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A Limited Positioning System for Memory

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Abstract

The 2014 Nobel Prize for Physiology or Medicine is an enormous triumph for John O'Keefe and May-Britt and Edvard Moser and an historic event for cognitive and behavioral neuroscience. Neuronal representations decoded from action potentials form a mechanistic bridge between brain and mind and demonstrate the continuity of psychology with biology and physical science. The cognitive map theory powered an ongoing, international research program inspired by Hebb (1949 The Organization of Behavior. New York, NY: Wiley) that showed the way toward linking specific patterns of neuronal activity to high level representation and processing. The prize celebrates a path that led from fundamental, philosophical questions about psychological space to enduring, scientific facts: place, head direction, grid, and boundary fields in the hippocampus, presubiculum, entorhinal cortex, and other brain circuits provide a cellular basis for spatial behavior, learning, and memory. By awarding this prize, the Nobel committee affirmed neuroethology and comparative psychology, marked the end of a chapter in one debate about the existence of animal cognition, and recognized cognitive neurophysiology. The "inner GPS" in the brain" demonstrates "a cellular basis for higher cognitive function." Animals represent, process, and use information defined by abstract relationships among items (O'Keefe and Conway, 1978) to guide flexible, goal-directed actions. Beyond raising the ontological status of "animal mind," the committee agreed that abstract mental representations can be investigated rigorously by recording single unit activity in the brain of behaving animals.

Keywords

hippocampus; episodic memory; cognitive mapping; comparative neuropsychology

INTRODUCTION

Neuronal representations decoded from action potentials form a mechanistic bridge between brain and mind and demonstrate the continuity of psychology with biology and physical science. The cognitive map theory powered an ongoing, international research program inspired by Hebb (1949) that showed the way toward linking specific patterns of neuronal activity to high level representation and processing. The enduring challenge is to determine how these medial temporal lobe (MTL) brain regions also contribute to the many nonspatial

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domains of learning and memory for which they are required. This article agrees that the functions of the hippocampus and other MTL structures can be described in terms of cognitive mapping and spatial computations but these maps compute both less and more than 2D spaces. The working hypothesis proposes that the representational space is multidimensional, with dimensions that are neither arbitrary nor unlimited but restricted to fundamental, ethologically defined “contexts” including aspects of space, time, motivation, and the rules and strategies used to achieve goals that are most relevant to a species’ niche. Future work will investigate how “place,” “distance,” “direction,” and “boundary” cells correspond to these dimensions of the cognitive map.

COGNITIVE MAPS, PLACE FIELDS, AND MEMORY

The Hippocampus as a Cognitive Map (O’Keefe and Nadel, 1978) proposed that context-dependent memory was represented by spatial maps and implemented in hippocampal circuits. The theory extended and helped specify a most general model of brain function, Hebb’s “conceptual nervous system,” which proposed mechanisms for representing, storing, and associating objects of perception (Hebb, 1949). The discovery of place fields (O’Keefe and Dostrovsky, 1971) identified hippocampal circuitry specifically as an excellent candidate for investigating high-level neuronal representations in a brain region already known to be crucial for recent memory (Scoville and Milner, 1957). Understanding the link between these two facts, the neuropsychology and the neurophysiology of hippocampal function, remains the central focus of dozens if not hundreds of laboratories around the world, including my own. In graduate school during the early 1980s, I had the enormous good luck to work with David Olton, who had just discovered that hippocampal lesions impaired recent memory for nonspatial items in rats (Olton and Feustle, 1981).

John O’Keefe visited the laboratory; during our first conversation, I asked him why he wanted to restrict the cognitive map to two-dimensional space and why not include other dimensions. With his jolly good humor fading to stern insistence, he argued that the map was two dimensional; seeing my abashed surprise, his kind and intellectually generous manner returned, and he explained his scientific strategy, something along the lines of, “My job is to make the strongest possible case for spatial mapping, and insist on rigorous evidence.” That approach has had enormous influence on the unfolding history of cognitive and behavioral neuroscience, a larger one than any arguments about theoretical interpretations.

But how do place fields contribute to memory in the everyday sense of the word, the kind lost in amnesia? People with brain damage restricted to the hippocampus have impaired memory for visuospatial information as well as verbal and pictorial information (Zola-Morgan and Squire, 1986; Rempel-Clower et al., 1996). The same layers of the entorhinal cortex in rats that have grid cells are among the first neurons lost early in Alzheimer’s disease and correlated with memory loss in people (Hyman et al., 1984). Medial temporal lobe circuits are needed to learn and remember events in place, as well as recent events in general whether or not the events are distinguished by or include locations.

The *Cognitive Map* argued that the hippocampus computes “an objective spatial framework within which the items and events of an organism’s experience are located and interrelated.” The book made two strong arguments and an important leap. The first argument was that places are represented within a spatial map, a Kantian, Euclidean, absolute space, an a priori framework that enclosed but did not depend on objects. The advantages of spatial representations included high-density storage, flexible addressing, and interference reduction, properties that are described now as the computational properties of distributed memory representations (Hinton et al., 1986). The map coded by hippocampal neurons performs spatial operations by computing angles between stimuli, the direction, and distance among these derived from movement through space and signaled by the constellation of distal cues and movement. Head direction (Ranck et al., 1987) and grid cells (Fyhn et al., 2004) discovered later provided the direction and distance signals required for spatial computations. Hippocampal processing integrates these signals and informs animals how to move from one place to another in the physical world. The second clam was that experiences and memories were contained, interrelated, and located in spatial context within hippocampal maps. The only “relational processing” by the hippocampus occurred within a Euclidean map of space and were based solely on plane geometry, computations relating the 2D location of items derived from the distance and direction among points on a plane. Spatial computations, context, and relational representations of items within events were restricted to this narrow, geometric sense of the word “spatial.”

The leap made at the end of the book generalized the mapping idea to a more abstract space: “…the central property of the locale system is its ability to order representations in a structured context.” By generalizing Euclidean geometry to more abstract spatial metaphors, O’Keefe and Nadel included visual imagery, language, and time to describe how the hippocampus contributed to memory for facts and events—episodic memory. The generalized cognitive mapping tied directly to memory and human amnesia, and both appeals to and promises to explain intuitive notions that we have about space: we are located somewhere just behind our eyes and represent ourselves in the world and in mind, traveling through time in a “memory space” (Tulving and Markowitsch, 1998). The intuitive appeal is helped by the abundant spatial metaphors in language: conceptual clarity is understanding, opinions are points of view, arguments are on or off target, etc. The spatial framework uses terms that can refer to plane geometry, serve as psychological metaphors, e.g., “in a bad place,” or “a problem space,” or describe formal operations, e.g., math functions that map domain to range.

Across species including rats the hippocampus is needed for nonspatial learning and memory, and its cells encode more than 2D locations (reviewed briefly later). Do MTL circuits map other dimensions and reveal “ordered representations in a structured context” other than space?

The generalized cognitive map can be viewed as a starting point for the “memory map” proposal by Eichenbaum and Cohen that the hippocampus represent items in context defined more broadly as events organized by associations in space and time (Eichenbaum and Cohen, 2014). The key point here is that the hippocampal “map” need not be absolute, Euclidian, or restricted to computations about 2D angles and distances. Place, time, goals, motives, and many types of rules and expectancies define “structured contexts” for organizing objects and events. The most unrestricted view of a “memory space” could suggest that higher dimensional maps allow events and objects to be related to one another by any types of associations in addition to spatial context (Eichenbaum and Cohen, 2014). The proposal here is that the hippocampus performs spatial computations on a species-specific multidimensional space that includes some aspects of place and time but not any arbitrary ordered representation. The dimensions are restricted to fundamental, ethologically defined “contexts,” biologically prepared reference frames that can either constrain or expand maps.

SPATIAL MAPS ARE LIMITED

Spatial maps are constrained by ethology, and navigation by rats’ hippocampus is typically restricted to planar representations normal to gravity. Rats have difficulty approaching spatial goals while clinging to a ceiling upside down; head direction coding by anterior thalamic neurons is disrupted until the animals return to ground (Gibson et al., 2013). CA1 neurons that fired in punctate place fields when rats explore the horizontal environment do not code altitude with the same precision while moving about a vertical peg board but fire in elongated, vertical “stripes;” while climbing ascending a helical “staircase,” the place fields fire in stacks, similar horizontal locations repeated through the vertical helix (Hayman et al., 2011). Grid fields also coded distance along the vertical axis in stripes on the pegboard and stacks in helix, providing little information about changes in altitude compared to horizon (Hayman et al., 2011). In contrast, bats forage and navigate through 3D space and their CA1 cells have 3D place fields (Yartsev and Ulanovsky, 2013). Even within the domain of 2D space, the cognitive map is shaped by natural history.

WHAT DIMENSIONS ARE CODED BY HIPPOCAMPAL MAPS?

I suggest that the expanded map includes at least space, time, motivation, and the rules and strategies used to guide behavior (Fig. 1). Each dimension helps frame crucial aspects of behavioral episodes and provides a “contextual” basis for representing both the similarities and differences among events as locations, distances, and angles among points in the space. If the hippocampus computes “location,” “direction,” and “distance,” among points in such an expanded cognitive map, then subpopulations of cells that code the relevant features analogous to head direction, grid, and place coding cells exist.

PARTIAL REMAPPING AND SPATIAL JOURNEYS

Hippocampal neurons encode multiple relationships among subsets of environmental cues. When subsets of local and distal controlled cues are rotated relative to one another providing two reference frames, simultaneously recorded CA1 neurons have place fields that “follow” the different cue sets, showing “partial remapping” (Knierim, 2002; Shapiro et al., 1997). Rather than indicating a single location in a global spatial map, hippocampal neurons indicate the relative location of the rat to two different sets of stimuli. If the cues within one set are interchanged so that their new locations do not correspond to a planar rotation, the partial remapping includes individual neurons that respond to new subsets of the local and distal cues, suggesting that the hippocampal computation is closer to “fragment fitting”

(Worden, 1992) than a global map of the environment. Along with the spatial distances and directions signaled by medial entorhinal grid cells, the hippocampus receives powerful input from lateral entorhinal cells that encode local objects (Neunuebel et al., 2013), and subsets of both inputs can control CA1 activity.

Hippocampal neurons also distinguish among identical places when they are between specific starting points and goals. Active CA1 ensembles recorded before the choice point of a maze distinguish future goals (prospective coding) and the origin of journeys before the choice point (retrospective coding) (Frank et al., 2000; Wood et al., 2000; Ferbinteanu and Shapiro, 2003). Although specific task parameters influence the extent to which these “splitter” responses occur (Bower et al., 2005; Griffin et al., 2007), they are highly reliable when individual trials are marked by distinct beginnings and ends. Unlike a GPS that presumably represents locations along a particular route identically independent of the start and goal of the journey, the rat hippocampus distinguishes spatially overlapping but temporally distinct episodes.

TIME CODING

We exist in space and time, the inescapable frame of being, and hippocampal neurons code both. Hippocampal neurons’ sensitivity to timing was first recorded during classical conditioning, when spiking modeled the temporal structure from the conditioned stimulus to response (Berger et al., 1976). Firing recorded during trace conditioning that requires hippocampal function also correlate with learning and model the conditioned response (Solomon et al., 1986; Moyer et al., 1990; McEchron and Disterhoft, 1997). Time alone seems to be sufficient for partial remapping of CA1 place fields even when tracking time is irrelevant to ongoing tasks, including when rats (Mankin et al., 2012) or mice (Ziv et al., 2013) simply explore the same spatial environment over several days. In contrast to the linear shift in CA1 place field populations over time, CA3 place fields recorded simultaneously were stable (Mankin et al., 2012). The extent to which place coding shifts over hours is specific to CA1 or varies across hippocampal circuits with task parameters is unknown.

Shorter-term time coding by CA1 neurons correlate with the delay between task phases in both spatial (Pastalkova et al., 2008) and nonspatial associative memory tasks (Kraus et al., 2013), even when movement speeds are varied (Kraus et al., 2013) or rats are immobile in a single location (MacDonald et al., 2013). By analogy to spatial remapping, some of the time cells “retimed” when the delay interval between sample and match changed, suggesting that the “temporal map” is not absolute, but signals the duration and content of event sequences (Kraus et al., 2013). Other time cells marked the start or the end of different delay intervals, as though coding the temporal boundaries common to the different episodes.

Lesions of CA1 or CA3 impair memory for recently presented odors after 10 sec (Farovik et al., 2010), suggesting that the time cell signal may be crucial for remembering recent nonspatial events. BOLD signals recorded in people suggest that hippocampus activity patterns in people also correlate with events in time (Ezzyat and Davachi, 2014; Hsieh et al., 2014).

Although some of the time cells may encode episodic boundaries, the cellular signals representing temporal direction, distance, and location have not been described directly. Hippocampal “replay” patterns suggests that CA1 population codes distinguish spatial sequences from the recent past toward potential futures as well as from current locations backward toward the origin of journeys (Foster and Wilson, 2006; Pfeiffer and Foster, 2013). The mechanisms that drive forward and reverse replay remain unknown, as are the consequences of these different firing sequences. Forward replay may strengthen synaptic links among cells that fire in sequence, while backward replay may weaken them, predicting that rewarded journeys should increase the proportion of forward replays (Raudies and Hasselmo, 2014). If time is represented by the hippocampus as a dimension of the cognitive map, then time cell replay should track temporally extended sequences across domains.

MOTIVATION CODING

The formation of cognitive maps was proposed to be motivated by “curiosity” rather than goal-directed action (O’Keefe and Nadel, 1978). Curiosity is not neutral, however, but a function constrained biologically to balance opportunity and danger, approach, and avoidance. Motivational factors, better described as a flexible and dynamic hierarchy of goals, can cause place field remapping and, therefore, may constitute another dimension of the cognitive map. Place fields recorded in a stable environment associated with foraging changed dramatically when the same environment was associated with foot shock and could not be explained by altered overt behavior (Moita et al., 2003, 2004). Cognitive maps distinguish between the same places when the meaning or significance of those places change.

Less-dramatic but equally biologically salient factors such as food or water deprivation also cause place field remapping. Deprivation state defined an internal discriminative stimulus for rats performing a nonspatial associative memory task (Kennedy and Shapiro, 2004). In alternate sessions, rats were deprived of either food or water and trained to select a white cue box to obtain food or a black box to obtain water. The cue boxes along with a third unrewarded box were moved from trial to trial so that their spatial location could not be used to find the desired goal. Intact animals selected the box associated with their deprivation state, and rats with a dysfunctional hippocampal system did not. The rats with hippocampal lesions made errors by approaching the incorrect rewarded box but never approached the unrewarded box, showing intact visual discriminations. When presented with a choice between food and water, the intact rats and those with hippocampal lesions approached and consumed the deprived substance, showing intact discrimination of internal states. The impairment was associative: the link between the deprivation state and the cue signaling the desired goal was broken (Kennedy and Shapiro, 2004). Most CA1 neurons coded identical locations with different activity patterns during the different deprivation states, and the extent of the remapping was greater when the deprivation state-guided memory retrieval (Kennedy and Shapiro, 2009). If motivational factors are represented by the hippocampus as a dimension of the cognitive map, then hippocampal codes should track the valence of events (e.g., McKenzie et al., 2014).

STRATEGY CODING

Identical behaviors including spatial trajectories can be guided by different strategies, and although “knowing how” is associated with procedural or taxon learning that is independent of the hippocampus, strategic facts are a key feature of episodes along with place, time, and motivation: the “how” included with the “what, where, when, and why” of memories. I can navigate from home to work by car, public transportation, or bicycle, and each of these means indicate different places on a cognitive map despite their spatial overlap.

If cognitive maps distinguish between the same places when the rules and strategies concerning those places change, then CA1 activity should do the same. In fact, CA1 codes distinguish identical trajectories guided by different task strategies (Ferbinteanu et al., 2011). Rats were trained to perform two tasks in the same + maze, a spatial discrimination and serial reversals, and a cue-approach task in which the rats selected the goal by approaching a visual cue. The tasks and goals were switched several times daily across blocks of trials, and the rats performed accurately on all the discriminations. CA1 cells distinguished overlapping journeys in each start arm on the way to different goals and different goal arms after leaving the different start arms, showing “journey coding” (Ferbinteanu and Shapiro, 2003). The proportions of cells coding journeys were equivalent in the two tasks, showing that spatiotemporal sequence representations were coded by the hippocampus whether or not it was required for task performance. Most crucial here, however, was that CA1 representations distinguished identical journeys in the place- and cue-approach tasks (Ferbinteanu et al., 2011). A limitation of this experiment was that the rat was informed about the strategy by the presence of the cue, which was not present during place-approach trials. More recently, we found that CA1 representations distinguish strategies during identical journeys guided only by memory for that strategy. In this experiment, the rat was trained to either approach a place or a lit LED, and the rat learned the appropriate strategy solely by contingency. As before, CA1 ensembles distinguished the spatial- and cue-approach strategies despite making identical trajectories toward the lit LED (Fig. 2). If strategic factors are represented by the hippocampus as a dimension of the cognitive map, then hippocampal codes should track the strategies that guide behavioral episodes. Such “strategy” codes may be signaled by medial prefrontal cortex (Guise et al., 2014).

GRID CELLS AND COGNITION

Neurons in the dorsal medial entorhinal cortex fire in grid fields that represent distance and direction as rats move through the environment (Hafting et al., 2005), as monkeys scan visual scenes (Killian et al., 2012), and as people move through virtual reality (Jacobs et al., 2013). Blood oxygen dynamics measured by fMRI in people exploring a virtual reality showed entorhinal cortical activity varied with the direction and speed of virtual movement that varied sinusoidaly in 60° intervals (Doeller et al., 2010). The same study found homologous patterns in widely distributed brain areas including the prefrontal cortex, suggesting that neuronal activity organized in 2D grids could provide a general mechanism for representing similarities and systematic changes (distance and direction) among episodes informed by any pair of ethologically relevant dimensions, such as affiliation and power in a person's "social space."

SUMMARY

The most compelling implications of place, grid, and other location-coding cells are their computational functions as mechanisms for cognitive maps, contextual representations of an individual in their environment. Many of the most intriguing and mysterious features of place fields, e.g., their independence of individual cues but dependence upon cue constellations, their "pattern completion" and "pattern separation," can now be understood as relatively straightforward properties of distributed representations (Hinton et al., 1986). These content addressable memory systems are powerful computational devices based on linear algebra with proximity and distance, direction or angle, and boundary defined by an arbitrary number of dimensions. The number and type of dimensions coded by the hippocampus, a product of evolution, are biologically constrained, species typical, and likely an elaboration of olfactory systems that encoded more than one concentration gradient simultaneously. The discovery of the "GPS of the brain" marks the beginning of a research program to identify the full power and limitations of cognitive maps implemented in the distributed brain networks connected with the MTL in rats, monkeys, and people.

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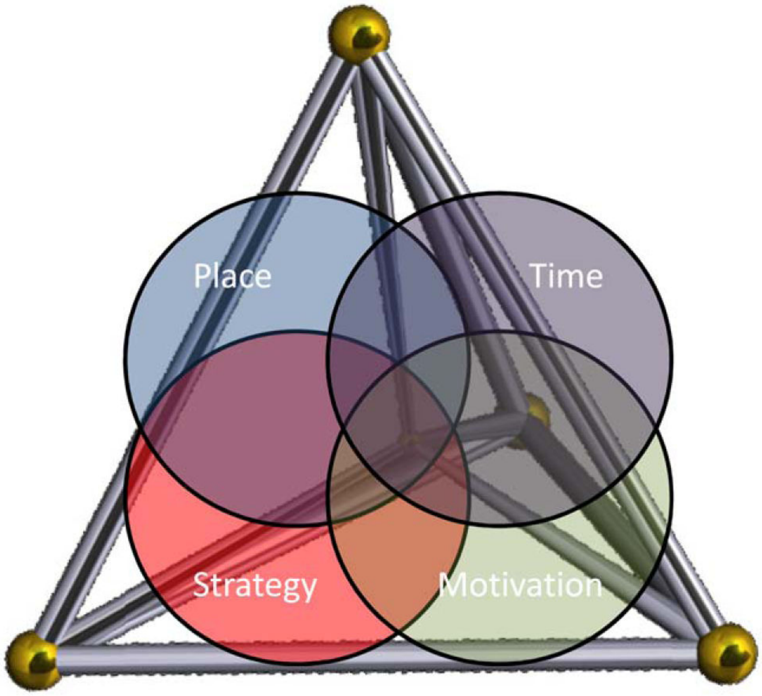

FIGURE 1.

A four-dimensional memory space. The Venn diagram is superimposed on a tetrahedron to emphasize the prediction that cells coding location, distance, and direction should exist for each dimension. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

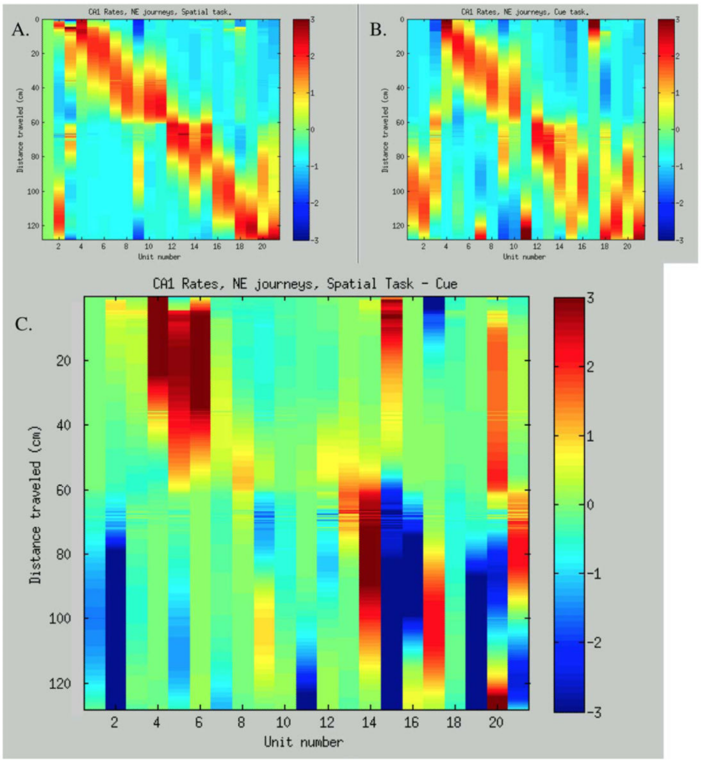

FIGURE 2.

Strategy coding by CA1 ensembles. An ensemble of 21 CA1 cells distinguish cue- and place-approach tasks during identical journeys. (A) Place approach: the neurons are ordered from left to right by firing rate and position from the beginning of the start arm to the goal (top to bottom, vertical axis). The start arm extends from 0 to 58 cm. The colors show standardized firing rates (*Z* scores). Cell 1 is solid green because it never fired in the place task. (B) Cue approach: the same neurons, order, and color scheme as in (A). (C) Place-cue difference plot: color scheme is different in firing rate between the tasks (Hz). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]