Restructuring Of The Cognitive Map Under Environmental Search

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Abstract

Different types of cognitive maps exist in distributed but interconnected regions around the hippocampus, enabling flexible navigation. In this project we looked at how neurons in the brain represent spatial relationships when animals are searching in the environment. In contrast to previous researches, we found that neurons reflect animals' behavior more than the spatial relationships in the environment.

Introduction

One of the fundamental things that humans and other animals do is to find our way around the world. To do this, animals need to know where they are, where other things are, and the relationship between these places. But how does the brain enable animals to navigate?

In 1948, Edward Tolman proposed that there are internal structures in the brain that represent the relationships in the environment in the form of cognitive maps. This allows the animal to navigate in a much more flexible manner. In 1971, places cells were found in the rat hippocampus, in a subregion called CA1 (O'keefe & Dostrovsky, 1971). These cell spikes at specific locations in the environment, while remaining much less active at other positions. If looking at the populational activities of place cells, the exact position of the animal in the environment can be mapped out quite precisely. Based on the discovery of place cells and building on Tolman's cognitive map theory, in 1978, John O'Keefe and Lynn Nadel wrote the famous book *The Hippocampus As A Cognitive Map*. They pointed to the hippocampus as the center of a brain system that constructs and stores the cognitive maps.

In the years following the initial discovery of place cells, different forms of cognitive maps have been identified in distributed but interconnected regions around the hippocampus. Place cells were later confirmed by numerous studies and also found in mice (Rotenberg et al., 1996), monkeys (Ludvig et al., 2004), bats (Yartsev & Ulanovsky, 2013), and humans (Ekstrom et al., 2003). Head direction cells were discovered in 1984 by Ranck and his co-workers in rat presubiculum, a region that gets input from the hippocampal CA1 region and output to areas for directing motor output. These cells represent the allocentric heading of an animal independent of its location. In 2005, grid cells were discovered in the

entorhinal cortex (Hafting et al.), showing multiple firing fields tesselating the environment in a triangular manner, providing information of the distance and direction of traveling. Cells whose firing encode a certain distance to environmental boundary in certain allocentric directions - termed boundary vector cells (BVCs) - were initially hypothesized through computational modeling (Hartley et al., 2000), and were subsequently discovered in subiculum (BVC) (Lever et al., 2009) and entorhinal cortex (border cells) (Solstad et al., 2008). Neurons carrying other more complex spatial information were also discovered through years of research, such as the axis-tuning neurons in subiculum (Olson et al., 2016), the route cell in posterior parietal cortex mapping the position along a specific route (Nitz, 2006), the object-vector cells in MEC (Høydal et al., 2019), cells coding egocentric relationship to external items in LEC (Wang et al., 2018), and egocentric boundary cells in dorsal-medial striatum and retrosplenial cortex (Hinman et al., 2019; Alexander et al., 2020). These spatial codings supported by different types of cells in distributed regions form cognitive maps that can support animals' navigation and behavior in a very flexible manner. Because CA1 region is well-established for its place-specific activities, and because the relatively lack of research in areas subiculum and posterior parietal cortex in complex spatial tasks, we focused on examining the neuronal activity pattern of CA1, subiculum, and posterior parietal cortex.

These previous studies were mostly done in either well structured environments, like mazes and tracks, including prominent spatial structures readily sensible, or open fields, where there are only distal cues and environmental boundaries. But there hasn't been any task design where there are embedded spatial relationships, but those relationships can't be readily seen. For example, food caching is a very common behavior in birds and rodents. When an animal caches food for winter, it buries them underground in distributed and interrelated positions, but needs to retrieve them afterwards. Under such circumstances, how would its brain enable the animal to map out those hidden food sources and to locate them without seeing the prominent visual cues marking them? How does the brain represent spaces that aren't seen?

In this project, we designed a novel behavior task in which the rats need to use their knowledge of the relationships between reward locations to navigate and locate hidden rewards. Through looking at the neuronal activity pattern of CA1, subiculum, and posterior parietal cortex both through spatial and temporal/task-related perspectives, we found that this task resulted in a much less than normal level of spatial mapping in CA1, while showing more neuronal activities related to the behavior of the rats in tasks.

Results

Animals behavior indicated understanding of hidden reward relationships

To urge the animals to understand the spatial relationships between unseen objects, we designed a task that demands the animals to learn the relationships between three hidden rewards. The three rewards always sat on the three vertices of an equilateral triangle, so they were always separated by a fixed distance and angle from each other. While all three rewards were buried under the bedding thus could not be seen, one of the reward sites will be marked by a stick with a star (Fig. 1a). For each trial, the animal

needed to search for the rewards using their relationships with each other; only when the animal got to the precise location over the reward could it actually sense the smell of the reward and dig it out.

After a period of training, both animals we used could find out the three rewards consecutively without traveling out the possible range or being distracted, and could reach about 75% to 80% success rate (Fig. 1b). An analysis of stereotypical search behaviors also revealed the potential knowledge the animals might have for the reward positions, such as distances, angles between rewards and even alternative possible locations of rewards (Fig. 1c). To eliminate the possibility that animals entirely depended on olfactory cues from buried rewards to locate them, a probe trial was included in each recording where there was no reward but a flag cue. From analysing the places the rat visited (the occupancy) after digging at the flag position, it was obvious that the rate visited places near the flag location much more than further away from the flag (Fig. 1d). This proved that even without olfactory cues, the rats would still search in a limited range around the flag but not searching every corner of the arena randomly.

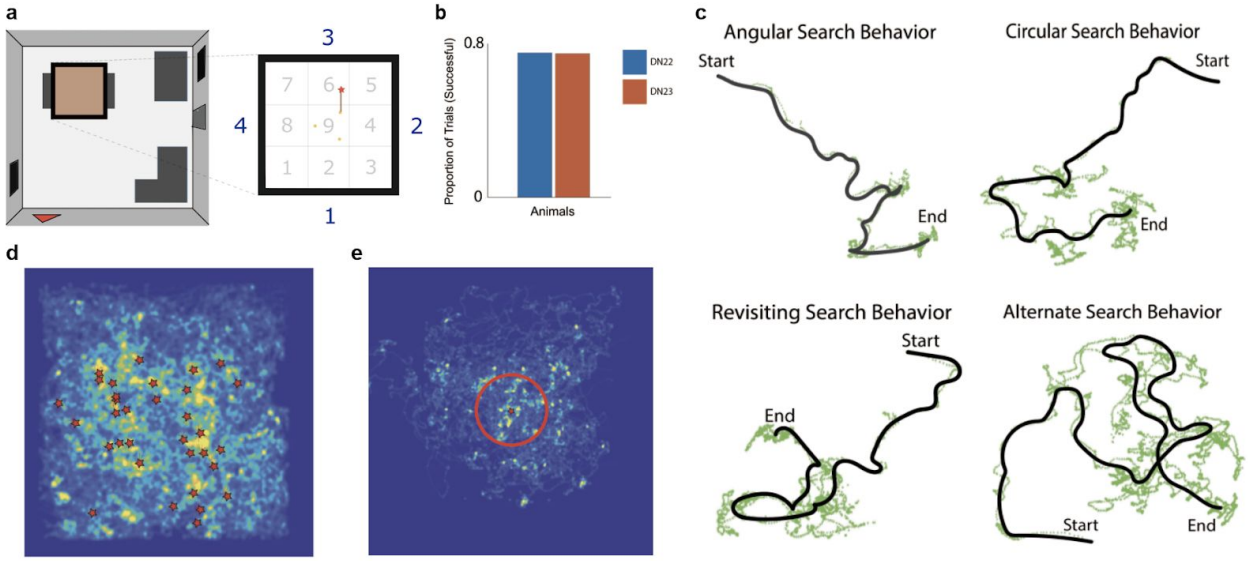

Figure 1 Animal training and behavior results. (**a**) Room scheme and reward positions in each trial. (**b**) Success rate of two animals. (**c**) Position tracking (green dotted trace) of animals during four stereotypical searching strategies. (**d**) Animal occupancy in arena perspective during probe trial (flag positions indicated by red stars). (**e**) Animal occupancy centered around the flag; the red circle has a radius as the side length of the triangle.

Spatial dispersion revealed less than normal place-specific activities in CA1

After gaining confidence that the animals acquired some knowledge of the relationships between the reward locations, we wanted to know in what frame of reference were the activities of neurons in CA1, subiculum, and posterior parietal cortex registered. While the CA1 region is well-known for its reliable place-specific activities, during the recording sessions we noticed less than normal level of place cell activities. Thus, we wanted to identify and quantify if the CA1 neurons in our task were still showing reliable place-specific activities. Place cells have clustered firings only in a small range of the

environment, which are the place fields. In order to identify the existence of place fields, we calculated the mean distances between high firing rate positions, terming this the dispersion score. Generally, place cells would be expected to have lower dispersion scores because of their location-specific firing pattern.

The dispersion score of CA1 neurons from our task was compared to a set of dispersion scores generated by another group of CA1 neurons under an open-field free foraging task. A majority of CA1 neurons are expected to show reliable place-specific activities under the open-field free foraging. CA1 neurons recorded under our task showed significantly higher dispersion scores (P = 0.0363, KS test), which indicated that CA1 neurons exhibited significantly less place-specific activities in our task's context (Fig. 2a). When comparing the dispersion score of each neuron to 100 scores generated from randomly shuffled spatial rate maps, CA1 neurons in our task also had significantly fewer neurons that would have a score lower than 5th percentile of random shuffled scores ($P = 4.5 * 10^{-4}$, KS test) (Fig. 2b). If comparing rate maps with low dispersion scores from two tasks (Fig. 2c), a neuron from our task showed a more dispersed firing range than a neuron in free-foraging, despite the fact that both had the similar dispersion score. These differences of dispersion scores from neurons under two different tasks revealed that CA1 neurons showed significantly less place-specific activities than normally expected. The well established allocentric cognitive map in CA1 seemed to be reconstructed under our novel environment searching task.

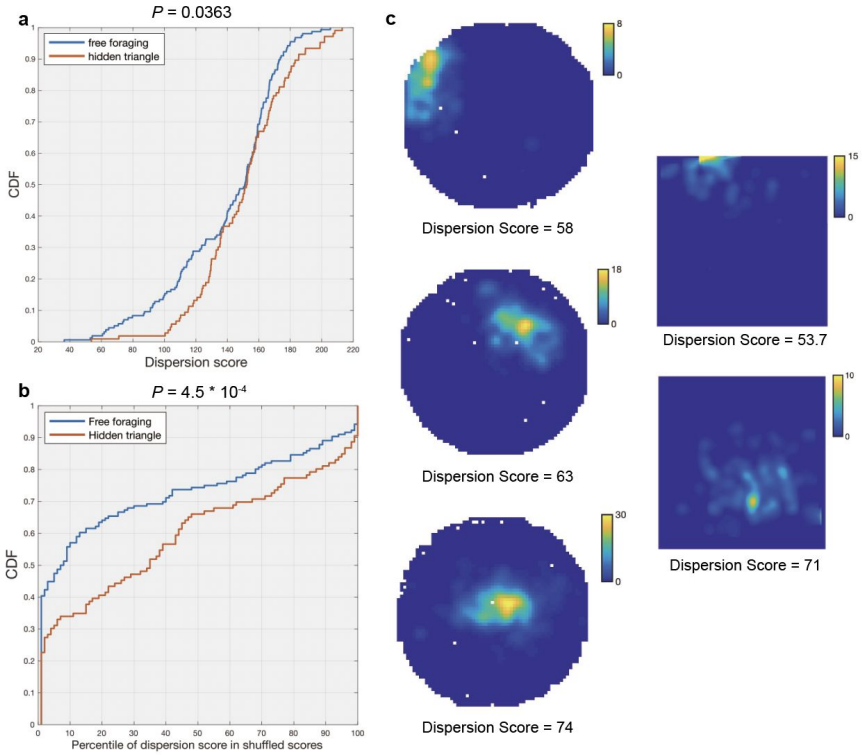

Figure 2 Dispersion analysis on CA1 neuron rate maps of current hidden triangle task compared to an open field free-foraging task. (**a**) Cumulative distribution function of dispersion scores of two tasks (P = 0.0363, KS test). (**b**) Cumulative distribution function of percentile of dispersion scores compared to scores after shuffling rate maps (P = 4.5 * 10-4, KS test). (**c**) Exemplary rate maps of neurons from two tasks (circle: free-foraging; square: hidden triangle task) having low dispersion scores.

Some mapping of the triangle space was observed in all three regions

After discovering that the CA1 region is mapping less about the allocentric space of the environment, we wondered if the neurons might be encoding some information about the repeated occurring ad behaviorally relevant triangle space, such as differentiating the different digging sites. In each trial, there would be three dig instances at the rewards - dig 1, dig 2, dig 3 - which were sequentially different; in addition, one of these digs would be a digging at the flag, which was also different from other digging sites since it was the only one marked by a visual cue. Neurons differentiating between these different digging categories might imply some encoding of the triangle space.

We took a 6 s window around each digging instance during which the rat was staying relatively stable and was in proximity of the reward site; thus, looking at the firing rate in this 6 second would also mean looking at activities taking place in a space surrounding the dig sites. We calculated a firing rate of each neuron during this 6 second window, and compared groups of firing rate at different digging categories. When counting the number of neurons in each region showing a significantly higher or lower firing rate at a certain digging site categories (thus potentially differentiating one digging category from others), for some digging categories there were more neurons than chance level that differentiated dig sites, found in all three regions recorded, but the number was not that many more (Fig. 3a). Extrapolating from this result, on the population level, the digging site, or the triangle space, could be mapped out, but it might be a weak signal. In conclusion, some level of differentiation of dig sites, or mapping of the triangle space, was observed in all three regions.

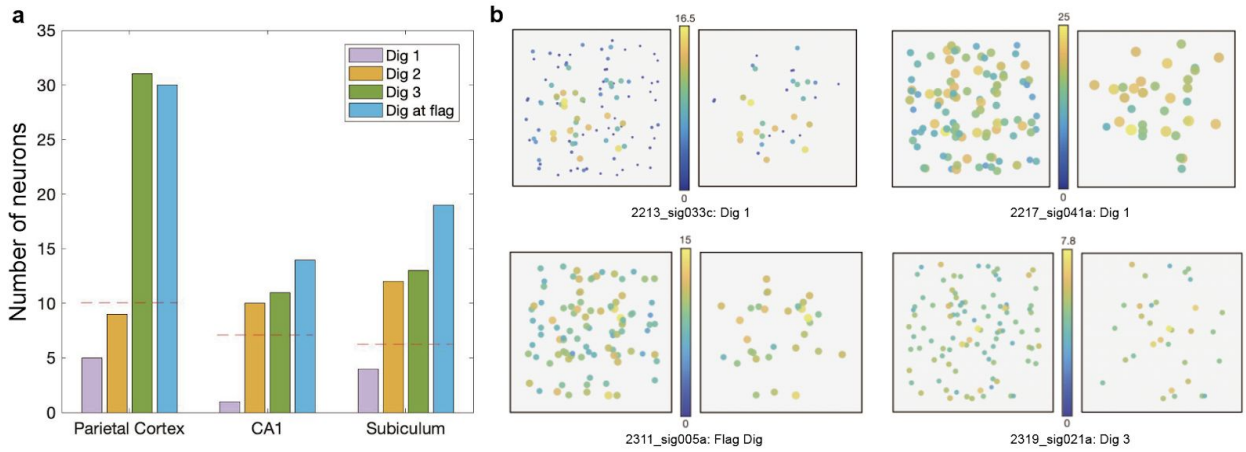

Figure 3 Firing rates around reward sites showing differentiation of dig sites. (**a**) Number of neurons in each region differentiating dig sites; red dotted lines indicate 5% of neurons in each region (parietal: $n = 201$; CA1: $n = 142$; subiculum: $n = 125$.). (**b**) Examples of neurons showing significantly higher firing rate around a certain dig site; (top panel: 2 neurons from CA1; bottom panel: 2 neurons from parietal cortex; left: firing rate surrounding all dig instances; right: firing rate only surrounding one type of dig site).

Neuronal activities in CA1 were related to task phases

This novel searching task entailed three bouts of searching behavior that was nearly identical. After looking at the potential mapping of the allocentric space and the triangle space, we switched to a

temporal perspective and looked at how neuronal activities might relate to the progression through the task or reflect different task phases.

By time-normalizing across each task phase, we could visualize how neuron firings were related to the major events of the task, including the beginning, the three diggings, and the end. All three regions showed heterogeneities in neuronal activities, with different neurons having different levels of activities for different task phases. For example, there were neurons having increased firing rate after each dig, having less firing rate only at the third dig (thus differentiating the third dig) (Fig. 4a), responding to the beginning of the task (Fig. 4b), or ramping up its activity through the progression of the trial (Fig. 4c). More analysis is needed to further categorize the activity of individual neurons in this task.

Through making correlation matrices of population activity vectors, we were able to see how similar or different the populational activities in each region were during different task phases. The subiculum and posterior parietal cortex populational activities generally had higher correlation across all trial phases (Fig. 4e & 4f). No obvious pattern could be discerned or concluded and more data might be needed to identify potential patterns in populational activities of these two regions.

For the CA1 region, we observed a noticeable checkerboard pattern in the correlation matrix - there were repeating high correlations and low correlations (Fig. 4d). The neurons seemed to have divided the task into two major components, one when the animal was engaging with the rewards (digging the reward out and eating it) and one when the animal was searching for the rewards. During the reward engaging phase, the neurons in CA1 as a population had higher correlation, which meant more similar activities, regardless of the sequential order of the rewards or task phases. Across all three searching phases, the CA1 region also had similar activities. This finding that the CA1 region showing activities corresponding to task phases or animals' behaviors instead of mapping out allocentric space was surprising and has not been shown in any previous research.

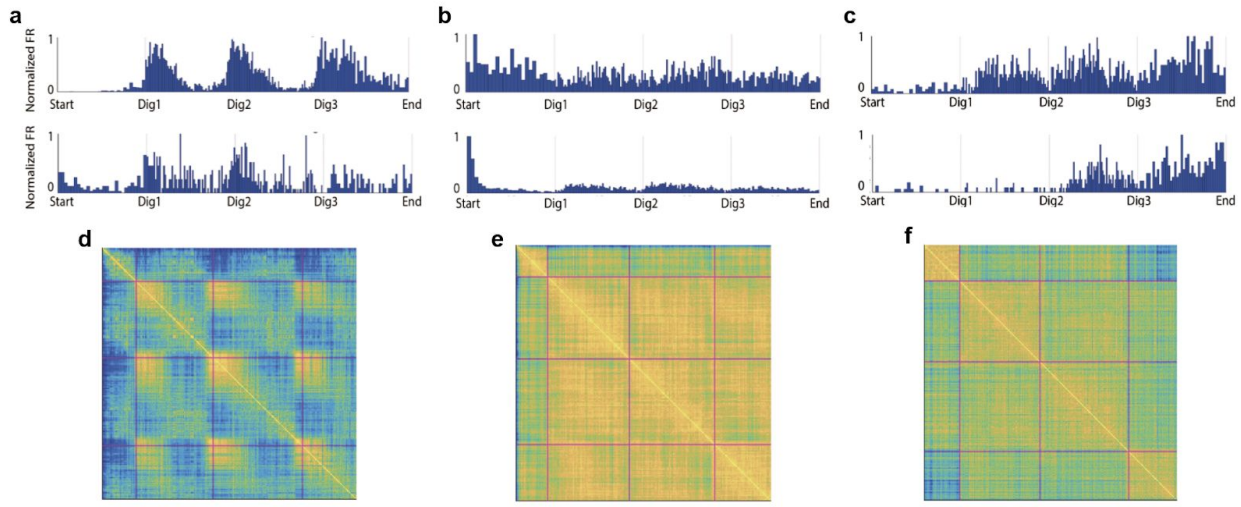

Figure 4 Individual and populational neuron activities in three regions related to task phases. (**a-c**) Time-normalized peri-event histogram of neurons from CA1, subiculum, and parietal cortex. (**d-e**) Correlation matrices of populational activities from CA1, subiculum, and parietal cortex; red lines indicate the time of digging at the reward sites.

Discussion

In this project, we showed how neurons, especially CA1 neurons, had activities related to task phases instead of space under a novel reward searching task. This was not expected from what we have known about CA1 before. Even though this project is still at its starting stage, and more data are needed to make conclusions about the activity patterns of neurons, the absence of spatial firing in CA1 is generally true.

The hippocampus has been the center of memory and spatial navigation, but it could also encode other types of information, such as tone frequencies, odors, or time (Aronov et al., 2017; Macdonald et al., 2013); to what degree the hippocampus codes for different types of information is still under active research. Thus, the hippocampal CA1 region being able to encode information about task phase and animal behavior, though was not frequently shown before, is not very surprising. However, previous research showing CA1 encoding information other than space were done in animals that were not actively moving around in space, thus partially eliminating changes in spatial parameters from animals' behavior. In our task, the animals were actively moving through space, but spatial activities were not observed. This begs the question of what was special in our environment navigation task that downplayed the spatial representation.

In Tolman's original paper proposing the cognitive map, he conceived that there could be two different types of cognitive map: one that is narrow and strip-like, only presenting a portion of the environment that the animal was trained on, and one that is broad and comprehensive thus can be adapted when changes are made in the environment. He also suggested that narrow strip maps could be induced when the animals are presented with an inadequate array of environmentally presented cues and through overdose of repetitions on the original trained-on path. In our case, a comprehensive map can be understood as the allocentric map that could potentially map out all positions in a space, while a narrow strip map could be a 'map' that's only presenting the animal's behavior but discarding the spatial context. Thus, the absence of visible spatial structures and cues together with the increased amount of training that was used to make the animals master this task could account for the presence of this narrow strip map instead of a broad comprehensive map.

Another possibility that I want to propose is that the hippocampus activities might reflect to a higher degree the information that is more relevant and necessary for the animal's behavior. Because experiments usually entail animals moving through space in order to perform a task, spatial information could be a major factor that is directing and influencing animal's behavior. But in an alternate situation, like our current task, where knowledge of the allocentric space is not highly relevant to the task's cognitive demand, space might be less represented while other information more necessary for memory and behavior will be encoded in the dynamics of hippocampal activities. Future research can further probe how the hippocampus and related regions can encode a diversity of information necessary for animals' behavior, and what triggers the change in the level of activities encoding each type of information.

Methods

Subjects. All subjects are adult male Sprague-Dawley rats. Rats were housed individually on a 12/12 light-dark cycle. During subsequent training and experiments, rats were food restricted and their weights were kept around 80% - 90% of free-fed weight to ensure physical health and optimal behavioral motivation.

Apparatus. Behavioral training and subsequent recordings were conducted on a square arena. The arena had an inner dimension of 83cm by 83 cm and an edge of 4 cm height and 4 cm width. It was filled with rat bedding of approximately 4cm deep. The arena was elevated 80 cm above the ground in the middle of the recording room. Between trials, rats were put in a high-walled pot that obstructed their view of the arena.

Behavior. All rats were handled and familiarized with experimenters for 2-3 weeks before training on the arena. After they felt comfortable being handled by people, they were put on the square arena and trained to search for halves of Honey Nut Cheerios embedded in the bedding.

Behavior shaping was used to gradually reach the target behavior. Initially, rats were trained to actively search for Cheerios and dig them out after being put on the arena. After rats showed active, careful searching and sniffing, we embedded three halves of Cheerios for each training trial. The positions of the three halves fell on the three vertices of an equilateral triangle with 25cm side length. The position of the 'triangle' relative to the arena is pseudo-randomly chosen. A star stick was also positioned on every vertice to help guide the rats locate the Cheerios. When the animals could go to the three stars and get the rewards consecutively, two star sticks were taken out, so there was only one star stick in each trial positioned at a location pseudo-randomly selected from the three vertices. After continuous training, as soon as the rats were put on the arena at a random start position, they were able to quickly dig out the first half Cheerio indicated by the flag, and use the first dig location to infer and locate the other two hidden reward locations.

Even though the rats did use olfactory cues in this task, we believe that the olfactory information was not the major factor determining where they go for searching. From the observation that sometimes even when they visited and sniffed the hidden reward location, they still could not locate the reward and dig it out, we deem that olfactory traces of the Cheerios were not able to provide them with cues for searching and navigating on the arena. The olfactory cues were only available when they got to the close approximation of the hidden reward location, but not strong enough to be available to guide their movements when they were further away. Another indication of olfactory cues not interfering with the searching came from the fact that the rats would generally not search at previous reward locations. In general, the old olfactory cue in the bedding, if there was any, would not interfere with animals' searching pattern. Half of the bedding was replaced by new bedding each week to make sure that the animals were still familiar with the arena but not being distracted by olfactory cues accumulated during the week. After the animals reached 75% success rate locating three reward locations consecutively, they were considered ready for the recording.

During recording, the animals ran 36 trials each day, which was approximately one hour and a half. The square arena was divided into 9 regions (a 3 by 3 grid) where the triangle shape might be, and

for each region, there were four possible rotations the triangle might have, ending up with 36 possible combinations of position and rotation. Each recording would go through all possible combinations in random order. Same with the end stage of training, for each trial there would be one reward position labeled by a star stick and two related hidden reward locations. After the rat finished finding all rewards, it was taken back to the pot, and the experimenter remixed the bedding near the old reward location and set up the new hidden rewards.

Surgery. Rats were implanted with tetrode arrays carried by customized microdrives either ipsilaterally or bilaterally to target PPC/SUB or PPC/CA1. Target locations were located relative to the bregma using a stereotaxic device and craniotomies were made over the target regions with the tetrode tips moving into the brain for about 0.5 - 0.8mm.

Recording. After surgery, the animals recovered for a week and were retrained for the task till they got back to optimal behavior. Across days of recordings, tetrodes were moved ventrally in short distance to collect neuronal data from different layers and regions of the brain.

Signals collected by the tetrodes were connected to electrical interface boards (EIB-16, Neuralynx), and were then sent to a series of amplifiers and a high pass filter. In the end, the signals were fed into a computer system running the Plexon SortClient software. After the primary neuronal activity data collection, waveforms were clustered through Plexon OfflineSorter software.

Besides the neuron firing data, animals' real time positions were tracked by the green and blue lights on animals' headstage, which were detected by a recording camera and analyzed by the Plexon CinePlec Studio. From the light tracking, animals' position coordinates, head directions, and velocities and accelerations could be calculated with high precision. The exact positions of the triangle reward locations were also tracked by briefly shining light right above the reward locations before each trial.

Histology. After anesthesia and injection of fatal-plus, the animals were perfused by phosphate buffer and then 4% paraformaldehyde. Brains were taken out and sliced into 40 μm slices and Nissl-stained to determine the actual targeting of each wire bundle and reconstruct the electrode track.

Neuron firing rate maps. From the neuron and tracking data, we constructed four types of rate maps with different reference frames. Firing rates of neurons were calculated by dividing the total number of spikes in each spatial bin by the total number of times the animal visited the spatial bin. The rate maps were then smoothed by a Gaussian filter.

A camera-frame (experimental room-based) rate map maps out the firing rate of a neuron in the original coordinates on the square arena. If a neuron reliably increases firing at a certain location on the arena, such as a place cell or a border cell, the camera-frame rate map will best visualize its firing pattern.

A "dig 1" centered rate map aligns all cases of the first dig of a trial in the center of the rate map and rotate/displace/reflect the dig 2 position coordinate so that the new dig 2 coordinates fall on the right side of dig 1 and the dig 1 and dig 2 coordinates fall on a line horizontal to x axis of the rate map. Dig 3 position coordinates are transformed according to dig 1 and dig 2 positions. If a neuron represents the sequence of action or spatial experience, then the dig map will be able to reveal the difference in firing rate at the three dig events.

A flag (the star stick) centered rate map set the flag position in the center of the map, and transforms the other two coordinates horizontally/vertically accordingly without rotation. The displaced positions of the non-flag locations formed a circle, the center of which was the flag position. If the star stick as a navigational landmark or as an object was represented in a neuron's firing rate, the flag map could be used to show such firings related to the object/landmark positions.

A second flag map is made from trials in which the animals visit the flag first, and the second and third dig locations are subsequently transformed in the same manner as the first flag map. This second flag map is mainly used to be compared with the flag 1 displacement map, to reveal if certain neurons show different firing patterns when the animal visits the flag first or not visiting the flag first.

Dispersion. This measurement was first used to quantify how sharply PPC cells were tuned to certain movement types (Whitlock et al., 2012). We modified the method and calculated the mean distance between the top 20% pixels with the highest firing rate in the occupancy filtered rate maps (pixels where the animals visited less than 3 times were excluded). The dispersion score was then compared to a group of dispersion scores generated by randomly shuffling spiking data.

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