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Behavioural Brain Research 169 (2006) 168–175
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Short communication

Specific changes in hippocampal spatial codes predict spatial working memory performance

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Received 7 July 2005; received in revised form 8 October 2005; accepted 18 December 2005
Available online 2 February 2006

Abstract

This study examined the relationship between hippocampal place fields and spatial working memory. Place cells were recorded while rats solved a spatial working memory task in light and dark testing conditions. Rats made significantly more errors when tested in darkness, and although place fields changed in multiple ways in darkness, only changes in place field specificity predicted the degree of impaired spatial memory. This finding suggests that more spatially distinct place fields may contribute to hippocampal-dependent mnemonic functions.

Keywords: Place cells; Place fields; Behavior; Spatial learning; Single units

Hippocampal (HPC) damage in several animal species impairs the ability to learn tasks that depend on the use of allocentric spatial information [1,5,19]. Furthermore, numerous electrophysiological studies have demonstrated that the firing rates of HPC pyramidal cells (place cells) are strongly modulated by the spatial location (place field) of the rat within the recording environment [21]. The entire area of the testing environment is represented by subpopulations of HPC place cells, and the moment-to-moment spatial location of the subject can be reliably predicted by the activity of neural population codes [34]. Furthermore, the spatial firing patterns of place cells (e.g., locations of their place fields) are sensitive to changes in the spatial environment such that manipulations of spatial cues can cause alterations of place fields (i.e., they reorganize) [11,20,26]. Despite this wealth of evidence, it has not been established how the activity of individual HPC place cells plays a role in spatial memory.

Some studies have investigated the relationship between place cell firing and task performance, but these studies have produced mixed conclusions. The majority of these studies have examined the relationship between changes in the locations of place fields and changes in performance of spatial tasks. For instance, it has been shown that manipulations of the visual environment that caused place fields to be out of register relative to their standard configuration also resulted in a decrease in rats' performance on a continuous alternation task [10]. In contrast, other manipulations that cause a robust reorganization of place fields do not always affect rats' performance of HPC-dependent spatial tasks [2,8]. These data suggest that, at best, the relationship between the locations of place fields (and changes therein) and the performance of spatial tasks is not consistent. This notion is at odds with the overwhelming evidence that HPC cells are important for accurate performance of spatial learning tasks [22].

This study addressed the extent to which aspects of place fields other than their locations (i.e., specificity or reliability of place fields) may relate more directly to the subject's performance of HPC-dependent spatial tasks, since they may be more indicative of the overall visuo-spatial acuity of the HPC representation. HPC place cells were recorded while rats performed a spatial working memory task, and then changes in task performance were compared with changes in place field characteristics in response to a visuo-spatial change in the testing environment. Portions of these results have appeared in preliminary form [25].

HPC single units were recorded from 13 adult (4–6 months old) male Long-Evans rats. Rats were housed individually and allowed 3–5 days to acclimate to the colony room prior to being reduced to 85% of ad lib feeding weights. All rats had unlimited access to water throughout the experiment. All animal care

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doi:10.1016/j.bbr.2005.12.007

and use was conducted according to University of Washington's Institutional Animal Care and Use Committee guidelines.

Rats were habituated to the testing environment and then trained to perform a win-shift spatial working memory task on an eight-arm radial maze using procedures reported previously [2,16,24]. Briefly, the end of each arm was baited prior to the start of each trial with three drops of chocolate milk. Each trial started with a study phase in which four of the eight arms were individually and sequentially presented to the rat in a predetermined random order. Immediately after presentation of the fourth arm, the test phase began by making all arms accessible. The trial ended once all eight arms were visited; entries into previously visited arms were classified as errors. In order to promote the use of a spatial navigation strategy, several distinct and prominent cues were attached to the black curtains that surrounded the maze. Once rats performed 15 trials (inter-trial interval = 2 min) in approximately 1 h for 7 consecutive days, recording electrodes were surgically implanted into dorsal HPC. After rats recovered from surgery (approximately 1 week), they were re-trained on the task.

Details concerning the construction of recording stereotrodes and microdrives and surgical procedures can be found in previous reports [15,16]. Briefly, stereotrodes were constructed by twisting together two laquer-coated tungsten wires (California Fine Wire) were and passed through a 30 ga stainless steel guide cannula. Three stereotrodes were then secured to each microdrive (one per hemisphere) with epoxy. Rats were anesthetized with sodium pentobarbital (Nembutal; 40 mg/kg I.P., followed by 0.05 ml supplemental doses as needed) and given atropine sulfate (5.0 mg/kg I.P.) to alleviate respiratory distress. The stereotrode microdrives and reference and ground electrodes were implanted according to previous procedures [2,16]. The stereotrodes were stereotaxically implanted above dorsal HPC according to the following coordinates [32]: +2.5 to +4.5 mm posterior to bregma, ±2.0–2.5 mm lateral, and 1.7 mm ventral to the brain surface. Reference electrodes were and the ground screw was implanted into the skull. Rats were then given 1 week of free feeding to fully recover from surgery before being placed back on food restriction to begin experimental procedures.

Once rats recovered from surgery, they resumed performance of the spatial working memory task. Prior to each session, rats were connected to the recording equipment by a pre-amplification headstage containing 16 field effect transistors and a pair of infrared diode arrays used to track the animal's position and directional heading. All stereotrodes were checked daily for spontaneous neural activity. If no clear neural activity was encountered stereotrodes were lowered in approximately 25 μm increments (up to 175 μm per day) until clear, isolatable units were observed. The animal's position and electrophysiological data were recorded on either the Datawave Discovery or Neuralynx Cheetah data acquisition systems. In both cases, the locations of animals' position were monitored by an infrared video camera mounted to the ceiling above the maze and recorded via automatic tracking systems (position data was sampled at 20 and 30 Hz, respectively). Single unit activity was recorded simultaneously and independently on each wire of the stereotrode. Incoming signals were amplified (3000–10,000 times), filtered between 600 Hz and 6 kHz, and passed through a window discriminator that triggered a 1 ms sampling period when an impulse from either channel passed a user-defined threshold. The Datawave and Neuralynx acquisition systems sampled the neural data at a frequency of 32 kHz.

Single units were isolated from the multiunit records using cluster-cutting routines. The Datawave Discovery software package contained a cluster-cutting routine, whereas spike data acquired via the Neuralynx acquisition system were separated using a custom version of MClust (A.D. Redish). Each software program calculated multiple waveform parameters including peak to valley amplitudes and spike widths (time between the peak and valley of the action potential) for each sample from all stereotrodes. In addition, a template-matching algorithm (written by C. Higginson) was used offline to facilitate separation of unique spike waveforms. We only included cells with a signal-to-noise ration of at least 3:1 and exhibited stable clusters throughout the recording session.

Each recording session consisted of two blocks of five trials each. During the first block of trials, rats performed the spatial working memory task with the extra-maze cues in their normal configuration (baseline trials). Following completion of the fifth trial, rats performed a second block of five trials with the maze room lights extinguished (dark trials), thereby eliminating all visuo-spatial context information. For comparison, control sessions in which the lights remained on throughout the two blocks of trials were also included. Rats remained on the maze and connected to the tether throughout the duration of the recording session.

HPC neurons can be readily classified as either complex spike (CS) cells (pyramidal cells) or interneurons based on their unique spike characteristics. CS cells have broader spikes (>300 μs from peak to valley) and typically exhibit lower firing rates than interneurons. In addition, CS cells fire in burst patterns of three to four action potentials. In order for a cell to be classified as a place cell, it had to first be classified as a CS cell as described above. Second, the cell had to have a specificity score greater than 3.0 and a reliability score greater than 50% (these terms are defined below) in at least one of the two blocks of trials. Also, only place cells with firing fields located on the maze arms (as opposed to the center of the maze) were included in these analyses. In contrast to CS cells, interneurons have narrower spikes (<300 μs peak to valley) and fire at higher firing rates. HPC interneurons were excluded from all analyses.

The performance of rats was assessed by calculating the average number of errors for each block of five trials. The average firing rate for all cells was determined for each block of trials. In order to evaluate spatial firing patterns, several different parameters were calculated for each cell. The specificity of spatial firing was calculated as the average firing rate on the arm associated with the highest firing rate divided by the average firing rate on all other arms for each block of trials. The reliability of spatial firing was calculated as the percentage of trials in which the cell showed its highest firing rate on the arm with the highest average firing rate for the block of trials. A given place cell was not required to have a place field in both blocks of trials. In

instances in which a cell lost or gained a place field, the specificity and reliability measures were still calculated based on the arm associated with the highest firing rate.

In order to quantify the effects of lighting condition on rat's performance and place field properties (place field reliability, specificity, in- and out-of-field firing rates, and size), difference scores (DS's) were calculated according to the following formulas: $DS_{Performance} = (X_{light} - X_{dark})/(X_{light} + X_{dark})$ and $DS_{Place\ Field} = (X_{dark} - X_{light})/(X_{light} + X_{dark})$. These DS's reflect the change in each of these measures relative to the first block of trials and can range from −1 to +1. Negative and positive values represent decreases and increases, respectively, in each parameter for the second block of trials. A spatial correlation score assessed the effects of lighting conditions on the spatial firing patterns of place cells by calculating a Pearson's correlation (r) for the firing rates in commonly visited pixels across the two blocks of trials. We then computed one-way ANOVA's ($\alpha = 0.05$) to determine if lighting condition had effects on DS's for each of the above parameters and spatial correlation scores. In order to examine potential confounding variables that influence place cell firing properties, such as running speed [3], we calculated the mean amount of time rats spent on each arm in each block of trials. Changes in time per arm choice were also computed in terms of DS's.

Finally, we investigated the relationship between changes in the rat's performance of the spatial working memory task and changes in place field properties. For this analysis, the place field specificity, reliability difference scores and spatial correlation values were correlated with performance difference scores for each place cell. In cases where more than one place cell was recorded simultaneously, an average response of the cells was computed.

Once the electrodes were lowered through the entire dorsal–ventral extent of dorsal HPC, the rats were given an overdose of sodium pentobarbital and transcardially perfused with a 0.9% buffered NaCl solution, followed by 10% formalin. The electrodes were retracted and the brain was removed and allowed to sink in a 30% formal-sucrose solution. Forty-micrometer-coronal sections were sliced through dHPC with a cryostat. The sections were then stained with Cresyl violet, and the recording locations were histologically verified by comparing electrode depth measurements at the time of recording with reconstructions of the electrode tracts.

Histological examination of the locations of recording electrodes indicated that electrodes passed through the CA1, hilar CA3, and dentate gyrus (DG) regions of dorsal HPC. We recorded a total of 72 place cells (n's: CA1 = 24, CA3 = 8, DG = 39, the location of one place cell was not able to be identified). The relatively small number of CA3 place cells (control = 4, light–dark = 4), precluded valid statistical comparison between responses of CA1 and CA3 place cells for control and light–dark manipulations. Additionally, due to the relatively small sample size (controls: CA1 = 12, DG = 18; light–dark: CA1 = 12, DG = 21) and the number of statistical tests required to perform the comparisons (increasing the occurrence of Type 1 errors), we were not able to determine whether there were differences in how CA1 and DG cells responded in control and light–dark manipulations. Therefore, all place cells were grouped together in all analyses.

Consistent with previous reports [18], there was a significant overall main effect of lighting condition on rats' performance ($F[1,45] = 5.90$, $p < 0.02$) in that performance difference scores were significantly lower for the dark manipulation when compared to controls. That is, rats made significantly more errors after darkness was imposed than following the control condition (Fig. 1A and Table 1). A more detailed analysis of rats' behavior on the maze indicated that, although rats spent significantly more time per arm choice during dark trials when compared to

Table 1
Summary of rats' performance (top) and place field (bottom) parameters

Performance summary	Baseline values	DS (raw value)		DS (absolute value)	
		Control, $n = 20$ sessions	Light–dark, $n = 26$ sessions	Control, $n = 20$ sessions	Light–dark, $n = 26$ sessions
Mean errors/trial	0.51 ± 0.09	−0.09 ± 0.15	**−0.49 ± 0.09**	0.50 ± 0.09	0.58 ± 0.07
Mean time/arm choice (s)	12.36 ± 0.60	0.04 ± 0.03	0.08 ± 0.03	0.08 ± 0.03	0.12 ± 0.03

Place cell summary	Baseline values	DS (raw value)		DS (absolute value)	
		Control, $n = 34$ cells	Light–dark, $n = 38$ cells	Control, $n = 34$ cells	Light–dark, $n = 38$ cells
Mean firinq rate (Hz)	0.48 ± 0.04	0.02 ± 0.04	0.03 ± 0.05	0.17 ± 0.02	0.21 ± 0.03
Place field reliability (%)	63.4 ± 2.51	0.10 ± 0.04	**−0.22 ± 0.05**	0.21 ± 0.03	**0.33 ± 0.04**
Place field specificity	4.75 ± 0.19	0.04 ± 0.03	**−0.17 ± 0.03**	0.14 ± 0.02	0.19 ± 0.03
In-field firinq rate (Hz)	7.90 ± 1.18	−0.01 ± 0.03	−0.13 ± 0.05[a]	0.16 ± 0.02	**0.26 ± 0.03**
Out-of-field firinq rate (Hz)	0.26 ± 0.03	0.02 ± 0.04	**0.14 ± 0.03**	0.15 ± 0.02	0.18 ± 0.03
Place field size (pixels)	2022.67 ± 189.07	0.04 ± 0.05	−0.12 ± 0.06[b]	0.22 ± 0.03	**0.33 ± 0.04**
Spatial correlation (r)—see note	NA	0.49 ± 0.05	**0.19 ± 0.03**	NA	NA

Baseline values represent averages of all parameters calculated from the first block of trials during control and light–dark recording sessions. Raw and absolute values of difference scores (DS's) are also listed for each parameter. Values represent means ± standard errors. The significant differences from controls ($p < 0.05$) are indicated by bold text.

Note: Spatial correlation scores listed in DS (raw value) columns represent Pearson's r values, not DS's.

[a] Marginally significant one-way ANOVA: $F(1,71) = 3.57$, $p = 0.06$.

[b] Marginally significant one-way ANOVA: $F(1,71) = 2.95$, $p = 0.09$.

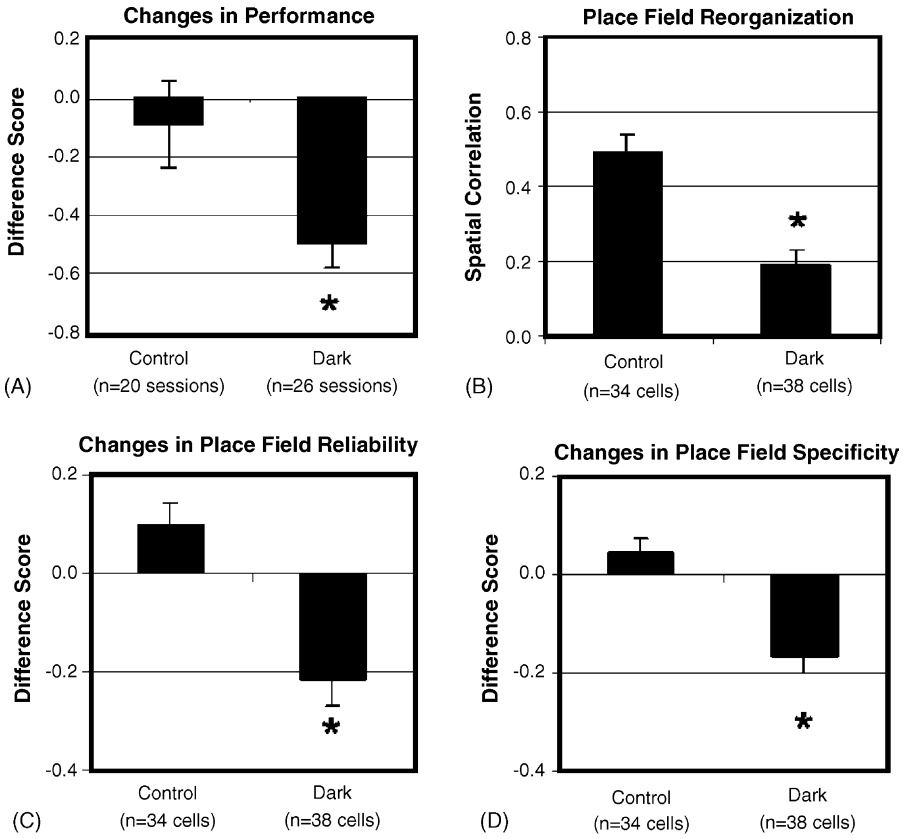

Fig. 1. Changes in rats' performance (A), place field reliability (C), and place field specificity (D) are presented as difference scores (DS's) relative to the first block of trials. Rat's spatial working memory was significantly worse in dark testing conditions, as reflected in decreased performance difference scores (A). Similarly, darkness caused place fields to reorganize location more (B), and become less reliable (C) and less specific (D). Asterisks indicate significant differences from control manipulations (p's < 0.01).

baseline (light) trials ($t_{25} = -2.37$, $p < 0.03$), the DS's for control and light–dark sessions were not different ($t = -0.34$, ns), indicating that the change in time per arm choice seen in light–dark sessions is no greater than that observed for control sessions (Table 1). This suggests that the decrease in task performance was not due to a generalized change in behavior during dark trials.

Next, we evaluated whether darkness significantly affected the mean firing rate, specificity, reliability, spatial distribution of firing, in- and out-of-field firing rates, and place field sizes of place cells. A summary of this analysis can be found in Table 1 and Fig. 1. We found that there were no significant changes in the mean firing rate of place cells in darkness relative to controls (raw averages: $F[1,71] = 0.02$, ns; absolute values: $F[1,71] = 1.0$, ns). The spatial distributions of place cell firing were affected by changes in the visual environment, as indicated by significantly lower spatial correlation scores (i.e., greater spatial reorganization) during dark trials relative to controls ($F[1,71] = 27.31$, $p < 0.001$, Fig. 1B). Place field reliability was significantly decreased in darkness when compared to control conditions ($F[1,71] = 20.17$, $p < 0.001$, Fig. 1C). Similarly, place field specificity was significantly decreased in dark testing conditions when compared to controls ($F[1,71] = 27.98$, $p < 0.001$, Fig. 1D). Consistent with a decrease in place field specificity, there was a marginally significant decrease in the in-field firing rates ($F[1,71] = 3.57$, $p = 0.06$), while out-of-field firing rates significantly increased in darkness compared to controls ($F[1,71] = 6.97$, $p < 0.02$). In addition, darkness was associated with a marginally significant decrease in place field size ($F[1,71] = 2.95$, $p = 0.09$). It should be noted that, although the raw DS values for in-field firing rate and place field size were not statistically significant, the absolute value of these DS's were (in-field firing rate DS_{abs}: $F[1,71] = 6.34$, $p < 0.02$; place field size DS_{abs}: $F[1,71] = 4.93$, $p < 0.04$). Although there was some variability in an individual place cell's response, this indicates that in the majority of cases, place fields became less specific in darkness because the in-field firing rates decreased, out-of-field firing rates increased, and place fields became smaller. Fig. 2 shows an example of two simultaneously recorded place cells in light and dark testing conditions. Darkness induced a striking change in the location of the place field, as well as a reduction in the reliability and specificity of each cells' place field. Consistent with previous reports [11,26], this indicates that place fields can change in multiple ways in darkness. We next evaluated which of these changes is related to the increased errors in dark testing conditions.

Changes in the firing patterns of place cells were correlated with changes in rats' performance of the spatial working memory task by comparing the animal's change in performance with changes in place field specificity, reliability, and degree of reor-

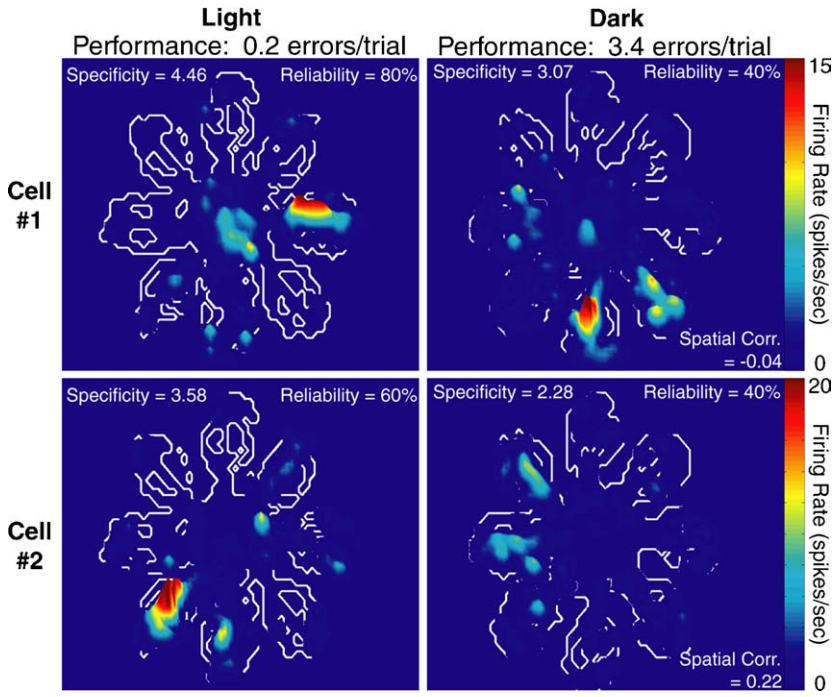

Fig. 2. Three-dimensional firing rate maps of two simultaneously recorded place cells in light (left column) and dark (right column) testing conditions. The plots represent the spatial firing patterns of each cell as the rat performed the spatial working memory task. The white outline represents the boundaries of areas on the maze the rat visited. The rat made significantly more errors in darkness (performance DS = −0.89). Both cells had highly specific and reliable place fields during light trials. Dark testing conditions caused each cell to change their spatial firing patterns in multiple ways. Both cells' place fields reorganized (as indicated by low spatial correlation scores), and became less specific (specificity DS's: Cell #1 = −0.18, Cell #2 = −0.22) and less reliable (reliability DS's: Cell #1 = −0.33, Cell #2 = −0.20) in darkness.

ganization for each light–dark recording session ($n = 26$). In cases where more than one place cell was recorded simultaneously, an average of the cells' response was computed. A Pearson's correlation analysis revealed that changes in performance were not significantly correlated with the degree of place field reorganization ($r = 0.01$, ns, Fig. 3A). Similarly, changes in performance were not correlated with changes in place field reliability ($r = 0.10$, ns, Fig. 3B), in-field firing rate changes ($r = -0.06$, ns, data not shown), out-of-field firing rate changes ($r = -0.19$, ns, data not shown) or changes in place field size ($r = 0.18$, ns, data not shown). In contrast, changes in performance were significantly correlated with changes in place field specificity ($r = 0.44$, $p < 0.03$, Fig. 3C).

Although place fields changed in multiple ways when rats perform a spatial working memory task poorly (e.g., reorganization of place fields and reduced place field specificity and reliability), we found that not all of these variables predicted the degree of task impairment. It was found that only the changes in place field specificity were correlated with changes in task performance. That is, the less specific place fields became in the darkness, the worse the rats performed the spatial working memory task. It appears that the decrease in place field specificity was due to reduced firing rates within the place fields along with an increase in out-of-field firing rates. This result is consistent with the fact that place fields of mice lacking functional CA1 NMDA receptors are less specific [13], a phenomena which might underlie the spatial learning deficits of these mice [33]. In the former experiment, place cells of these mice were not recorded during the performance of a HPC-dependent task, making it difficult to define a relationship between the place field properties and learning deficits. The results of the present study therefore, provide direct evidence for a relationship between place field specificity and spatial memory.

Similar to the present findings, Markus et al. [11] showed that place fields reorganized and became less specific and reliable in the darkness. In contrast to our results however, they found that, on average, rats that had a higher tendency to make errors (in both light and dark testing conditions) had less reliable place fields, while the specificity of their fields did not correlate with task performance. Important methodological differences may account for this discrepancy. First, the reliability and specificity measures used in the Markus et al. [11] and the current study were computed differently. Markus et al. [11] calculated place field specificity in terms of information content [30], which reflects how well an individual cell's firing predicts the rat's location. In addition, Markus et al. [11] assessed place field reliability by computing average spatial correlation scores (as used in the current study to assess place field reorganization) for each pair of trials in light and dark testing conditions. As mentioned in the Markus et al. [11] study, both of these measures are very sensitive to a cell's firing rate, and can yield highly variable results when analyzing low rate cells (such as place cells). In the present study, only cells with place fields on an arm (as opposed to the center of the maze) were included in the analysis. Therefore, the reliability and specificity measures used in the present study were sufficiently powerful to assess these aspects of HPC

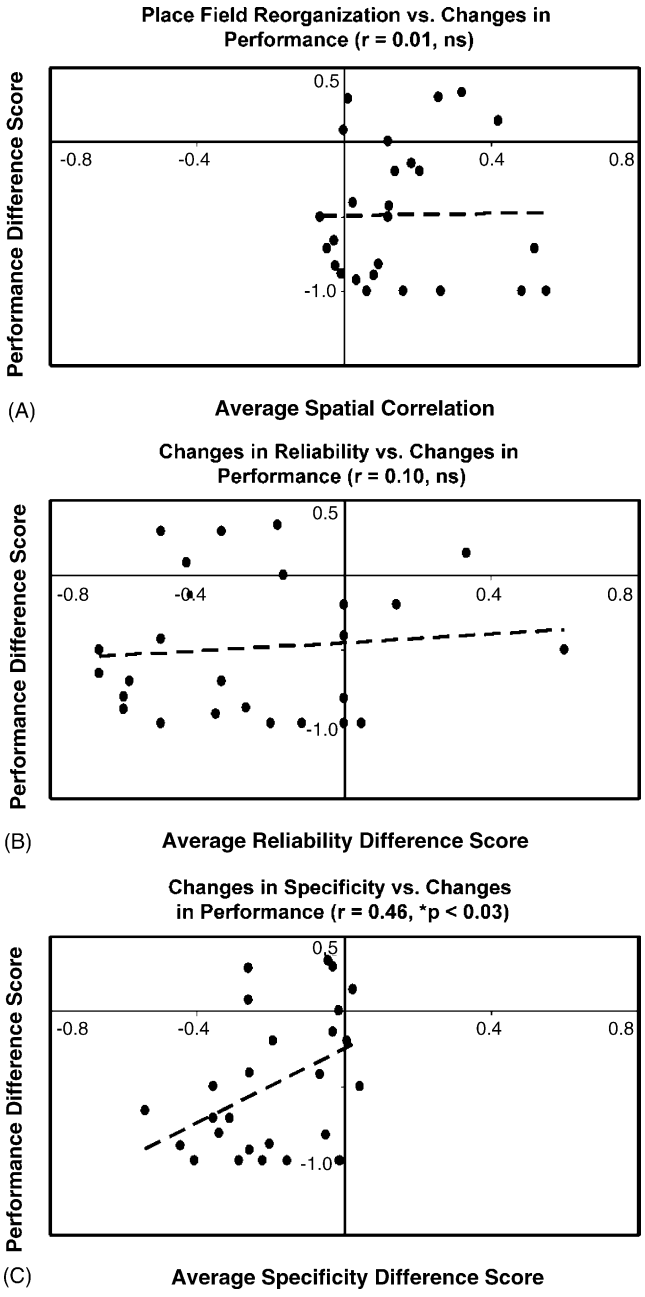

Fig. 3. Changes in task performance were assessed for correlations with changes in place field characteristics (*r* values indicate Pearson's correlation coefficient). Each light–dark recording session with at least one place cell represents one data point ($n = 26$). In cases where more than one place cell was recorded simultaneously, an average response of the place cells was computed. This analysis indicated that the dark-induced changes in task performance are correlated with changes in place field specificity (C), but not changes in place field reliability (B) or the degree of spatial reorganization (A).

place fields, while avoiding the variability due to low firing rats.

A second methodological difference between the current and Markus et al. [11] studies is the task rats were performing. Markus et al. [11] used a 'forced-choice' eight-arm radial maze task which does not require spatial or working memory, and does not depend on an intact HPC. Accordingly, Zinyuk et al. [35] have shown that the extent to which the task is HPC-dependent can dramatically affect how place cells respond to environmental manipulations. Therefore, the increased memory demands of the spatial working memory task could also account for the different results of the current study.

Another explanation for the different findings between the Markus et al. [11] study and this one could be differential inclusion criterion for the analyses. Markus et al. [11] only included cells that had place fields in both the light and dark testing conditions. Such a selection method could have biased their sample towards place fields that were more stable and more strongly driven by a pattern completion process in the absence of complete visual information [12,14]. The analyses in the current study included all cells that had place fields in one or both of the two blocks of trials, and therefore, included cells that maintained, lost, and gained place fields in darkness. The current study included cells that exhibited all types of changes in order to more accurately describe the alterations in the population representation of the spatial context sent to HPC efferent structures, such as the prefrontal cortex [7,31]. This was an important consideration, since accurate performance of the task used in this study is thought to depend on HPC-prefrontal circuitry [4]. Degraded spatial context information sent from HPC would impair the working memory functions of prefrontal cortex, thereby impairing performance of the spatial working memory task.

It should be noted here that it has been demonstrated that the spatial organization of place fields can be important for accurate performance of some spatial tasks [6,9,10,23]. However, performance of the tasks used in these studies depended on the organization of the available spatial cues in the environment. That is, rats could use the configuration of the spatial cues in order to navigate to a single goal location. When the cues were rotated [6,9,10] or unavailable [23], the rat's behavior and spatial organization of its place fields were bound to the rotated cues [6,9,10] or the rat's previously established internal representation of the goal location [23]. Therefore, there appear to be certain conditions in which the spatial organization of place fields is very important for performance of spatial tasks. Since the organization of the spatial cues did not predict the location of a goal in the current study (i.e., rats were required to visit all eight arms regardless of the status of the available spatial cues), the place field reorganization we observed in darkness could have been the result of place fields realigning to the remaining information rats had available to them during dark trials (i.e., local maze or self-motion cues).

Although we found that overall, rats' spatial working memory was impaired in dark testing conditions, there were recording sessions during which their performance did not change in darkness, despite the fact that highly specific place fields reorganized (see Fig. 3C). Our results are consistent with previous explanations of darkness-induced effects on place field properties [17]: place fields that persist in dark testing conditions may reflect memories about familiar features of the spatial context. Therefore, the highly specific place cells recorded in sessions in which rats performed well may have been strongly driven by mnemonic inputs about the remembered spatial context, thereby enabling the rat to guide its behavior

appropriately in darkness. Alternatively, these cells may have relied on self-motion [27] or local environmental [28,29] cues that may have been present in darkness. Since rats were performing a well-learned task, the population of active place cells may have been able to reorganize their spatial firing patterns to align to the information available to the rat in the darkness. This could have led to an overall spatially different, yet still highly specific representation of the spatial context that the rat could use to maintain proper HPC activity and flexible spatial working memory. Recording sessions in which rats performed poorly in darkness could have been associated with place cells that were not able to integrate non-visual information to develop specific place fields rats could use to guide their behavior.

The current study utilized the fact that rats' performance of the spatial working memory task declined in dark testing conditions to test which properties of place fields are important for accurate spatial working memory. Darkness was associated with significant reorganization of place fields as well as decreases in place field specificity and reliability. Importantly, however, changes in performance were correlated with decreases in place field specificity, and not the overall degree of place field reorganization or decreases in place field reliability. The selectivity of the correlation suggests that, at least in some cases, the specificity of place fields is more directly related to accurate spatial working memory than place field reliability or the degree to which fields reorganize in space. The quality of representation of the spatial context in HPC could have impacted the degree to which HPC efferent structures, such as the prefrontal cortex, could use spatial context information for working memory computations.

Acknowledgements

This research was supported by grant MH58755 to S.J.Y.M. The authors would like to thank Chris Higginson for developing some of the software programs used in these analyses.

References

[1] Astur RS, Taylor LB, Mamelak AN, Philpott L, Sutherland RJ. Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. Behav Brain Res 2002;132(1):77–84.
[2] Cooper BG, Mizumori SJ. Temporary inactivation of the retrosplenial cortex causes a transient reorganization of spatial coding in the hippocampus. J Neurosci 2001;21(11):3986–4001.
[3] Czurko A, Hirase H, Csicsvari J, Buzsaki G. Sustained activation of hippocampal pyramidal cells by 'space clamping' in a running wheel. Eur J Neurosci 1999;11(1):344–52.
[4] Floresco SB, Seamans JK, Phillips AG. Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. J Neurosci 1997;17(5):1880–90.
[5] Gaffan D, Harrison S. Place memory and scene memory: effects of fornix transection in the monkey. Exp Brain Res 1989;74(1):202–12.
[6] Huxter JR, Thorpe CM, Martin GM, Harley CW. Spatial problem solving and hippocampal place cell firing in rats: control by an internal sense of direction carried across environments. Behav Brain Res 2001;123(1):37–48.
[7] Jay TM, Glowinski J, Thierry AM. Selectivity of the hippocampal projection to the prelimbic area of the prefrontal cortex in the rat. Brain Res 1989;505(2):337–40.
[8] Jeffery KJ, Gilbert A, Burton S, Strudwick A. Preserved performance in a hippocampal-dependent spatial task despite complete place cell remapping. Hippocampus 2003;13(2):175–89.
[9] Lenck-Santini PP, Muller RU, Save E, Poucet B. Relationships between place cell firing fields and navigational decisions by rats. J Neurosci 2002;22(20):9035–47.
[10] Lenck-Santini PP, Save E, Poucet B. Evidence for a relationship between place-cell spatial firing and spatial memory performance. Hippocampus 2001;11(4):377–90.
[11] Markus EJ, Barnes CA, McNaughton BL, Gladden VL, Skaggs WE. Spatial information content and reliability of hippocampal CA1 neurons: effects of visual input. Hippocampus 1994;4(4):410–21.
[12] Marr D. Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci 1971;262(841):23–81.
[13] McHugh TJ, Blum KI, Tsien JZ, Tonegawa S, Wilson MA. Impaired hippocampal representation of space in CA1-specific NMDAR1 knockout mice. Cell 1996;87(7):1339–49.
[14] McNaughton BL, Morris RG. Hippocampal synaptic enhancement and information storage within a distributed memory system. Trends Neurosci 1987;10(10):408–15.
[15] McNaughton BL, O'Keefe J, Barnes CA. The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records. J Neurosci Methods 1983;8(4):391–7.
[16] Mizumori SJ, McNaughton BL, Barnes CA, Fox KB. Preserved spatial coding in hippocampal CA1 pyramidal cells during reversible suppression of CA3c output: evidence for pattern completion in hippocampus. J Neurosci 1989;9(11):3915–28.
[17] Mizumori SJ, Ragozzino KE, Cooper BG, Leutgeb S. Hippocampal representational organization and spatial context. Hippocampus 1999;9(4):444–51.
[18] Mizumori SJ, Williams JD. Directionally selective mnemonic properties of neurons in the lateral dorsal nucleus of the thalamus of rats. J Neurosci 1993;13(9):4015–28.
[19] Morris RG, Garrud P, Rawlins JN, O'Keefe J. Place navigation impaired in rats with hippocampal lesions. Nature 1982;297(5868):681–3.
[20] Muller RU, Kubie JL. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J Neurosci 1987;7(7):1951–68.
[21] O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 1971;34(1):171–5.
[22] O'Keefe J, Nadel L. The hippocampus as a cognitive map. New York: Clarenden Press; 1978.
[23] O'Keefe J, Speakman A. Single unit activity in the rat hippocampus during a spatial memory task. Exp Brain Res 1987;68(1):1–27.
[24] Pratt WE, Mizumori SJ. Neurons in rat medial prefrontal cortex show anticipatory rate changes to predictable differential rewards in a spatial memory task. Behav Brain Res 2001;123(2):165–83.
[25] Puryear CB, Mizumori SJY. Are hippocampal place fields related to spatial behaviors? 2002 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience; 2003, 719.13.
[26] Quirk GJ, Muller RU, Kubie JL. The firing of hippocampal place cells in the dark depends on the rat's recent experience. J Neurosci 1990;10(6):2008–17.
[27] Russell NA, Horii A, Smith PF, Darlington CL, Bilkey DK. Long-term effects of permanent vestibular lesions on hippocampal spatial firing. J Neurosci 2003;23(16):6490–8.
[28] Save E, Nerad L, Poucet B. Contribution of multiple sensory information to place field stability in hippocampal place cells. Hippocampus 2000;10(1):64–76.
[29] Shapiro ML, Tanila H, Eichenbaum H. Cues that hippocampal place cells encode: dynamic and hierarchical representation of local and distal stimuli. Hippocampus 1997;7(6):624–42.
[30] Skaggs WE, McNaughton BL, Gothard KM, Markus EJ. In: Hanson SJ, Cowan JD, Giles CL, editors. Advances in neural information processing, vol. 5. San Mateo, CA: Morgan Kaufmann; 1993. p. 1030–7.

[31] Swanson LW. A direct projection from Ammon's horn to prefrontal cortex in the rat. Brain Res 1981;217(1):150–4.
[32] Swanson LW. Brain maps: structure of the rat brain. 2nd ed. Amsterdam: Elsvier Science Publishers B.V.; 1998.
[33] Tsien JZ, Huerta PT, Tonegawa S. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. Cell 1996;87(7):1327–38.
[34] Wilson MA, McNaughton BL. Dynamics of the hippocampal ensemble code for space. Science 1993;261(5124):1055–8.
[35] Zinyuk L, Kubik S, Kaminsky Y, Fenton AA, Bures J. Understanding hippocampal activity by using purposeful behavior: place navigation induces place cell discharge in both task-relevant and task-irrelevant spatial reference frames. Proc Natl Acad Sci USA 2000;97(7): 3771–6.