Place field repetition and spatial learning in a multicompartment environment

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Place Field Repetition and Spatial Learning in a Multicompartment Environment

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ABSTRACT: Recent studies have shown that place cells in the hippocampus possess firing fields that repeat in physically similar, parallel environments. These results imply that it should be difficult for animals to distinguish parallel environments at a behavioral level. To test this, we trained rats on a novel odor-location task in an environment with four parallel compartments which had previously been shown to yield place field repetition. A second group of animals was trained on the same task, but with the compartments arranged in different directions, an arrangement we hypothesised would yield less place field repetition. Learning of the odor-location task in the parallel compartments was significantly impaired relative to learning in the radially arranged compartments. Fewer animals acquired the full discrimination in the parallel compartments compared to those trained in the radial compartments, and the former also required many more sessions to reach criterion compared to the latter. To confirm that the arrangement of compartments yielded differences in place cell repetition, in a separate group of animals we recorded from CA1 place cells in both environments. We found that CA1 place cells exhibited repeated fields across four parallel local compartments, but did not do so when the same compartments were arranged radially. To confirm that the differences in place field repetition across the parallel and radial compartments depended on their angular arrangement, and not incidental differences in access to an extra-maze visual landmark, we repeated the recordings in a second set of rats in the absence of the orientation landmark. We found, once again, that place fields showed repetition in parallel compartments, and did not do so in radially arranged compartments. Thus place field repetition, or lack thereof, in these compartments was not dependent on extra-maze cues. Together, these results imply that place field repetition constrains spatial learning. © 2016 The Authors Hippocampus Published by Wiley Periodicals, Inc.

KEY WORDS: spatial cognition; place cell; hippocampus; odor discrimination; context discrimination

INTRODUCTION

An influential view of the hippocampus is that it provides a cognitive map of the environment via place cells which represent specific locations (O'Keefe and Nadel, 1978). However, recent studies have shown that place cells exhibit recurring firing patterns in environments comprised of repeating, parallel compartments (Derdikman et al., 2009; Spiers et al., 2015). In the Spiers et al. study, place cells typically fired in the same relative locations in each of four identical chambers that were parallel to one another and connected by a corridor along one side. In the Derdikman et al. experiments, both grid cells and place cells showed repeated firing in multiple parallel alleyways of a hairpin maze when the animals traversed in the same direction. These results agree with earlier findings that place cells exhibit similar firing fields in two visually identical environments oriented in the same direction and connected by a corridor along one side (Skaggs and McNaughton, 1998; Fuhs et al., 2005). Together, these results suggest that place cells are driven primarily by local cues such as the boundaries, shape, and color of local environments (O'Keefe and Burgess, 1996; Barry et al., 2006; Hartley et al., 2000; Monaco et al., 2014), and are not influenced significantly by linear self-motion cues, which could be used to distinguish these environments (Fuhs et al., 2005, Spiers et al., 2015).

These results also suggest that the hippocampus and the entorhinal cortex do not encode complex environments in a holistic way, but rather with local "submaps" (Derdikman et al., 2009; Krupic et al., 2015). This is consistent with the finding that changing one part of a multi-compartment environment fails to affect the majority of place fields in the unchanged portion of the environment (Paz-Villagrán et al., 2004; Spiers et al., 2015). However, it is possible that with extensive experience, local maps, at least in the entorhinal cortex, may shift to a more global representation (Carpenter et al., 2015).

What is not known is whether place field repetition constrains spatial behavior. It is commonly assumed

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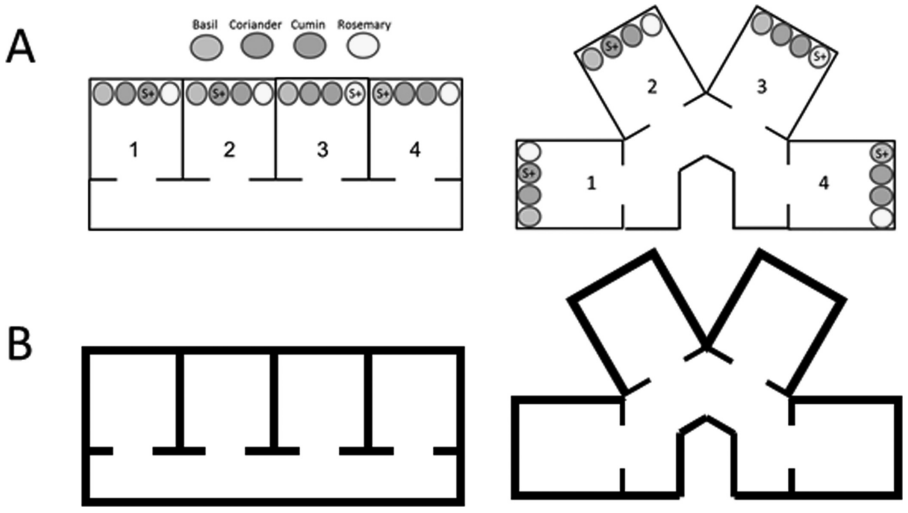

FIGURE 1. Schematic of the maze environments used in the current experiments. A: Rats were trained in a four compartment environment where the same compartments could be arranged in parallel, or at a 60° angle to one another. Each compartment contained four pots of sand, and each pot was scented with a different household spice. A different scented pot was correct for each compartment. One group of rats was trained on this discrimination in the parallel compartments, and a second group of rats was trained on this discrimination in the radial compartments. B: Place cells were recorded in the same four compartment environments, but without the scented pots of sand. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

that place cells provide a representation of the environment that is used for spatially guided behavior. Early work indicated that place cells predicted the animal's choice of a goal arm on a maze (O'Keefe and Speakman, 1987), and subsequent work has shown this to be the case in identifying reward locations (Lenk-Santini et al., 2002) and in the planning of routes (Pfeiffer and Foster, 2013). If the hippocampus provides a neural substrate for spatial and episodic memory (O'Keefe and Nadel, 1978; Poucet, 1993; Morris and Frey, 1997; Eichenbaum et al., 1999; Wood et al., 1999), then when there is place field repetition, animals should have difficulty discriminating between individual compartments. To test this, we trained animals in a novel odor-location discrimination task in environments where place field repetition is likely, or where it is less likely.

In previous studies using radial arm mazes (O'Keefe and Conway, 1978; McNaughton et al., 1983; Mizumori et al., 1989), place field repetition has not been observed, despite the presence of similar elements in the apparatus, the arms of the maze. Differences between these recording environments and the ones in which place cell repetition has been reported include the absence of high walls on the maze arms and the different directions in which the arms are oriented. A previous study found that while place field repetition occurred between two similar boxes oriented in the same direction as one another, the place cells remapped between the same boxes when they were oriented at 180° to one another (Fuhs et al., 2005). This finding suggests that directional information is sufficient to cause remapping between identical compartments. This explanation may also account for the pattern of grid cell fragmentation and place field repetition observed by Derdikman et al. (2009), as repeated fields were observed only in alleyways in which the animal ran in the same direction.

To test whether local environments that give rise to place field repetition are difficult to discriminate from one another, we trained different groups of rats on a four-way odor-location discrimination in parallel compartments and in radial compartments. We found that learning was impaired in the former, compared to the latter. To confirm that compartment orientation is the crucial factor in place cell repetition and to extend the results of Fuhs et al. (2005), we recorded from hippocampal place cells as rats explored four parallel compartments, and with the same compartments oriented at a 60° angle to one another (radial). Such an arrangement allows assessment of place cell repetition at varying angular separations. We found that strong place cell repetition occurred in the parallel compartments, but not in the radial compartments. A similar pattern occurred both in the presence and absence of an extra-maze orientation cue, indicating that the relative orientation of the compartments and self-motion cues are likely to allow place fields to discriminate among the radial, but not the parallel, compartments.

MATERIALS AND METHODS

Experiment 1

Animals

Twelve male Lister hooded rats, with an average weight of 300 g, were used in this experiment. Animals were housed in groups of four in standard cages, and maintained under a constant 12 h light/dark cycle. Throughout training, the rats were maintained on a restricted diet such that they maintained ~90% (and not <80%) of their expected free-feeding weight (corrected for normal growth). They were given free access to

water at all times when in their home cages. Behavioral training was usually performed 5 days per week, and was always conducted during the light phase of the light/dark cycle. In this and the following experiments, compliance was ensured with national [Animals (Scientific Procedures) Act, 1986] and international [European Communities Council Directive of November 24, 1986 (86/609/EEC)] legislation governing the maintenance of laboratory animals and their use in scientific experiments. Experiments underwent further ethical and procedural approval by the Named Veterinary Surgeon and Named Animal Care and Welfare Officer responsible for overseeing experiments in the laboratory.

Apparatus

The four-compartment environment was constructed from wood and consisted of four rectangular boxes (35 × 40 cm, width × length) with 30 cm high walls, painted blue (Fig. 1A). Corridors were 20 cm wide with 30 cm high walls and were also made of wood and painted blue. Two different corridors were used; one allowed a parallel configuration of the compartments, and the other allowed a 60° separation between compartments. Large wooden blocks could be used to close off compartments and make them inaccessible to the rats when desired. Each compartment was equipped with four pots of scented sand near the back wall, as described below. The environments were elevated 80 cm from the floor using wooden stools. The four-compartment environment was placed inside a black curtained enclosure with an opaque white ceiling. A 100 × 50 cm^2 white sheet acted as a directional cue within the curtained enclosure. This was placed on the curtain wall opposite the four compartment environment. For initial shaping, a separate apparatus was used, consisting of a 1 × 1 m painted, wooden square box with 20 cm high walls, placed outside the curtained enclosure.

Odor-location task

Shaping. Shaping took place in a square box located outside the curtained maze environment. Rats were first shaped to dig for food rewards (Chocolate cereal loops, "Weetos," Weetabix, UK) in pots of odorless sand. The pots were transparent and cylindrical (6.5 × 7.6 cm^2, diameter × height, Nalgene, NY). Once rats reliably retrieved buried rewards they were trained on a simple odor discrimination with two sand pots (only one of which was rewarded). To create the scented sand, a household spice (0.5 g/100 g sand) was mixed with baked children's play sand. Two grams of chocolate cereal dust were also mixed per 100 g of sand to control for reward odor. Each sand pot was filled with 200 g of this odorised sand mix to give a maximum depth of 4 cm. The cereal loop rewards were buried between 1 and 2 cm below the surface of this medium.

Odor-location training. After acquiring the simple discrimination, rats were divided into two performance matched groups. One of these groups was assigned to the parallel compartment configuration, and the other to the radial configuration. Four pots of sand were placed at the back of each compartment, and each pot was scented with one of four odors (Fig. 1A; from left to right: basil, coriander, cumin and rosemary). A different odor was rewarded in each compartment, and the same odor was always correct in a given compartment for a given rat. Within each group of rats (parallel and radial) the pattern of rewarded odors across the four boxes was different for each rat. To start a trial, the door to a compartment was opened and the rat was permitted to make a choice (a displacement of the sand with the paw or snout). The animal was allowed to consume the cereal loop reward if it had dug in the correct odor pot for that compartment, and was then placed in the alleyway while the door was replaced. If the rat chose an incorrect pot of sand, it was not permitted to make another choice, but instead was placed or guided back into the alleyway. Rats were given six such trials per day in each compartment, according to a pseudorandom schedule. The trial order was different each day, and scheduled in such a way that rats visited a compartment on no more than two trials in a row (but visited each compartment on two trials in a row at least once). To retrieve the food rewards reliably, the rat had to distinguish between the compartments and learn the correct pot of sand for each compartment. This could be based on learning either which odor was rewarded or which pot position was rewarded in a given compartment (e.g., in compartment three, the leftmost pot, which is scented with basil, was rewarded). Regardless of the strategy used, the rat was required to distinguish between the compartments in order to determine which pot was rewarded.

Rats were trained on the task in stages (Fig. 2). In the first stage, two compartments were used, and rats received 12 trials (6 in each compartment, in a pseudo-random order as above). The reinforced odor pots were present in each of these compartments, as well as two non-odorised sand pots. When rats were able to distinguish two compartments (by making five out of six correct choices per compartment on two consecutive days), they were moved to the second stage of testing in which trials were run in three compartments (the two used in stage 1, and an additional compartment). The odor associated with that compartment replaced one of the plain sand pots in the original two compartments. Rats received 18 trials per day (6 in each compartment) until reaching the same performance criterion of five out of six correct choices per compartment on two consecutive days, before moving onto the final, four-compartment stage. For practical purposes, limits on the number of days spent training at each stage were imposed: 30 days for the two-compartment stage, 30 days for the three-compartment stage, and 15 days for the four-compartment stage. If a rat did not reach criterion at a given stage they were unable to progress to the next stage.

The mazes were cleaned daily with scented detergent and the positions of the compartments, the sand pots, and the doors were changed twice a day. Sand pots were kept filled to the same level with sand and odors were replenished at least once a week.

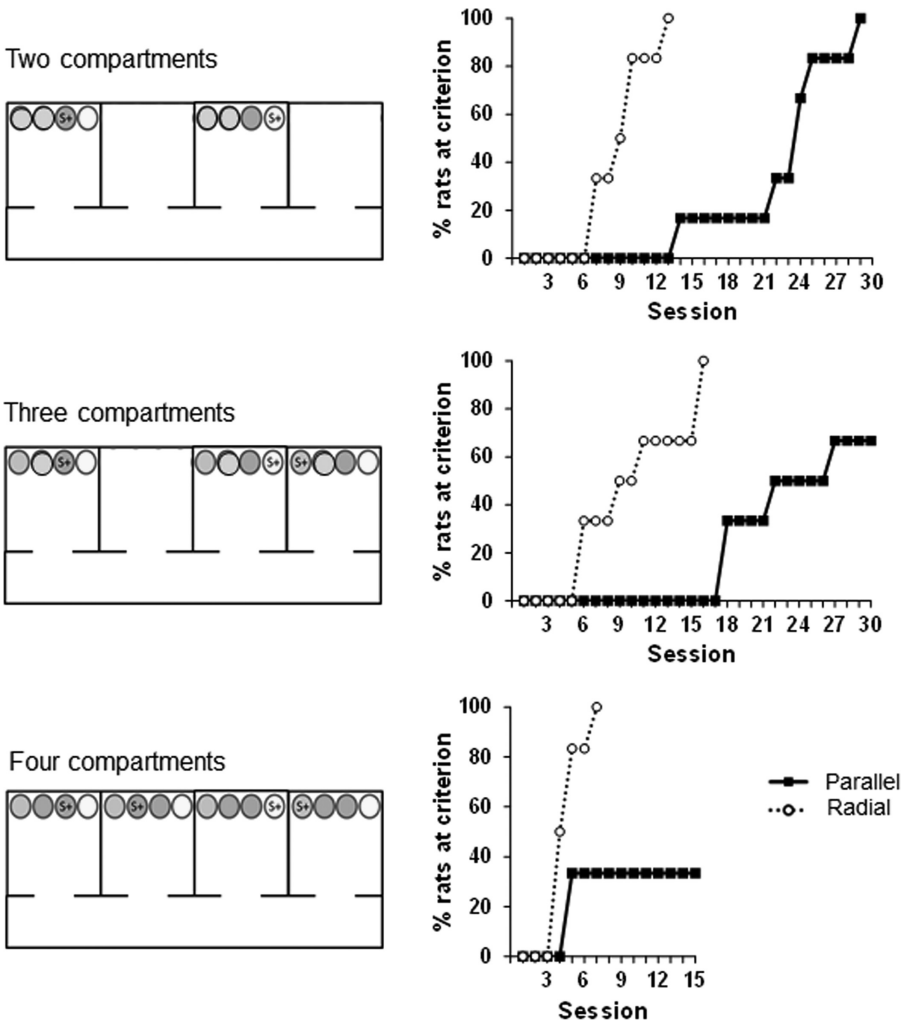

FIGURE 2. Acquisition of odor-location discrimination. Left plots: Rats were initially trained to discriminate between two odors in two compartments, and upon acquisition of this, were trained on three odors and three compartments, and then on the full task with four compartments. A separate group of rats was trained on the same task with the compartments arranged radially (apparatus not shown). Colored circles depict pots with different odors; gray circles depict pots with unodorised sand. S+ indicates the baited pot. Right plots: Cumulative frequency plots of the percentage of rats that reached criterion (five correct responses in six trials in each compartment) at each stage of training across days. Animals trained in radial compartments (open circles) reached criterion in fewer sessions than those trained in parallel compartments (black squares) at each stage of training. Only four of the six animals trained in the parallel compartments reached criterion in the three box training, and only two of the six animals reached criterion in the four box training. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Nonrewarded probe sessions. Once rats had completed all stages in the task, or failed to meet criterion performance before the cut-off training limit, nonbaited probe trials were conducted. The purpose of these was to test whether the rats relied on the scent of reward in the baited pot to solve the task (although the sand in all pots was mixed with reward dust), rather than on learning to associate each compartment with a specific rewarded sand pot odor or location. For the probe sessions, rats completed two days of the task as if they were still training. However, on each day two trials in each compartment were not baited. The rat's choice of sand pot on these trials would thus be based on their learned odor or spatial associations.

Training in the alternative environment configuration. Following the probe sessions, the assignment of animals to conditions was reversed. Animals formerly trained with radially arranged compartments were trained on a new discrimination with the compartments arranged in parallel. The rats trained in the parallel compartments, upon completion of at least 50 days of testing, were trained on a new discrimination with the compartments arranged radially. For the new discrimination, the four sand pot odors were replaced with four novel ones (left to right: tarragon, marjoram, cinnamon and oregano), and rats were rewarded for sand pots in different locations to those used previously in at least three of the four compartments. The rats were trained in the same staged manner as in the first task, first with two compartments, then three, and finally four.

Experiment 2

Animals

For the first electrophysiological study, four naïve male Lister hooded rats (200–250 g) were used. Animals were housed individually in custom designed cages following electrode surgery, and maintained under a constant 12 h light/dark cycle. To motivate the rats to seek food pellets during the screening and recording sessions, they were mildly food deprived such that they maintained ∼90% (and not less than 80%) of their free-feeding weight.

Apparatus

Recordings were done in four different environments, all constructed from wood and painted blue: a square, open field environment (1 × 1 m^2 floor with 25 cm high walls) for screening; a cylindrical environment (80 cm diameter wooden base, 30 cm walls) for characterising place cell stability; and the two configurations of the four-compartment environment, as described in the previous experiment (Fig. 1B). For the recording experiment no pots of sand were placed in the compartments.

Recording electrodes

Tetrodes were attached to prefabricated Axona microdrives (Axona, St. Albans, U.K.) (two animals; four tetrodes per animal) or to drives built with Mill-Max connectors (Mill-Max, Oyster Bay, NY; two animals; eight tetrodes per animal). All implants were unilateral, and in the left hemisphere. Tetrodes were composed of four HML coated, heat annealed 17 μm 90% platinum 10% iridium wires (California Fine Wire, Grover Beach, CA). Electrodes were gold plated (Non-Cyanide Gold Plating Solution, Neuralynx, MT) to reduce the impedance of the wire from a resting impedance of typically 0.7–0.9 MΩ to a plated impedance in the range of 180–250 kΩ (200 kΩ being the target impedance).

Surgery

The surgical procedures used here were identical to those described previously (Ainge et al., 2007). Briefly, animals were anaesthetised using Isoflurane inhalation anaesthetic (Abbott Laboratories) delivered using medical oxygen. Hydration was maintained by administration of 2.5 ml 5% glucose and 1 ml 0.9% saline. Animals were also given anti-inflammatory analgesia (small animal Carprofen/Rimadyl, Pfizer, UK). In a stereotaxic frame, the electrode tips were lowered to the CA1 coordinates (−3.48 mm AP from bregma, +/−2.4 mm ML from the midline, −1.8 mm DV from dura surface). Skull screws were embedded in the skull and the drive assembly was anchored using dental cement mixed with silver sulfate to a 1% concentration (Ag_2SO_4, Sigma-Aldrich, St. Louis). At least one week of recovery time passed before screening and recording took place.

Screening and single unit activity

Single unit activity was observed and recorded using a 32-channel Axona USB system (Axona, St. Albans, UK). Rats were attached to the recording system via a light, flexible, elasticated recording cable. The recording cable passed signals through a ceiling mounted slip-ring commutator (Dragonfly Research and Development, Ridgeley, West Virginia) mounted on a moveable ceiling track to a pre-amplifier, and then to a system unit and desktop computer. The position of the animal was recorded using infra-red LEDs fixed to the base of the recording cable and a ceiling mounted, infra-red sensitive CCTV camera.

Rats were screened for single unit activity and for the presence of theta oscillations once or twice a day, five days a week. Screening was conducted in 1 m^2, open environment. If no single unit activity was detected, tetrodes were advanced by up to 50 μm. At least 6 h (typically 24) were allowed to pass between advancing screws and assessing or recording activity. If complex spike activity was observed, the animal completed a session of the experimental protocol.

Experimental protocol

Rats were recorded in the cylinder environment for a minimum of 8 min, the maze in either the parallel or radial configuration for a minimum of 18 min, the maze in its alternate configuration for a further 18 min, and then again in the cylinder environment for 8 min. Between each of these environments, rats were removed to a small, tall sided, opaque cylinder within the curtained enclosure where they were given access to drinking water for approximately two minutes (without detaching the recording cable). The maze and cylinder environments were cleaned with scented detergent between rats and the individual maze compartments were swapped between sessions and between rats.

Data analysis

Cluster cutting. Spike data were analysed offline using custom Matlab scripts. The energy, first principal component, peak amplitude, time at peak and width of waveform were used to sort spikes using the Klustakwik spike sorting algorithms (Kadir et al., 2014). Clusters were then manually checked and refined using the manual cluster cutting GUI, Klusters (Hazan et al., 2006) and clusters which were not recognisable as a single neurons were removed. Isolation distance (Iso-D), $L_{ratio,}$ signal to noise ratio (*S*/*N*) and spatial information content were also calculated (Schmitzer-Torbert et al., 2005; Skaggs et al., 1993).

A unit was classified as a place cell if it satisfied the following criteria: (i) the width of the waveform was >250 μs and (ii) the mean firing rate was >0.1 Hz but <5 Hz, and (iii) the spatial information was >0.5 b/s in at least one of the environments (parallel, radial, or cylinder). A place cell was considered to be active in a given environment only if these criteria were met in that environment.

Repetitive firing analysis. To assess the spatial correlation between place fields across the four compartments of the four-compartment environments, the position data for each compartment were extracted and adjusted to fill an area equivalent to the dimensions of the actual compartment. This was required to compensate for optical distortion arising from the camera tracking. For compartments in the radial configuration, the data were also rotated around the compartment center to align them vertically before correlation.

Firing rate maps were produced for each compartment individually by dividing the compartment area into a grid of 3 cm square bins. The firing rate in each bin was calculated as the total number of spikes which occurred in that bin divided by the total length of time spent there. Bins in which the rats spent <0.1 s were treated as if they had not been visited. Bins were smoothed using a Gaussian filter with the following parameters:

$$g(x) = \exp\left(\frac{-x^2/2\sigma^2 - y^2}{2\sigma^2}\right)$$

Pearson correlations were calculated between the firing rate maps for the six unique compartment pairs. This was done separately for the parallel and radial configurations of the multicompartment environment. All correlations excluded bins that had not been visited. Correlations were computed only if a cell satisfied the criteria for being an active place cell (outlined above) in that environment, and only on compartment pairs in which the peak firing rate in the firing rate map for one or both of the compartments exceeded 1 Hz. This meant that for a significant proportion of cells correlations were calculated only for one of the two maze configurations. Moreover, the number of correlations within a maze configuration varied from 3 to 6 for active cells, depending on whether the cell's peak firing rate exceeded 1Hz in just one compartment (three pairwise correlations), two compartments (five pairwise correlations) or either three or four compartments (six pairwise correlations). Correlations between the two cylinder sessions were calculated only if the place cell satisfied the above criteria for being active in one or both of the cylinder sessions and contributed correlation values in one or both of the maze sessions.

Shuffling. To test whether the repetition of fields differed from randomly located fields, the observed correlations were compared with correlations obtained from shuffled data, similar to that employed by Spiers et al. (2015). For the parallel maze, compartment rate maps were shuffled, paired randomly without replacement, and if the peak firing rate in at least one compartment exceeded 1Hz the correlation between a pair was calculated. This process was repeated for the radial compartment rate maps and the cylinder rate maps.

Autocorrelation. As an additional means of identifying place field repetition across compartments, firing rate maps for each compartment (each 12 × 14 3 cm bins, width × height) were concatenated along the longest edge to produce a 48 bin wide combined rate map which was used to generate self-normalised spatial autocorrelograms using custom Matlab scripts. The combined rate map was correlated with itself before being shifted laterally by a distance of one bin (3 cm). The correlation was then recalculated and the process repeated until the maps no longer overlapped.

Angular and linear separation. To test whether place field repetition varied as a function of the angular differences between radial compartments, we compared the spatial correlations for compartments in the radial arrangement that were separated by 60°, 120°, and 180°. A similar analysis was conducted for the parallel compartments, but here the variable was the distance between compartments (as they faced the same direction).

Histology. At the end of the experiment, rats were given an overdose of sodium pentobarbital and perfused transcardially with saline followed by 4% Formalin. The brains were extracted and further fixed in a 4% Formalin solution for at least five days. Brains were then sectioned on a freezing microtome, with 32 μm sections taken from the area surrounding the electrode track. Sections were stained with a 0.1% cresyl violet solution and imaged in tiles using a microscope mounted camera and ImageJ software (ImageJ, NIH, Bethesda, http://imagej.nih.gov/ij/, 1997-2014).

Experiment 3

Experimental protocol

To address the potential interpretation that the differences in place field repetition across parallel and radial environments observed in Experiment 2 were due to different views of the extra-maze orientation cue from each apparatus, data from a second cohort of animals was assessed. This cohort was comprised of five additional naïve male Lister hooded rats (200–250 g) who served as the control subjects for a lesion experiment (to be reported elsewhere). All experimental procedures were as in Experiment 2, with the exception that the parallel and radial recording sessions were conducted within the black curtained enclosure in the absence of the white orientation cue.

RESULTS

Experiment 1

Spatial learning is easier in compartments facing different directions compared with compartments facing the same direction

Task acquisition was more difficult for animals trained in parallel compartments than for those trained in radial compartments. At both the two and three-compartment stages, animals in the parallel compartments required significantly more trials to reach criterion compared to those trained in the radial

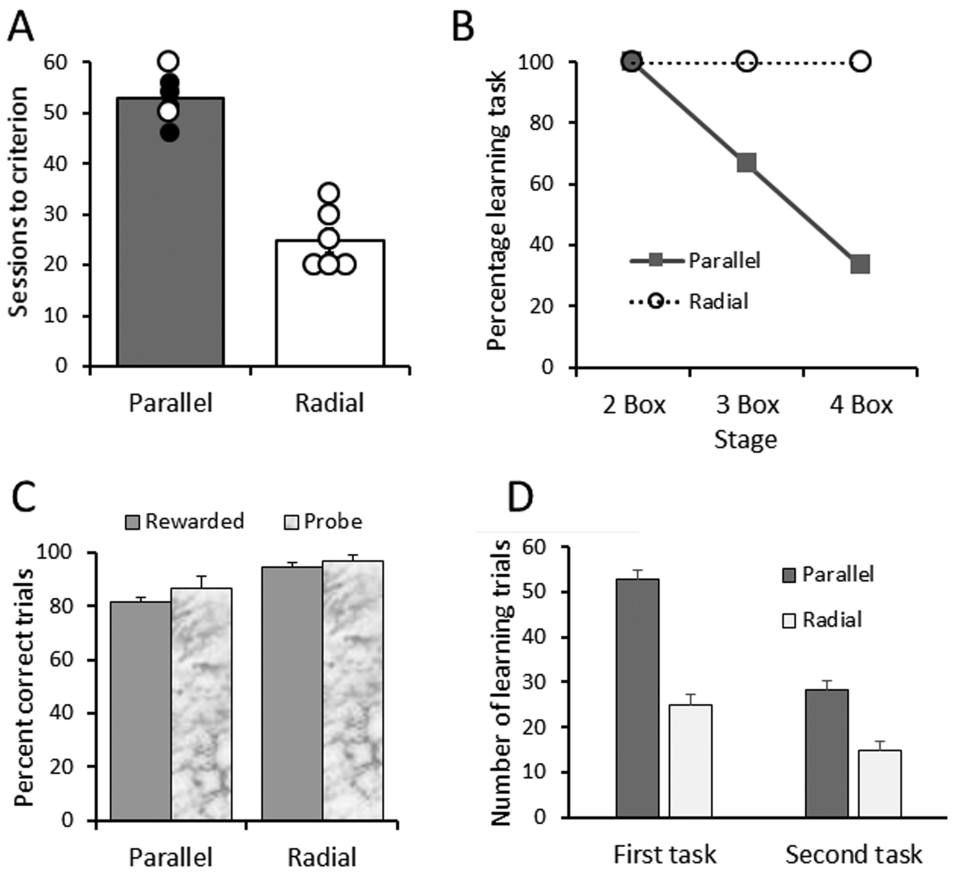

FIGURE 3. Comparison of the performance in the parallel and radial compartments in the original training, cross-over, and probe sessions. A: Rats trained in the environment with radially arranged compartments acquired the odor-location discrimination in significantly fewer trials overall that those trained with compartments arranged in parallel. Dots indicate performance of individual rats, and hollow dots are animals who reached criterion on the task. B: All six animals trained in the radial compartments reached criterion in each stage of training (box = compartment), whereas only a subset of the animals trained in the parallel compartments were able to do so in the three- and four-compartment stages. C: Performance on probe sessions in which the correct odor pot did not contain reward (lighter shaded bars) was equivalent to performance in which the correct pot was baited (darker shaded bars). This indicates that the animals did not use the any scent of the reward to guide their behavior. D: After training on the initial task, the assignment of rats to training conditions was reversed, and a second odor-location discrimination was trained. The second task was learned faster than the first task, although learning in the parallel compartments (filled bars) was still slower than learning in the radial compartments (hollow bars).

compartments (Fig. 2; univariate ANOVA: two compartments: $F(1,10) = 5.6$, $P < 0.0002$; three compartments: $F(1,10) = 4.6$, $P < 0.001$; analysis of four compartments was not done as only two animals in the parallel compartments reached this stage).

Overall, the animals in the parallel compartments required significantly more days of training than those in the radial compartments (Fig. 3A; $F(1,10) = 70.8$, $P < 0.001$). All rats trained in the radial compartments reached criterion at every stage of training, whereas only 4/6 rats trained in the parallel compartments reached criterion at the three-compartment stage, and only 2/6 reached criterion in the four-compartment stage (Fig. 3B). Nonbaited probe sessions confirmed that the animals were as accurate in choosing the correct odor when it was not baited as they were when it was rewarded. Thus, the animals used the scent of the sand, and/or the location of the sand pot, but not the scent of the reward itself, to guide behavior (Fig. 3C).

The assignment of animals to conditions was then reversed. Animals initially trained in the parallel compartments were trained on a new discrimination in the radial compartments and vice versa. Overall, in term of the number of trials to reach criterion, learning of the second discrimination was quicker than learning of the first discrimination (Fig. 3D; $F(1,10) = 44.0$, $P < 0.001$). However, this effect differed depending on the configuration of the compartments (interaction effect: $F(1,10) = 63.7$, $P < 0.001$). In contrast to their limited success in the first task, all six animals trained originally in parallel compartments learned the new discrimination in the radial compartments. In terms of the number of trials to reach criterion, their learning in the radial compartments was significantly faster than in the parallel compartments ($t(5) = -12.0$, $P < 0.001$). This suggests that the initial impairment in learning in the parallel compartments was not due to a problem

TABLE 1.

Number of Place Cells Included in the Analysis from Each Animal in Each Environment

Animal	Parallel only	Radial only	Active in both
Rat 1	27	82	53
Rat 2	48	67	109
Rat 3	83	222	194
Rat 4	6	14	14

with this group of animals in particular, but was rather due to the configuration of the compartments.

Interestingly, rats trained originally in the radial compartments were able to learn in the parallel compartments. As evident in Figure 3D, they took slightly longer to acquire the new discrimination in the parallel compartments (filled bar, second task) compared to their initial acquisition in the radial compartments (open bar, first task), though this difference did not reach significance ($t(5) = 0.85$, $P = .44$; paired sample t-test). Thus, learning in the parallel compartments is possible if the animals have first learned to tell the compartments apart in the radial configuration. Overall, however, learning in the parallel compartments required more training sessions than learning in the radial compartments, both in the initial odor-location discrimination ($t(10) = 8.8$, $P < 0.001$) and in the second discrimination ($t(10) = 4.7$, $P < 0.001$; independent sample t-tests).

Experiment 2

Place cells show repetition in parallel compartments, but not in radially arranged compartments

Across the four rats, for all recording sessions, 534 place cells were active in at least one of the parallel compartments, and 755 cells were active in at least one of the radial compartments (see Table 1 for breakdown). For computational simplicity, we did not attempt to identify repeat recordings of the same cells across days, and thus the number of unique cells is lower. To be included for analysis, a place cell had to fire at > 1 Hz peak rate in the firing rate map in at least one compartment (see Methods), and thus place cells with fields only in the alleyways were not included in the analyses.

In the parallel compartments, individual place cells often exhibited repeated fields (Fig. 4B). However, when the same compartments were arranged radially, significantly less place field repetition was apparent. Recordings in a cylindrical apparatus before and after exposure to these environments suggested that these differences were not due to instability in the place fields, as place cells typically fired in the same way in both cylinder sessions (differences between pre-cylinder and post-cylinder shifts were occasionally observed).

To quantify place field repetition in the parallel and radial environments we performed bin-by-bin correlations between the firing rate maps of the four compartments within an environment (parallel or radial) for each place cell that was active in that environment. From these correlations, we also calculated the mean correlation for each cell for each apparatus. We compared the spatial correlations in the parallel and radial environments using: (i) all of the correlations between individual compartments, (ii) the mean correlation for each of the cells active in each environment, and (iii) the mean correlation for each cell for the subset of cells that were active in both environments (Fig. 5A).

The rate maps in the parallel compartments showed significantly higher correlations than those in the radial compartments in each data set [Fig. 5B; all correlations: $t(5251) = 29.5$, $P < 0.00001$ (independent samples t-test); all cells: $t(1287) = 22.3$, $P < .0001$ (independent samples t-test); cells active in both maze configurations: $t(369) = 17.4$, $P < 0.0001$ (paired t-test)]. As is evident in Figure 5C, the distribution of correlations or mean correlations for the parallel compartments (dark bars) is shifted to the right of the distribution of the corresponding correlations in the radial compartments. The higher correlations between parallel compartments relative to radial compartments were seen in all four animals (all P's < 0.001), and were evident across repeated recording sessions (Fig. 5D). A univariate ANOVA restricted to the most conservative data set, the mean correlations of cells active in both the parallel and radial environments across days, confirmed the differences between the two environments (maze effect: $F(1,714) = 305.9$, $P < 0.00001$). In this data, there was no main effect of session ($F(12, 714) = 1.3$, $P = 0.23$), and the differences between the parallel and radial correlations did not change across testing sessions (maze $\times$ session interaction: $F(12,714) = 0.8$, $P = 0.64$).

To test whether the observed repetition in place fields differed from randomly located fields, the observed correlations were compared to a shuffled distribution of correlations (as in Spiers et al., 2015). As is evident in Figure 6A, the observed correlations between parallel compartments were higher than the shuffled distribution of correlations [observed correlations vs. mean of the shuffled distribution: $t(2290) = 38.8$, $P < 0.001$ (one sample t-test)]. However, because of the large sample size in this comparison, the t-statistic here is overpowered. Thus, a more appropriate focus is on the effect size (the difference between the observed scores and the mean of the shuffled distributions), as this is not influenced by sample size. Using Cohen's d measurement, the effect size was large (>0.8) for the difference between the observed correlations and the shuffled distribution ($d = 0.83$).

In contrast, the correlations for the radial configuration resembled those of the shuffled distribution. Although the observed correlations differed significantly from the mean of the shuffled distribution ($t(2961) = 5.8$, $P < 0.001$; one-sample t-test), the effect size was small ($d = 0.11$). The spatial correlations for the cylinder sessions before and after the multicompartment sessions were typically high ($r >= 0.7$), indicating that the place cells showed stable fields. Statistically, this was reflected in a large effect size for the comparison between the correlations observed across cylinder sessions and the mean correlation of the shuffled data ($d = 1.9$; a one-sample t-test: $t(553) = 46.8$, $P < 0.001$).

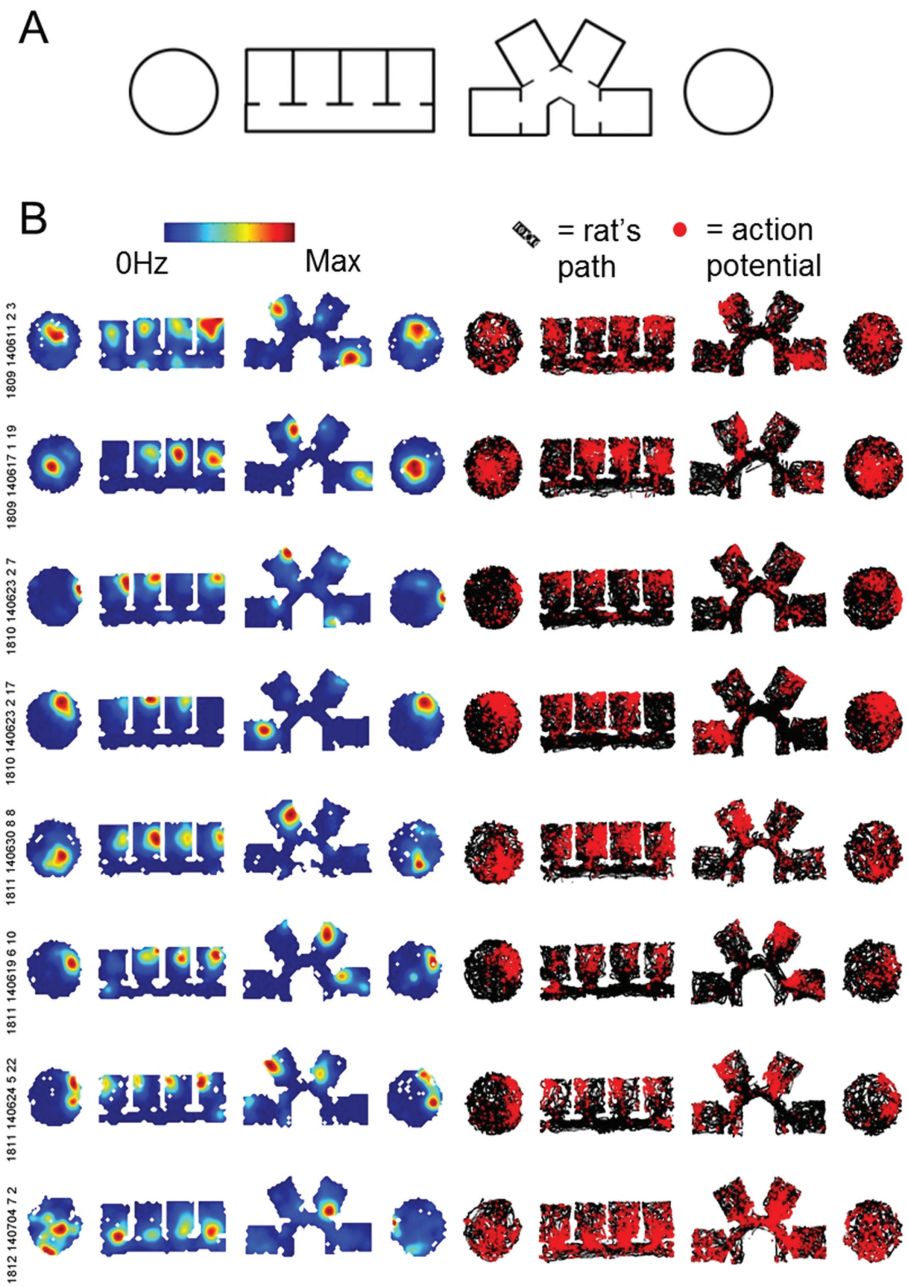

FIGURE 4. Examples of place cells recorded in the cylinder, parallel, and radial environments. A: Schematic of the environments used. Rats were recorded in the cylinder apparatus, the parallel compartment apparatus, the radial compartment apparatus (or vice versa), and again in the cylinder. B: Place fields show frequent repetition in parallel compartments, but significantly less repetition in compartments facing different directions. The plots in the left column are smoothed firing rate maps for individual place cells, with warmer colors indicating higher rates of firing. The plots in the right column show the same cells with the rat's path (black lines) and the location of individual spikes (red dots).

The higher rate of place field repetition in the parallel environments was also evident when maze compartment firing rate maps were correlated to one another in a 1D spatial autocorrelation (Fig. 7). As shown in Figures 7A,C, repeating higher correlations were observed with shifts of the rate maps in the parallel compartment maps, but these repeating correlation harmonics were less evident when the radial compartment maps were shifted (Figs. 7B,C).

Spatial correlations decreased with greater angles between radial compartments, and with greater distances between parallel compartments

Although the spatial correlations between compartments in the radial arrangement were low, we sought to test whether place cell repetition varied as a function of the angular separation between compartments. A comparison of the correlations

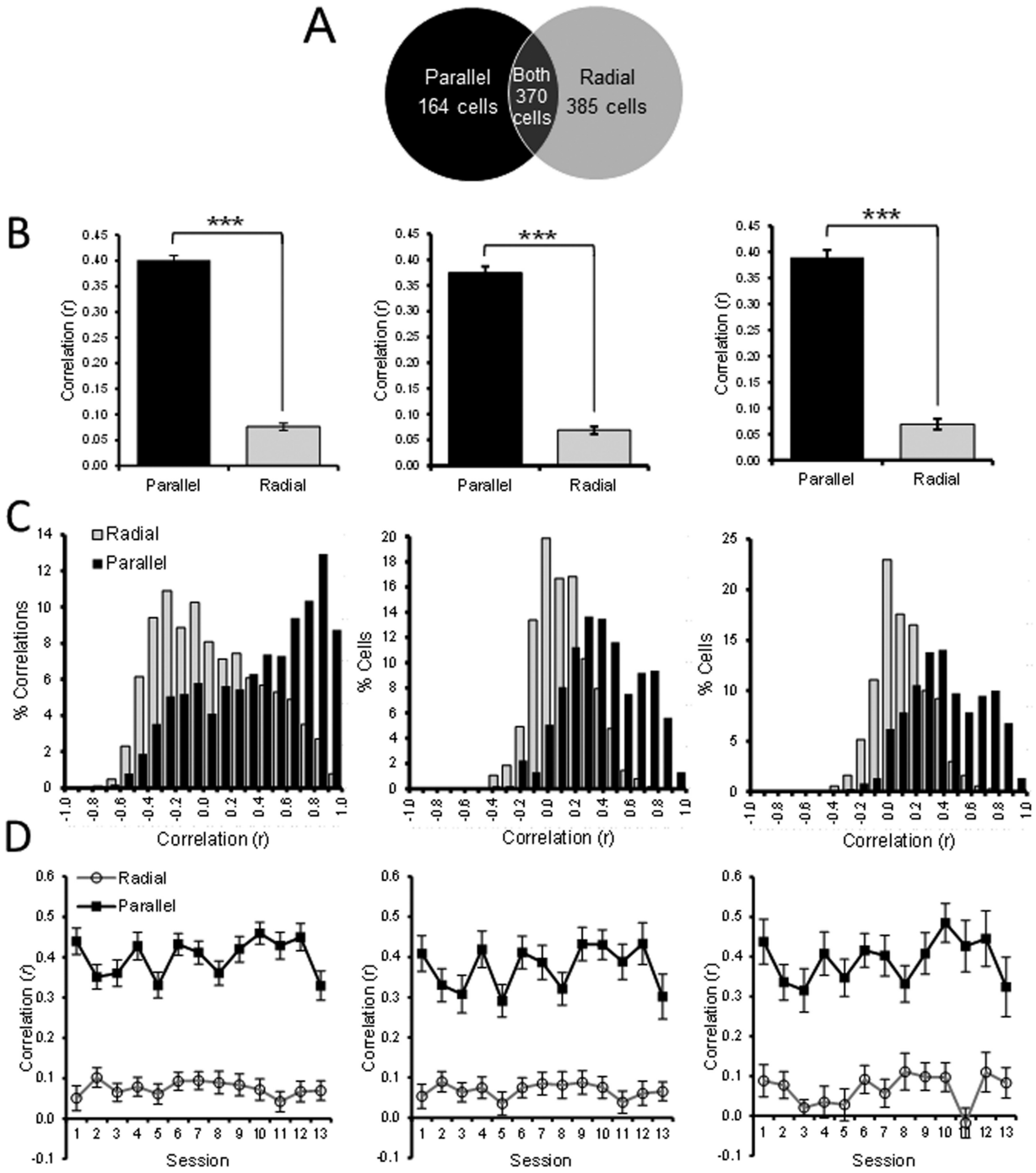

FIGURE 5. Comparison of the firing map correlations for the parallel and the radial compartments. A: Number of cell recorded in each environment. B: Correlations (mean + SEM) from the firing rate maps of the parallel compartments were significantly higher than those of the radial compartments using all correlations (left), the mean for each cell (middle), or the means for cells active in both parallel and radial environments (right). C: the distribution of all correlations between radial compartments (light gray bars) and parallel compartments (dark bars) using the data from B. D: The higher correlation between parallel compartments compared with radial compartments was evident across repeated recording sessions. Data as in B.

between compartments separated by 60°, 120°, and 180° revealed that the similarity of place field maps between compartments decreased with greater angles between the compartments (Fig. 7D, left panel; repeated measures ANOVA, linear effect: $F(1, 307) = 13.3$, $P < 0.001$). For the parallel compartments, the spatial correlations between compartments likewise decreased the farther the compartments were away from one another (Fig. 7D, right panel; repeated measures ANOVA,

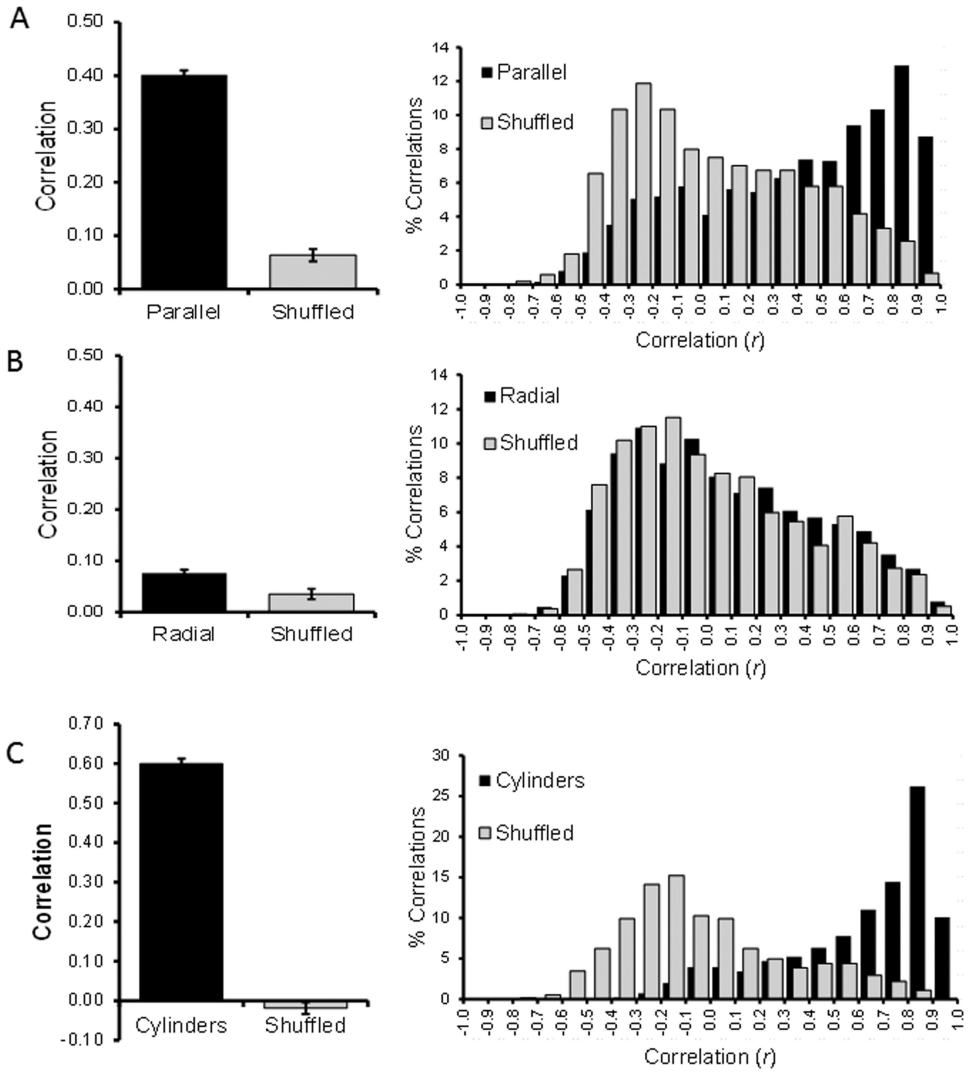

FIGURE 6. Comparison of the observed correlations between compartment firing maps and shuffled distributions. Left plots: The mean and SEM correlation value observed in each environment and the data shuffled as in Spiers et al. (2015; top: parallel compartments; middle: radial compartments; bottom: cylinders). Right plots: The distribution of observed and shuffled correlations.

linear effect: $F(1, 269) = 119.1$, $P < 0.001$), indicating some sensitivity to linear distance.

Differences between parallel and radial compartments did not depend on cell isolation

We assessed the relationship between three measures of recording quality and the compartment correlation values for the cells contributing to the repetitive firing analyses above. Signal to noise ratio was not found to affect correlation outcome in either the parallel ($r(532) = -0.01$, $P > 0.90$) or radial ($r(753) = -0.04$, $P > 0.30$) mazes, nor did isolation distance ($r(532) = 0.01$, $P > 0.80$ and $r(753) = 0.01$, $P > 0.90$, respectively) or L_{ratio} ($r(532) = -0.02$, $P > 0.70$ and $r(753) = 0.01$, $P > 0.80$, respectively). These quality measures cannot account for the firing patterns observed in either maze environment. All tests were independent, pairwise, Pearson's correlations.

Histology. Histological assessment of the electrode tracks confirmed that the electrodes were placed in the CA1 cell layer of the hippocampus (Fig. 8).

Experiment 3

Differences between place cell repetition in parallel versus radial compartments are evident in the absence of extramaze landmarks

A total of 238 active place cells were recorded in the parallel compartments, and 301 active place cells were recorded in the radial compartments. As in Experiment 1, clear place field repetition was evident in the parallel compartments, and less place

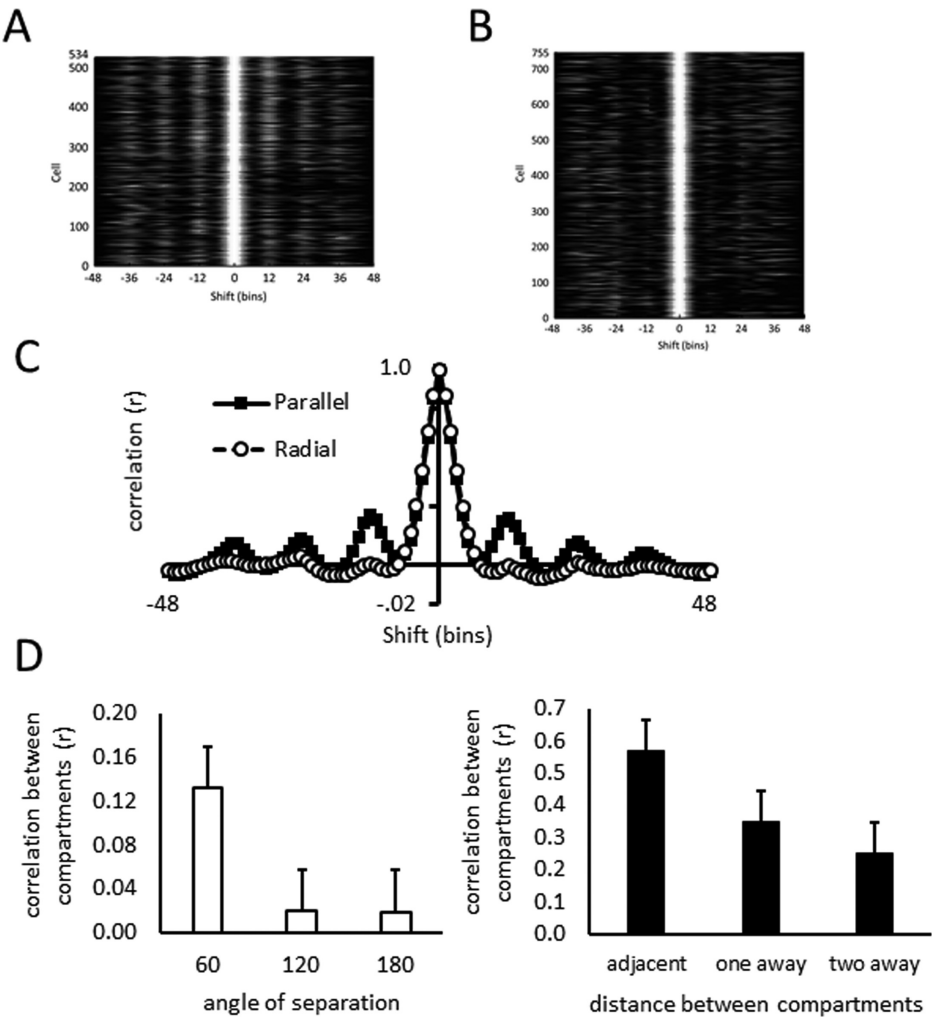

FIGURE 7. Autocorrelogram plots for the parallel and radial compartments. A: The results of spatial autocorrelograms calculated for every cell included in the parallel analyses ($n = 534$), with one cell per row. The horizontal axis represents the 96 bin range of shift (each compartment was divided into 12 × 14 bins, width × height), and the bright central band represents a correlation value of 1 (complete overlap of rate maps). A series of six, weaker, periodic bands can be observed, at the +/−12, +/−24, and +/−36 bin points. At these points, the maze compartments overlap and the repetitive firing across compartments yields a significant correlation. B: The results for every cell included in the radial analyses ($n = 755$). A series of weaker bands is not nearly as visible. C: The mean and SEM autocorrelation values for all of the parallel and radial compartment data. The vertical axis represents the self-normalised autocorrelation score and the horizontal axis represents the 96 bin range of shift. The central peak of 1.0 is at a shift of zero, and a series of weaker peaks in the parallel data indicate the repetition of place fields across compartments. The same periodicity cannot is less evident in the radial compartment data. D: The spatial correlations between radially arranged compartments was higher when the angular separation between them was 60°, as opposed to 120° or 180° (left plot). For the parallel compartments, the correlations were higher for adjacent compartments compared with those one or two compartments away. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

cell repetition was found in the same compartments were arranged radially (Fig. 9A). Likewise, the mean correlation for each cell in the parallel compartments was higher than that in the radial compartments (Fig. 9B; Univariate ANOVA: $F(1,532) = 366.1$, $P < 0.001$; Cohen's $d = 1.64$). Nearby compartments showed higher correlations in the parallel configuration (Fig. 9C; repeated measures ANOVA: $F(2,224) = 40.9$, $P < 0.001$), though this effect did not reach significance with the radial configuration ($F(2,164) = 0.9$, $P = 0.92$). A potential reason for this, however, is that the correlations between compartments were markedly lower in the radial configuration.

DISCUSSION

This study tested whether environments in which place field repetition is observed are more difficult to tell apart. Using a novel, four-compartment discrimination task which required

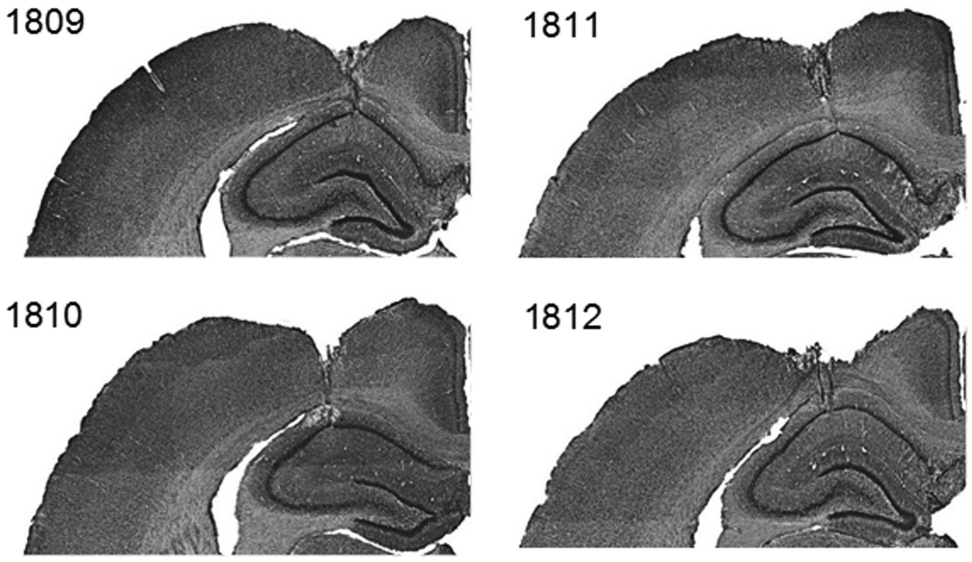

FIGURE 8. Histological sections for each experimental animal. Each photograph represents the final placement of the electrode in the hippocampus of each rat. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

animals to associate specific odorised sand pots with specific compartments, we found that learning was significantly impaired when the compartments were arranged in parallel compared to when they were arranged at 60° angles to one another. Furthermore, we found high levels of place field repetition between the parallel compartments (replicating previous findings of Spiers et al., 2015), but significantly less repetition between the same compartments arranged radially. Taken together, these data indicate that behavioral discrimination of compartments is impaired under conditions in which place field repetition is observed. Finally, we found that disambiguation among radially arranged compartments by place cells was not dependent on the presence of an extramaze polarizing cue, suggesting that directional information provided by the configuration of the radial maze and/or angular self-motion is sufficient to allow place field discrimination between visually and geometrically similar local compartments. We consider each of these findings in more detail below.

Spatial Learning Is More Difficult in Environments Where Place Field Repetition Is Observed

Our results suggest that if different local compartments look the same, and are oriented in the same direction (as in the parallel configuration of our environment), then the hippocampus produces similar maps. In contrast, when the same local compartments are oriented in different directions (as in the radial configuration), the hippocampus produces different maps. If hippocampal place cells provide the substrate for identifying locations, then similar place cell firing patterns in different compartments should make it difficult to tell the compartments apart.

The current results support this prediction. When tested on a four-odor discrimination task across multiple compartments, only two of the six animals trained in the parallel compartments reached our criterion level of performance on the full task, whereas all of the animals trained on the radial compartments did so. Thus, rats had a great deal of difficulty establishing unique odor-environment associations in compartments arranged in parallel, whereas such associations were readily acquired when these compartments were arranged radially. The results of the task switch also indicate that the initial impairment in learning for the animals was likely due to the arrangement of the compartments, and not an inherent difference in spatial abilities, as these same rats readily learned a subsequent discrimination in the radial compartments.

For practical reasons, different animals were used in the recording experiments and in the behavioral studies, and thus the link between our place cell and behavioral observations is not definitive. However, in both experiments the same apparatus was used, and in both the differences between the parallel and radial compartments were robust. Thus, the current findings are consistent with the view that the place cell representations underlie the disambiguation of similar local regions within a connected environment.

In the behavioral experiment, two out of six animals eventually learned the initial odor discrimination in the parallel compartments, though they took much longer to do so compared with the animals trained in the radial compartments. Further, the results of the task switch indicate that learning in the parallel compartments is possible for animals previously trained on a discrimination in the radial compartments. This suggests that the animals can disambiguate similar parallel compartments after extensive training.

How might the place cell representation of the parallel compartments support this? One possibility is that the subtle

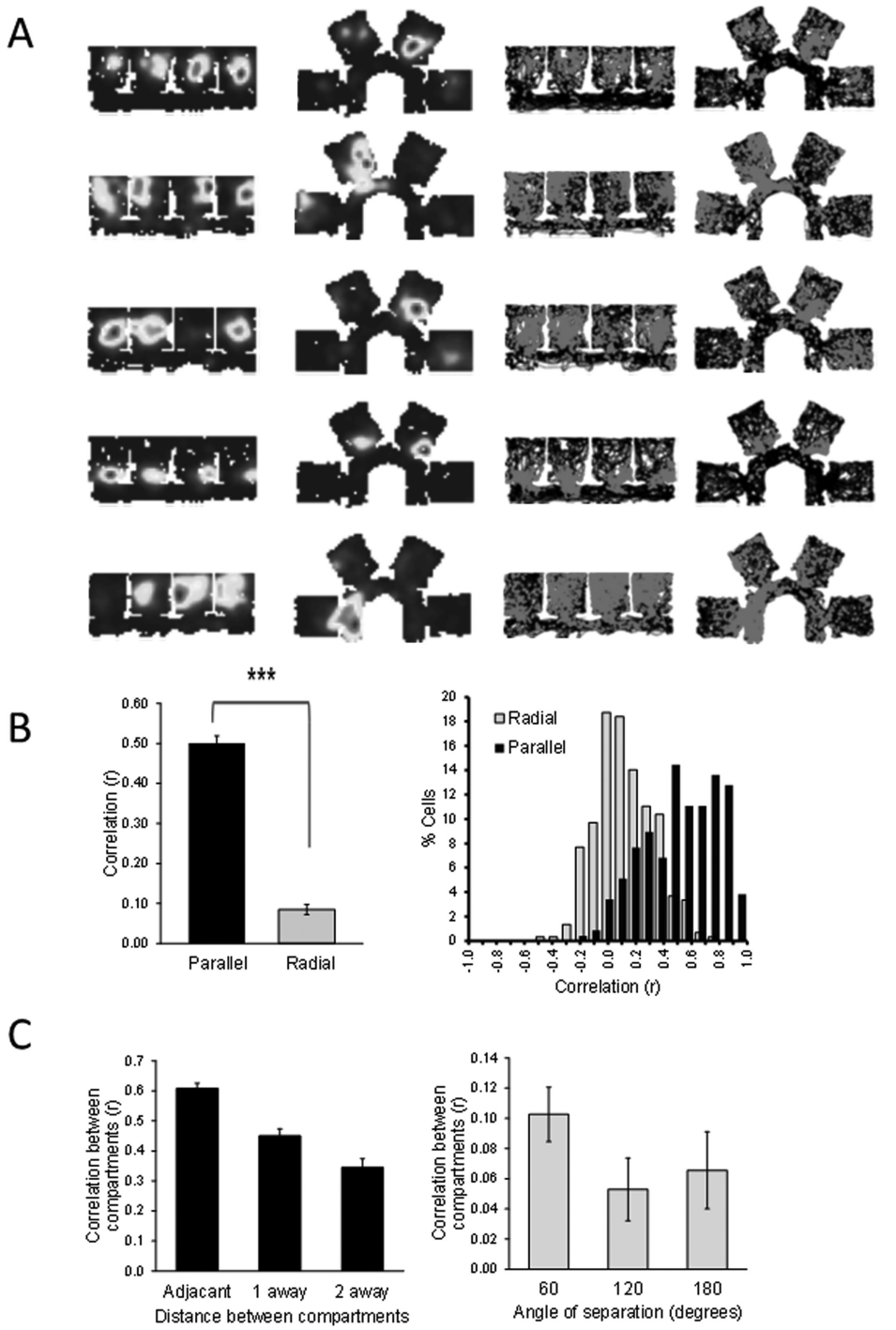

FIGURE 9. A greater amount of place field repetition in the parallel compartments compared with the radial compartments was observed in a separate set of animals, recorded in the absence of the cue curtain. A: Place cell examples in the parallel and radial compartments. B: A higher level of spatial map correlations was found in the parallel compartments, compared with the radially arranged compartments. C: Place field maps were less correlated the larger the linear or angular separations between compartments. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

degree of disambiguation between the parallel compartments observed in our place cell recording experiment is sufficient to support behavioral disambiguation. A second possibility is that stronger discrimination of parallel compartments by place fields might be evident with extensive experience. No changes in the degree of place field repetition were observed over the two-

week course of the recording experiment (Fig. 5D), but it is possible that more extensive experience, and/or explicit training on the odor-environment association task would have elicited a reduction in place field repetition in the parallel configuration of the environment. Indirect support for this comes from recent data by Carpenter et al. (2015), who found that grid cells showed repetition in parallel maze compartments initially, but that a global representation began to appear after about 15 training sessions. To the extent that grid cell firing may influence or be influenced by place cell firing, such a process might allow a shift from repeated local representations to a single, global representation.

Place Field Repetition Is Sensitive to Directional Orientation

A second finding of this study is that when different local compartments are oriented in the same direction, significantly more place field repetition is observed than when the local compartments are arranged at an angle to one another. Previous studies have shown that place cells (and grid cells) exhibit repeated fields across compartments with similar geometries that are in the same orientation as each other (Skaggs and McNaughton, 1998; Fuhs et al., 2005; Derdikman et al., 2009; Spiers et al., 2015; Carpenter et al., 2015). Other work has demonstrated that place cells show path equivalence in parallel alleyways of a W maze, and it is possible that this represents the same phenomenon (Frank et al., 2000). Together, these results suggest that place cells are strongly influenced by local cues including the borders of the compartment (O'Keefe and Burgess, 1996; Hartley et al., 2000), and that these exert greater control over place fields than any sense of linear path integration as the animal moves between compartments. Our data confirm this finding, as place cells showed high spatial correlations between the parallel compartments. However, in the current study, the spatial correlations between compartments decreased significantly as a function of the distance between them. This was observed both in Experiment 2 (when an extramaze cue curtain was present) and to an extent in Experiment 3 (when it was not present), making it unlikely that the distance information was derived from extra-maze cues. One possible explanation for this sensitivity to the distance between compartments is that the place cells access linear path integration information to differentiate between geometrically similar environments, but that its influence is subtle in comparison to that of local visual and geometric cues, and of angular information (discussed below).

The current results differ somewhat from an earlier study of Tanila (1999). Tanila found that when animals travelled between one box to an adjacent, identical box, the place cell maps in each box did not correlate with one another. However, in the Tanila study, animals moved from one box to the other through a removable doorway in the wall between the two boxes. Thus it is possible that the rats utilized this doorway, even though it was closed behind the animal, as either a source of orientation or as a distinguishing cue. Alternatively, information about their direction when entering each box (facing east in one case and facing west in the other) may have caused remapping between the boxes.

The results from the radial compartments suggest that place cells are sensitive to the angular orientation of the local environments. This is in agreement with Fuhs et al. (2005) who reported remapping between two identical boxes arranged at 180° to one another which animals walked between via a doorway connecting the two. Our results confirm and extend this finding in three ways. First, in the Fuhs et al. study, the animal walked between the two boxes via a doorway connecting them with each other. In the current study, the four compartments were accessed via a common corridor. Our data indicate that directional information allows remapping between otherwise similar local environments even when animals do not walk directly from one compartment into another. Second, the current data show that an angular separation between compartments of only 60° (the smallest separation tested) is sufficient to cause significant place field remapping (low spatial correlations compared with even the most distant boxes in the parallel condition). Third, the spatial correlation between compartments varied depending on the angle of separation between compartments, with larger angles of separation yielding lower spatial correlations. This suggests that directional information has slightly less influence on place cells when there is less mismatch between directional information and local geometry. However, as the spatial correlations were low at all separations tested, it is clear from the current data that directional information allows otherwise similar compartments to be disambiguated at the level of place cell activity. It would be interesting to test the limits of this further using even smaller angles of separation between compartments.

In these experiments, angular orientation could be derived purely from self- motion cues, by which the animal could maintain its inertial angular orientation as it moves around the environment (Fuhs et al., 2005). Alternatively, the animal's sense of direction in the four-compartment environment could be maintained by a combination of self-motion cues and external directional cues, including the orientation of the compartments relative to one another (which would be apparent when the animal is in the corridor connecting them; Muir and Taube, 2004; Dudchenko and Zinyuk, 2005; Fuhs et al., 2005), or from the orientation of the compartments or corridor relative to the polarising, white cue curtain.

The data from Experiment 3 show that even in the absence of the extramaze cue curtain, place cells show high levels of place field repetition in the parallel compartments, and very little place field repetition in the radial compartments, similar to the pattern observed when the cue curtain is present (Experiment 2). These data suggest that directional information derived from the animal's self-motion, and from the overall shape of the environment (relative orientation of compartments to one another and the corridor), are sufficient to support differential firing between compartments in the radial configuration of the environment.

The interpretation that place cells are sensitive to the angular orientation of local environments may be relevant to the findings of Paz-Villagrán et al. (2006). They found the place field maps of portions of a cylinder that was divided into three (with the insertion of a Y-shaped wall) showed no significant correlation to one another. Paz-Villagrán et al. argued that landmarks in one of the cylinder portions corrected the self-motion information in the remaining two, identical portions of the cylinder which contained no landmarks. Based on the current findings, an additional explanation for this finding may be that the place cells were able to differentiate otherwise identical local compartments of the cylinder because the animal's self-motion allowed it to recognise that the compartments faced different directions.

Finally, it may be speculated that place cell sensitivity to angular orientation arises from the head direction cell system, a known input to place cells (Zhang et al., 2013). A prediction that arises from this is that abolishing the head direction cell input would result in repetition of place fields even in compartments facing different directions.

SUMMARY

Previous studies have shown that place cells and grid cells show repeated fields in maze compartments that face the same direction within a room (Skaggs and McNaughton, 1998; Fuhs et al., 2005; Derdikman et al., 2009; Spiers et al., 2015). Our results imply that this repetition limits the animal's ability to tell local compartments apart. The observed sensitivity to angular orientation of both place cells and spatial learning suggests that directional information likely underlies the disambiguation of radially arranged environments and, presumably, the global representation of location.

Acknowledgments

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