson, AZ, USA), amplified 5000 times, filtered between 300 Hz and 6 kHz, and sent to a PC-based analog-to-digital signal capture board (Keithley Instruments, Cleveland, OH, USA). Whenever spike amplitude exceeded a preset threshold, a 1.0-ms sample of data was acquired at a rate of 25 kHz. Neuronal and position data were sampled concurrently and time stamped using a synchronization clock board (ComputerBoards, Mansfield, MA, USA). A channel from one of the other tetrodes was used as a reference for differential recording.

Once the post-surgical animals displayed pre-surgical levels of behavioral discrimination on the runway task, the tetrodes were slowly advanced into the CA1 cell body layer of the DH until clear signals from individual units were detected. The location of the electrodes was established based on physiological criteria (i.e. sharp waves or 'ripples') and depth estimates, and the final position of the electrode was confirmed following recording using standard histological procedures.

Once the recordings appeared stable, a baseline period of approximately 10 min was recorded while the animal sat/slept in a holder tub outside the recording apparatus. Following this baseline period, the animal was placed in the apparatus and run on the task. Animals had to run a minimum of three times in each direction, in each of the tone and no-tone conditions (i.e. a minimum of 12 crossings over the apex region) in order for the electrophysiology data to be included in the analysis. Immediately after the last trial, the animal was removed from the apparatus and placed back in the holder tub for another 10 min before the recording was ended.

Place field analysis

Place field analyses were performed using software written by Dr Bill Skaggs (University of Arizona, USA). Individual units were isolated off-line on a Solaris Workstation (Sun Microsystems, Santa Clara, CA, USA) using a spike parameter cluster separation method (Dr Matt Wilson, MIT, USA). Many of the units recorded displayed little or no activity in the apparatus. Only those cells with a minimum of 100 spikes while in the apparatus were included in the place field analysis. Additionally, high-rate 'theta' cells, putative inhibitory interneurons (Ranck, 1973; Freund & Buzsáki, 1996), classified by a mean firing rate ≥ 2.5 Hz in both tone and no-tone conditions (Markus *et al.*, 1994), and a place field that covered the majority of the track were excluded from the present analysis.

The recording environment was divided up into a 64×64 bin array. Each bin was approximately a 2.0×2.0 cm square. Firing rate-maps were constructed for each cell using an 'adaptive smoothing method' (Skaggs *et al.*, 1993). Place fields were defined as an area of at least 12 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 (Muller *et al.*, 1987). A velocity filter was used to ensure that all data recorded while the animal was moving slower than 8 cm/s were excluded from the analysis. This was done to ensure that the data used for analysis of place field properties were taken from when the rat was moving (i.e. in theta) and not resting, grooming or during hesitation (i.e. sharp wave EEG state; Chrobak & Buzsáki, 1998).

Place cells are directionally selective on linear track mazes (Markus *et al.*, 1995). Accordingly, the comparison of place cell activity across tone/no-tone conditions was performed separately for clockwise and counter-clockwise headings, and only on those regions of the apparatus sampled in both conditions. A sampled region was defined by at least two passages by the animal at a minimum speed of 8 cm/s.

Recording during US presentation was problematic, because the current applied to the rungs around the apex generated a large electrical field that created noise in the recording system during tone trials. To circumvent this potential confound, in addition to the sensors at the entrances to the food chambers, two more recessed photocell/light-emitting diode pairs were placed opposite one another in the runway walls. These sensors were located on either side of the track apex, at the boundaries of the shock region. Therefore, during a tone trial, when the animal's nose came between the photocell and diode, a relay could be closed that would initiate the shock generator. As the animal rounded the apex and exited the shock region, the animal's body came between the second photocell and diode pair, and the current was terminated. It should be noted that the sensors at the entrances to the food chambers initiated tone presentations. Thus, while the tone was turned on at the beginning of, and remained on for the duration of, each tone trial, during recordings the shock was only activated when the animal was inside the shock region. Consequently, the data from when the shock was presented were excluded from the analysis.

Probe trials

It should also be pointed out that several of the tone trials during recording were randomly presented without a shock. This manipulation permitted the examination of place cell firing in the shock region, allowing place fields located in the track apex to be analysed. Furthermore, these 'probe' trials provided data to ensure that it was the tone that the animals were using as a discriminative conditioned stimulus, and not that the animals were somehow sensing the current or the activation of the shock generator (Oler *et al.*, 2005).

Re-mapping

To statistically compare changes in place fields between conditions (tone vs. no-tone), two rate-map correlation coefficients were calculated for each cell, one for each direction, using pixel by pixel comparisons of the firing rate-maps for the tone and no-tone segments of the task (i.e. '*r*-clock' and '*r*-counter-clock'; see Fig. 1C). To quantify and statistically compare changes in place fields between behavioral situations, a relative tone–effect score was calculated for each place cell (R_{tone}). The following formula was used to calculate the relative score:

$$R_{\text{tone}} = \frac{(r\,\text{within-condition})}{(r\,\text{within-condition} + r\,\text{between-conditions})}$$

where '*r* within-condition' is the rate-map correlation between the first and second halves of all no-tone trials, and '*r* between-conditions' is the rate-map correlation between the tone and no-tone trials. Thus, a relative score of 0.5 indicates no change in place fields across the two conditions because the within-condition correlation is equal to the between-conditions correlation. A relative score closer to 1.0 indicates a change in spatial firing across tasks because the between-conditions correlation is smaller than the within-condition correlation. The relative score is a better statistic than the raw rate-map correlation for comparing changes in place field location, because it takes into account each cell's reliability. We have used a similar analysis in the past to quantify re-mapping (Markus *et al.*, 1995; Oler & Markus, 2000).

Given the fact that very little re-mapping was observed in the present study, a lower cutoff was used than previously. A cutoff of $R_{\text{tone}} = 0.55$ was used to delineate between cells that were affected by the discrimination from those that were not. This threshold was approximately two standard errors above the relative score of 0.50, indicating no change (see Table 2, Oler & Markus, 2000). Additionally, fields that fell above the 0.55 cutoff were put into three groups, those that appeared during tone trials, those that disappeared and those that simply differed between conditions (Oler & Markus, 2000). Place fields were categorized as 'changed' if the rate-map score was > 0.55, and there were significant place fields in both the tone and no-tone conditions. Place fields were categorized as 'appeared' if the rate-map score was > 0.55, with a significant field in the tone condition only. Place fields were categorized as 'disappeared' if the rate-map score was > 0.55, with a field in the no-tone condition only. It should be noted that for those fields classified as 'appeared', the R_{tone} was calculated using a '*r* within-condition' generated from the first and second halves of all tone trials, as by definition there was minimal firing during the no-tone condition.

Histology

After the last recording session, the animal was killed with CO_2 and perfused intracardially with a 10% formalin solution. The electrodes were withdrawn, and the brains were removed and placed in formalin for at least 24 h. Forty-micrometer coronal sections were cut using a cryostat and mounted on a gelatin-coated slide. The tissue was stained using thionin and examined microscopically for electrode tracks in the hippocampus.

Results

A total of 173 rate-map scores were generated from 118 complex spike cells with place fields, which were recorded in 42 sessions from 13 animals ranging in age from 11 to 29 months (Table 1). The animals made an average of 36.7 traversals per recording session (middle age = 38.8 ± 1.7; old = 33.8 ± 1.9); and in all the recording sessions the rats showed significant hesitation on tone trials in the zones adjacent to the shock region (ANOVA, all $P < 0.05$). As a result of the velocity filter, data from when the animals were actually hesitating in

TABLE 1. Data from the individual animals, including their age during recording sessions

Rat number	Age (months)	Recording sessions	Cells with place field	Rate-map correlations
799	11	6	15	22
687	11–13	3	11	15
803	11–14	3	7	12
804	12	1	3	4
818	15–16	2	3	5
801	16	2	6	6
820	16	1	1	2
364	16–17	6	9	15
865	22	3	7	11
809	27	5	38	55
691	28	2	2	2
815	28	1	2	3
810	29	7	14	21
Totals (n = 13)	11–29	42	118	173

TABLE 2. Descriptive statistics of place cell firing characteristics*

	Middle-aged (11–16 months)		Old (27 + months)	
	CA1	CA3–DG	CA1	CA3–DG
Firing rate (Hz)	0.81 ± 0.17	0.52 ± 0.10	0.61 ± 0.17	0.41 ± 0.06
Reliability†	0.80 ± 0.03	0.75 ± 0.10	0.74 ± 0.05	0.75 ± 0.09
R_{tone}‡	0.49 ± 0.02	0.46 ± 0.05	0.49 ± 0.01	0.48 ± 0.04
Specificity§	1.69 ± 0.09	1.49 ± 0.23	1.42 ± 0.23	1.23 ± 0.16
Number of fields (bits)	1.62 ± 0.09	1.44 ± 0.07	1.54 ± 0.17	1.49 ± 0.19
Size of largest field (bins)	33.7 ± 3.3	36.0 ± 5.1	38.9 ± 0.51	41.5 ± 5.3

*Data from the intermediate aged rat (865) are not included. †Within-condition rate-map correlation. ‡Relative score between tone and no-tone condition (0.5 indicates no re-mapping). §Information (in bits) a single spike conveys about the animal's location.

the area adjacent to the shock region were not included in the analysis. Interestingly, both age groups showed equivalent learning of the discrimination task ($P > 0.1$).

Based on histological and physiological landmarks, place cells were identified as recorded from either the CA1 or the CA3–DG (dentate gyrus) regions of the hippocampus. Electrode position was not always clearly discernible, and in these cases the lamina of the recorded place cells was considered unidentified. Of the 79 directional place fields recorded under baseline (i.e. NO TONE) conditions from middle-aged rats, 51 were from CA1, 21 were from CA3–DG and seven were unidentified. Of the 70 directional place fields recorded from old rats, 27 were from CA1, 36 were from CA3–DG and seven were unidentified. The basic firing properties were examined (by animal) during the no-tone trials for comparison with previous studies (Table 2). A two-way ANOVA (age × lamina) revealed no significant differences in the basic properties between cells identified as CA1 and those identified as CA3–DG (all $P > 0.1$). Therefore, all recorded cells were combined for the re-mapping analysis.

Re-mapping to a change in context

The principal finding of the present study was that despite clear differences in the animals' behavior between the two conditions, most of the neurons displaying place responses remained unaffected by the change in context/behavior. This was revealed by the high degree of stability in place cell activity across the two conditions. The average relative score for all cells was approximately 0.5, indicating no change in place fields across conditions (mean $R_{tone} = 0.47 \pm 0.01$, $n = 173$). As can be seen in Fig. 2A, when all of the raw rate-map correlations are combined across animals, the strongest peak in the distribution is at 0.9. This is indicative of the

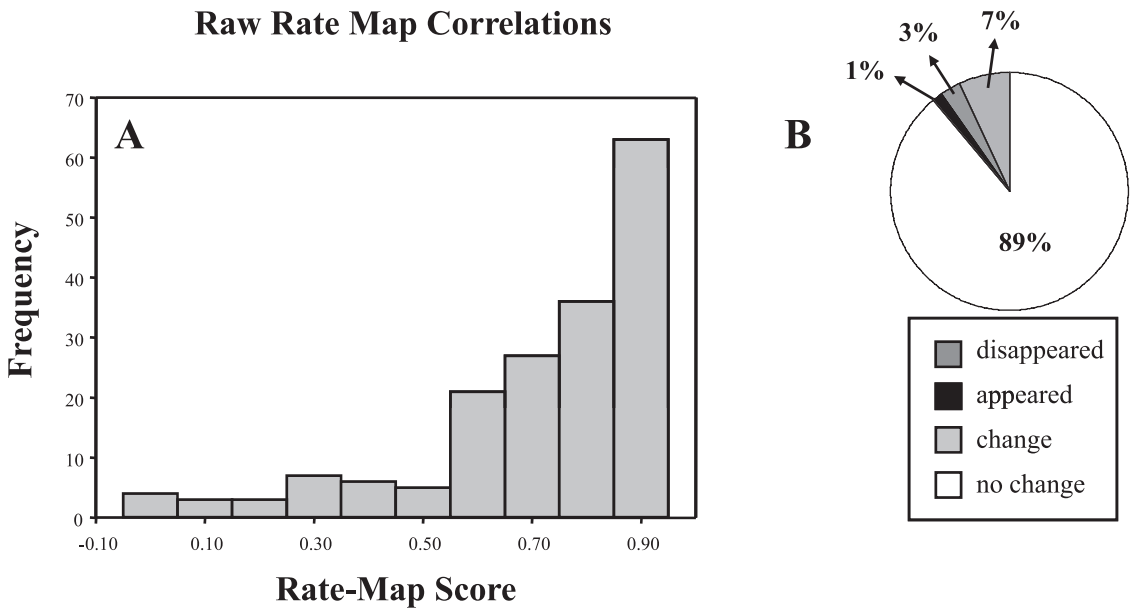

FIG. 2. Results of the rate-map correlation analysis. (A) Distribution of the raw rate-map correlations for all cells recorded in this study. The average correlation coefficient was 0.767 ± 0.015 ($n = 173$). The greatest peak in the histogram is seen at 0.9, indicating that the vast majority of place cells were not affected by the discriminative behavior. (B) Proportion of place fields affected by the behavioral discrimination in this study. A relative rate-map correlation score (R_{tone}) was calculated to compare re-mapping across subjects (see text). An arbitrary cutoff of $R_{tone} = 0.55$ was used to delineate between cells that were affected by the discrimination from those that were not. Place fields were categorized as 'changed' if the R_{tone} was > 0.55, with significant place fields in both the tone and no-tone conditions. Place fields were categorized as 'appeared' if the R_{tone} was > 0.55, with a significant field only in the tone condition. Place fields were categorized as 'disappeared' if the R_{tone} was > 0.55, with a significant field only in the no-tone condition.

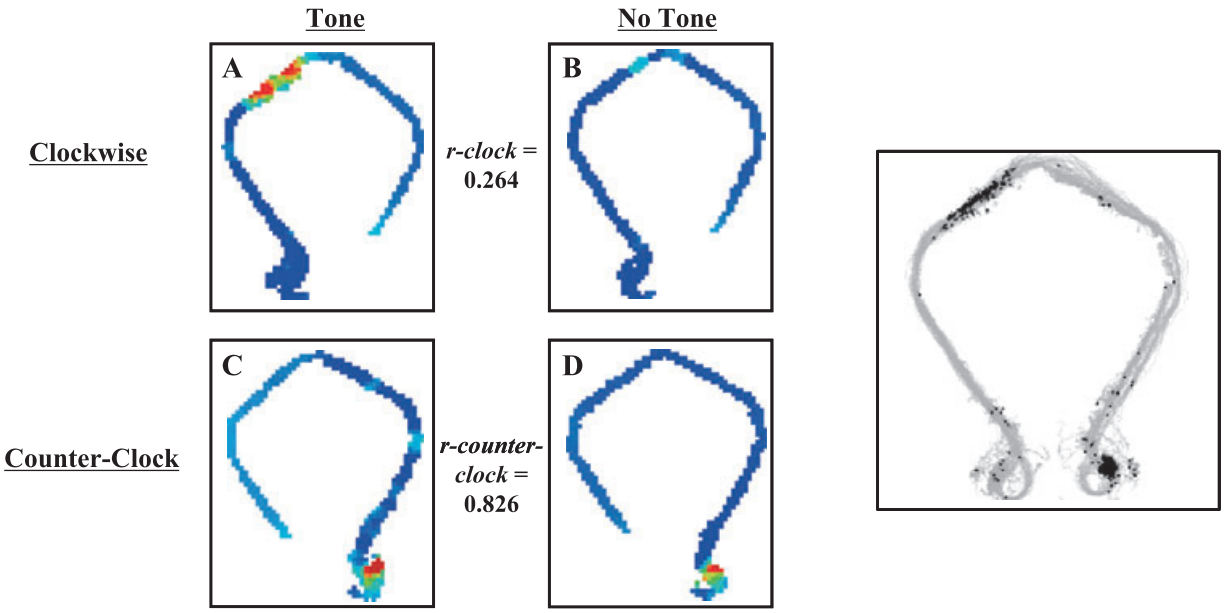

FIG. 3. Differential response of a place cell on the discrimination task. In this example, the data from the entire recording session (right) were subdivided into four segments based on heading and trial condition (left). Occupancy with maximal firing is indicated by red and occupancy with no firing by blue. The firing rate scale was held constant across the different conditions (red = 3 Hz). This cell displayed two firing fields: one in the right food chamber, which was not affected by tone presentation; and one in the runway area adjacent to the shock region while heading in the clockwise direction. The appearance of this second field was a function of tone presentation. The rate-map correlation analysis revealed a very high correlation between maps (C) and (D) (*r*-counter-clock = 0.826), and a low correlation between maps (A) and (B) (*r*-clock = 0.264). The figure on the right is the raw data of the entire recording on which the correlation analysis was performed.

relatively low incidence of re-mapping in this study. However, a small percentage of fields did display quite low correlations across task segments (Fig. 2B), suggestive of re-mapping between task conditions. Therefore, cells with a relative score of over 0.55 were examined in greater detail.

Figure 3 presents an example of the results of the rate-map analysis for a cell with a place field that 'appeared' during the tone trials, while there was very little, if any, firing in that same region during the no-tone trials. Figure 4 presents a trial-by-trial depiction of the activity of the place cell shown in Fig. 3. Note that on almost every clockwise tone trial the cell fires action potentials in the zone adjacent to the shock region. This never occurred in the no-tone condition. Also note that the cell fired in its place field during tone presentation on the probe trials, when the shock was not on (TONE ONLY).

Effect of age on re-mapping

To explore the possibility that aging influences the nature and extent of re-mapping, regression analyses were performed to examine the relationship between age (in months) and the relative score (R_{tone}) described in the 'Place field analysis' section above. The data were analysed in two ways, once examining all relative scores (n = 173), and then again by mean score per animal (n = 13). The second approach (by animal) is more conservative, as it reduces the sample size and the possibility that disproportionate sampling from a single animal/electrode will bias the data. As can be seen in Fig. 5, both approaches yield similar results of no correlation between age and degree of re-mapping. Relative scores were not related to age regardless of whether they were examined individually (r = −0.045, $F_{1,172}$ = 0.357, P > 0.1; Fig. 5A) or by animal (r = −0.121, $F_{1,12}$ = 0.162, P > 0.1; Fig. 5B).

Effect of location on re-mapping

In Oler & Markus (2000), we noted that while re-mapping was observed throughout the maze, it tended to occur on those parts of the track where the animals were making new turns (Oler & Markus, 2000; fig. 8, p. 346). A similar analysis was conducted on the current data to see if the re-mapping was concentrated on any one part of the track. Place fields that changed (i.e. R_{tone} above the 0.55 cutoff) were singled out for further analysis. The apparatus was separated into six regions based on the significance of the location (Fig. 6). The distribution of fields that appeared/disappeared/changed was calculated for the six regions. Fifteen cells had an R_{tone} above 0.55, and showed clear changes in their fields. An examination of the rate-maps showed 28 place fields that either appeared or disappeared. A large proportion of the changed fields were in or adjacent to the shock zone (42.9%), there were also more changed fields on the shock-approach path than in the path leaving the shock area (see Fig. 6). Thus, in the few cases that re-mapping was found it tended to occur for fields adjacent to or on the path approaching the region where the aversive event took place.

Comparison of the present results with a task change that encompassed trajectory change

In Oler & Markus (2000), middle-aged (12–16 months) rats were compared with aged (24–28 months) rats. To facilitate the comparison of the current and previous results, animals who were 16 months or younger at the time of recording were grouped together as 'middle-aged' rats, and 24 months or older at recording were grouped together as 'aged' rats (one animal's data were dropped because he fell in between these age cutoffs – 22 months – at recording). In our previous study, using a similar analysis as the one described here, a relative score

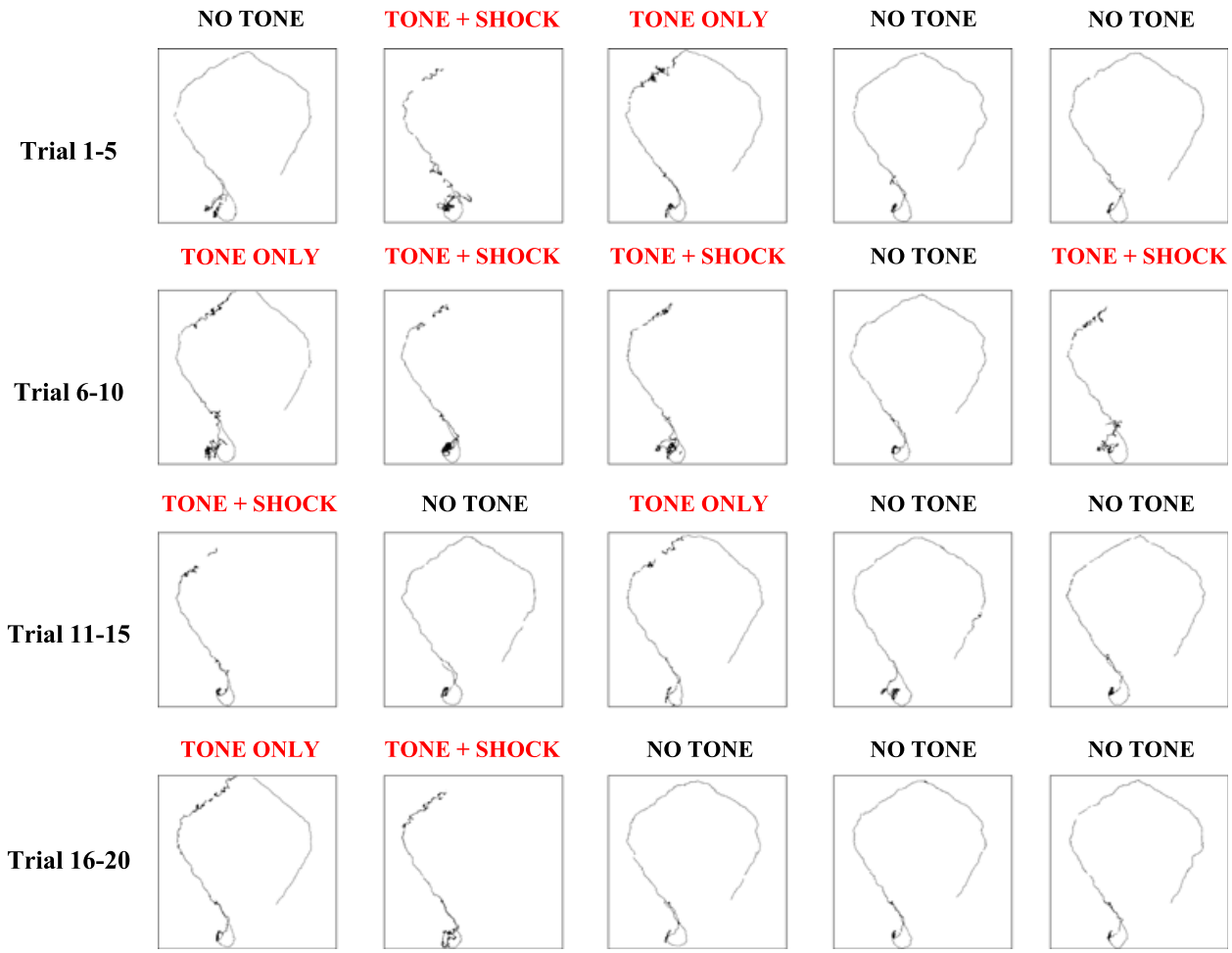

FIG. 4. A trial-by-trial depiction, from the same cell, of the first 20 clockwise runs from a discriminating animal demonstrating a place field that 're-maps' between tone and no-tone conditions. Each box represents a single clockwise trial. Trials are denoted by type, 'tone + shock', 'no-tone' and several 'tone-only' trials. During 'tone + shock' trials, the data were excluded once the shock generator was initiated. Gray represents the location of the animal, and a black dot is a spike from the neuron. Note the selective firing during tone trials in the runway area adjacent to the shock region.

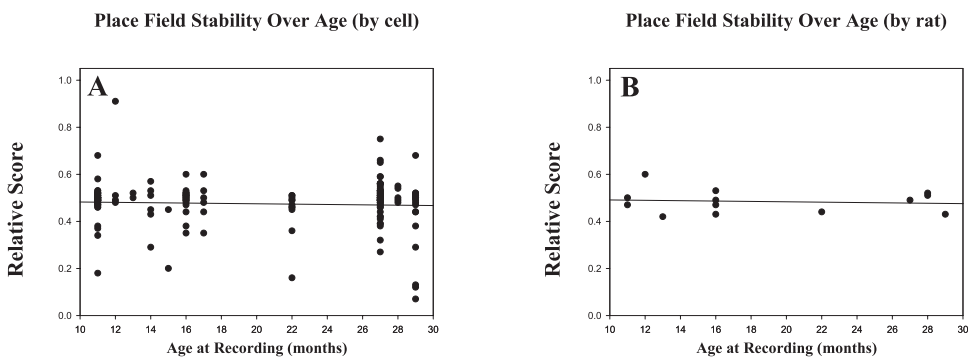

FIG. 5. Relationship between the re-mapping score and age. (A) When all the rate-map scores (R_{tone}) were plotted by age, no relationship ($r = -0.045$, $P > 0.1$) between the relative score and age at recording was revealed. (B) The same analysis, by animal, reveals a similar non-significant result. When all the relative scores were averaged per animal, and then plotted over age, no was relationship was revealed ($r = -0.121$, $P > 0.1$).

cutoff of 0.7 was selected to classify place field maps as changed across conditions. When the cutoff for re-mapping is compared across studies [$R_{AB} > 0.7$ in Oler & Markus (2000) vs. $R_{tone} > 0.55$ in the current study], it is apparent that far more place fields show re-mapping in the previous experiment than in the present one (Fig. 7). Similarly large proportion of the cells re-map in other paradigms with changes in trajectory/task demands (Markus *et al.*, 1995; Frank *et al.*, 2000; Oler & Markus, 2000; Wood *et al.*, 2000; Ferbinteanu & Shapiro, 2003).

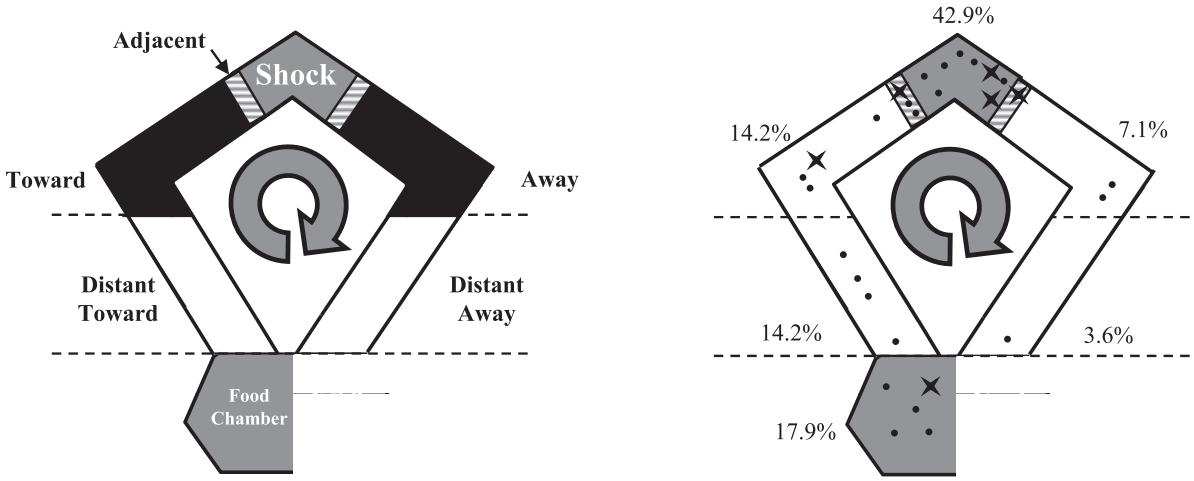

FIG. 6. Re-mapping between tone conditions in relation to field location on the track. Left: Diagram illustrating the six regions examined for re-mapping. Right: The distribution of place fields that changed during tone trials. Filled circles denote fields that appeared, 'x' fields that disappeared. Note that the majority of the changes tended to occur for fields adjacent to, or on, the path approaching the shock.

Discussion

Place cells respond to more than just the location of the animal or changes in the environment. Even when the spatial environment is held constant, the hippocampus displays re-mapping in response to changes in task demands (behavioral context). However, to date it was impossible to differentiate whether the place field re-mapping was a consequence of the change in the animal's trajectory or in response to a change in behavioral context. Knowing the degree to which changes in hippocampal representation are yoked to – or independent of – changes in spatial navigation has important implications for understanding hippocampal function. At first glance it seems like one cannot separate the two. Any change in trajectory is a consequence of what the animal is trained to do at that point of the task, and therefore involves a behavioral response to changing implicit or explicit task demands. The separation of trajectory and context was achieved in the current study by having the animals constrained to traverse the same pathway (trajectory) during 'safe' and 'unsafe' trials (changed behavioral context). Far fewer cells showed re-mapping than in previous experiments in which trajectories changed between conditions; and the degree of re-mapping was unrelated to the animals' age. These findings replicate and extend upon Markus *et al.* (1995), in which a much smaller proportion of cells re-mapped when a task change was conducted in a trajectory-constrained environment (elevated plus maze) than when the same task change occurred in an open field environment.

Before concluding that the reduced re-mapping in the current study was due to constraining the animal's trajectory, some alternative explanations must be addressed.

(i) The contextual manipulation may not have been strong enough. In previous studies animals exhibiting re-mapping were food deprived and highly motivated to perform the task. Possibly the shock was not perceived as a significant change in context, therefore did not produce a change in hippocampal representation. This possibility seems unlikely because foot-shock induces marked changes in heart rate, blood pressure, hormone levels and behavioral responses (Blanchard *et al.*, 1976; Fendt & Fanselow, 1999). In fact, Moita *et al.* (2004) reported substantial re-mapping of place fields after fear conditioning in an unconstrained environment. Additionally, we normally deprive animals to about 85–90% of their *ad libitum* weight on food reward tasks (Oler & Markus, 1998, 2000; Ward *et al.*, 1999; Tropp *et al.*, 2005). In the current experiment the animals had to be deprived to about 80% before they would cross the shock zone in a reliable manner. Consequently it would seem that the discrimination task used in the present study is a much stronger manipulation of context than simply moving the location of a food reward.

(ii) Reduced re-mapping is a function of maze constraints. It is possible that using a fixed pathway with high walls constrained the rats to proceed down the runway in a more consistent manner than in previous studies with open runways. This would suggest previous reports of re-mapping are erroneous, and simply a consequence of the animals occupying different sides of the runway during different tasks (e.g. tilting the head/body to the right or left in anticipation of a future turn). This issue has been parametrically addressed in previous studies and seems unlikely (e.g. see Frank *et al.*, 2000).

(iii) The current task was hippocampus independent. It has been shown that while running on mazes, with repeated training there is a shift from hippocampus- to striatum-dependent behavior (Packard & McGaugh, 1996; Korol *et al.*, 2004). Therefore, it may be that the animals in the present study are not using their hippocampi to perform the task. However, re-mapping has previously been shown in hippocampus-independent tasks (e.g. Markus *et al.*, 1995). In addition, animals with hippocampal lesions show impaired performance of this task (Oler *et al.*, 2005).

(iv) Overtraining may reduce hippocampal re-mapping. The animals in the current study were extensively trained. It is possible that this reduced the degree of re-mapping. However, most of the previous studies showing re-mapping examined overtrained animals (Frank *et al.*, 2000; Oler & Markus, 2000; Wood *et al.*, 2000; Ferbinteanu & Shapiro, 2003). In addition, it has been demonstrated that re-mapping increases with repeated exposures to a changed environment (Lever *et al.*, 2002; Leutgeb *et al.*, 2004, 2005a; Wills *et al.*, 2005; Wilson *et al.*, 2005).

Taken together it would seem that the reduced re-mapping in the current study was due to constraining the animal's trajectory, and that only a small proportion of DH cells are affected by alterations in emotional state, motivational context or task demands.

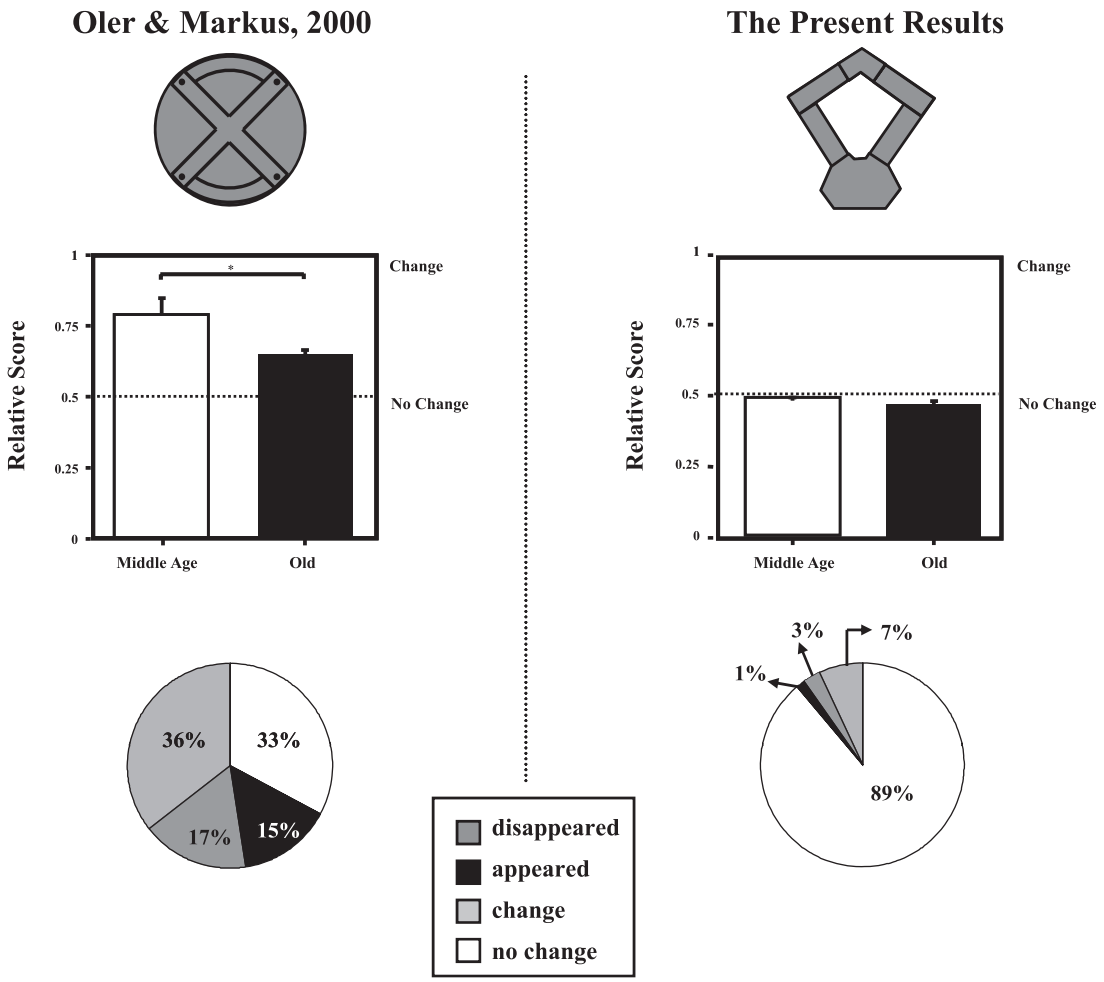

FIG. 7. A comparison of the data from Oler & Markus (2000) with the present results. Place field re-mapping in the DH appears to be driven by changes in routes navigated. Left: Diagram and summary results from a previous study (Oler & Markus, 2000) in which animals changed journeys between tasks. A relative score = 0.5 is indicative of high reliability of place fields between tasks; scores closer to 1.0 denote changes in spatial firing. Note that many of the place fields (67%) in this experiment displayed re-mapping. Right: Diagram and summary results from the present study. On this task animals expressed discriminative fear behavior between conditions (tone/no-tone trials), yet the routes traveled under both tone conditions were identical. Note that few place fields (11%) in this experiment displayed re-mapping.

No age-related changes in re-mapping

Previous studies have shown an age-related reduction in the degree to which the hippocampus shows re-mapping (Tanila *et al.*, 1997a, b; Oler & Markus, 2000; Wilson *et al.*, 2004, 2005; see, however, Barnes *et al.*, 1997). In the current study no such aging effects were found. It is conceivable that this is due to a floor effect. With so few cells responding to the contextual manipulation in young rats, it would be hard to discern a decreased response in the aged animals. Conversely, these data may indicate a disparity between trajectory information processing and context discrimination. The former, which is more 'spatial' in nature, may be predominantly affected by aging, while 'non-spatial' information is not. This possibility is supported by the fact that the old rats were not different from young rats on the acquisition of the present discrimination task. Further studies will be needed to address this issue.

Hippocampal unit response to fear conditioning

The majority of neurons recorded in the present study were unaffected by the animals' expression of discriminative fear behavior, despite data indicating hippocampal involvement in eye-blink conditioning (McEchron & Disterhoft, 1999; Christian & Thompson, 2003). Examining place fields, Moita *et al.* (Moita *et al.*, 2003, 2004) found that fear conditioning results in partial re-mapping of place fields in the conditioning context. Their results demonstrate that an aversive experience can alter the hippocampal place cell representation of the environment. However, the animals in that study were performing a random search task whose unconstrained trajectories were not subjected to analysis. This prevented them from dissociation of behavioral trajectories from the influence of emotional context.

Some cells do show a context-related change

While it seems apparent that most behavior-induced re-mapping is trajectory related, a small percentage of cells in the present study responded to changes in behavioral context. Given the fact that the DH is involved in contextual fear conditioning (Anagnostaras *et al.*, 2001), it is somewhat surprising that only a small proportion of the cells were responsive to the contextual change. There are several possible explanations for these results.

(i) Spatial/navigational vs. contextual demands. The current findings may indicate that a greater number of hippocampal cells need to be recruited for spatial than for contextual discrimination. Re-mapping in order to plan trajectories may involve the whole sequence of cells active along the new trajectory, conversely the signal for a context change may involve only a small number of cells.
(ii) Spatial vs. context cells. It has been shown that some hippocampal cells respond to non-spatial stimuli, such as in trace eye-blink conditioning (McEchron & Disterhoft, 1999) or operant conditioning (Eichenbaum *et al.*, 1987). The current experiment was designed to detect place cell re-mapping. If behavioral context is coded for in a non-spatial manner, the current approach would not have been able to detect the change. Similarly there could be two populations of hippocampal principle cells. The current study focused on cells with place fields. It is possible that it is this group of cells that responds to trajectory changes. There may be a second class of cells that responds to non-spatial input, including context changes.
(iii) Relationship to septo-temporal location. The spatial activity of DH neurons has been the subject of extensive work. There are only a few studies of ventral hippocampus (VH) unit activity in freely behaving rats, and to our knowledge no studies of re-mapping in the VH. The DH and VH receive different complements of neo-cortical inputs from the entorhinal cortex. Visuospatial information predominantly targets dorsal regions, and olfactory/periamygdaloid (and direct amygdalar) information targets ventral regions (Burwell, 2000; Pitkänen, 2000). In comparison to the DH, cells in the VH exhibit lower spatial selectivity (Jung *et al.*, 1994; Kjelstrup *et al.*, 2008). Consequently there seems to be a functional segregation along the hippocampal septotemporal axis (Moser & Moser, 1998; Bannerman *et al.*, 1999, 2003; Richmond *et al.*, 1999; Pothuizen *et al.*, 2004). With regard to fear conditioning, it has been shown that population activity of CA1 pyramidal cells (as measured by immediate-early gene expression) undergoes a shift from DH to VH following consolidation of fear conditioning (Inoue *et al.*, 2005). Given the fact that the animals in the current study were well trained on the task, it is possible that the expression of the discriminative fear behavior involved predominantly VH cells, with the DH showing predominantly trajectory-responsive cells. This may explain the small proportion of context-related re-mapping in the current study.

Implications and future directions

Re-mapping provides a window into understanding what aspects of experience play a role in hippocampal processing. Previous research highlighting the importance of where the animal has come from and where it is planning to go can provide a link between the spatial and the mnemonic aspects of hippocampal processing. The current study explored the degree to which the link to memory processing is independent of spatial output. The fact that few cells were responsive to such a strong manipulation indicates that the hippocampus processes contextual information in a qualitatively different manner than spatial information. The degree to which the context/trajectory difference is based on hippocampal subregion, or on different types of processing within the same region of the hippocampus, must still be examined.

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Abbreviations

DG, dentate gyrus; DH, dorsal hippocampus; VH, ventral hippocampus.

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