



Review

Coordinating different representations in the hippocampus

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ABSTRACT

The processes that organize different thoughts and memories, allowing the separation of currently relevant and irrelevant information, are collectively known as cognitive control. The neuronal mechanisms of these processes can be investigated by place cell ensemble recordings during behaviors and environmental manipulations that present cognitive control challenges to selectively represent one of multiple possible alternative estimates of location. We review place cell studies that investigate responses to manipulations that dissociate the environment into two or more spatial frames of locations, often times to test notions of pattern separation. Manipulations, such as continuously rotating the recording chamber reveal that the ensemble discharge in hippocampus self-organizes into multiple, transiently-organized representations of space, each defined by the subset of coactive cells. Ensemble discharge in the hippocampus alternates between separate representations of frame-specific positions on timescales from 25 ms to several seconds. The dynamic, functional grouping of discharge into transiently co-active subsets of cells is predicted by the animal's changing behavioral needs. In addition to identifying neural correlates of cognitive control in hippocampus, these observations demonstrate that the separation of neuronal activity into distinctive representations depends on ongoing cognitive demands and that what can appear as noise, deviations from receptive field tuning, can substantially be the result of these internal knowledge-guided fluctuations. These findings inspire a new perspective that should be taken into account when investigating pattern separation – a perspective that emphasizes changes in hippocampal neural discharge that are happening on a short timescale and does not assume that patterns of neural discharge are steady and stationary across the several minutes of the recordings.

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1. Introduction

To succeed in life people and other animals must not only acquire vast amounts of information about the world, but they must also be able to distinguish the information that is worth using and learning, from what is irrelevant. To be adaptive they must selectively use the appropriate information in appropriate situations. Mammals must react quickly to the changing environment and often it is necessary to multitask. The processes behind the ability to select and use appropriate information at proper situations, specifically the processes of goal-directed action selection, response activation and inhibition, performance monitoring, and

reward-based learning, are collectively called cognitive control (Posner & Snyder, 1975; Ridderinkhof, van der Wildenberg, Segalowitz, & Carter, 2004). While, in the past a lot of abundantly rewarded attention has been paid by the neuroscience community to the neural processes underlying single neural representations and the formation and storage of single memories, the neuronal processes that organize and manage multiple neural representations and memories are becoming an area of increasing research interest, in part because cognitive control inability is a prominent symptom in diverse forms of mental illness (Carter & Barch, 2007; Lesh, Niendam, Minzenberg, & Carter, 2011; Phillips & Silverstein, 2003; Uhlhaas & Singer, 2006, 2007). Subtle manipulations and monitoring of hippocampus function has implicated a role of hippocampus in cognitive control functions (Olypher, Klement, & Fenton, 2006; Wesierska, Dockery, & Fenton, 2005) and importantly, study of hippocampal physiology offers a neural

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system optimized for investigating the basic neural information processing mechanisms that may underlie cognitive control. Here we review recent progress in this research effort to investigate the hippocampus role in cognitive control.

The neural computations of pattern separation (increasing the difference between two similar input representations) and pattern completion (decreasing the difference between similar input representations) (Marr, 1971; O'Reilly & McClelland, 1994) have been traditionally studied by making discrete environmental dissociations such as using a circle-to-square morphable box (Leutgeb et al., 2005a; Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005) or double rotation experiments (Brown & Skaggs, 2002; Knierim, 2002; Lee, Yoganarasimha, Rao, & Knierim, 2004; Tanila, Shapiro, & Eichenbaum, 1997). Such studies are predicated on an assumption of representational stationarity, an assumption that we question. The standard analysis of firing fields assumes that the responses of cells will be qualitatively the same throughout the experience of the recording session in a stable experimental environment. This implies that a cell's characteristic firing is appropriately captured by the time-averaged response of the cell. However, we observed representational switching indicative of pattern separation but the process is dynamic and multistable, in violation of the stationary assumption. This multistability is observed in standard place cell recordings but becomes especially apparent during environmental dissociations that are continuous.

2. Early studies – assessing the organization of distinct hippocampal representations by manipulating independent sets of landmarks between experimental sessions

After the discovery of hippocampal place cells – principal neurons with a location-specific organization of discharge (O'Keefe and Dostrovsky, 1971) – an elegant method of constructing firing rate maps was used extensively to characterize place cell spatial discharge properties (Muller, Kubie, & Ranck, 1987). A firing rate map is created by computing for each location that was visited, the average firing rate of the neuron. A firing rate map averages the activity of a cell over the entire recording session, which typically lasts several minutes. The tacit assumption is that the activity in each location is appropriately represented by the session-averaged firing rate. The method was immensely successful and was instrumental for discovering many fundamental properties of place cells, and to this day shapes the way experiments are planned and data are analyzed and interpreted. This way of analysis and data presentation is implicitly oblivious to processes that might be occurring on short time scales, relative to the several minutes it takes the animals to visit most locations in the environment. Partly due to the success of this method, hippocampal place cell activity was often implicitly considered to be a system that does not change spontaneously on a short timescale. It was assumed that the place cells respond to the location of the animal (or other task-related parameters) essentially the same way, at every moment of a recording session.

A number of studies investigated changes in place cell responses across subparts of experimental tasks, for example on inward and outward journeys on a radial arm maze (McNaughton, Barnes, & O'Keefe, 1983), or during cue-sampling and goal approach in odor discrimination tasks (Eichenbaum, Kuperstein, Fagan, & Naqode, 1987), and distinct phases of matching-to-sample tasks (Hampson, Heyser, & Deadwyler, 1993), as well as before and after moving a prominent visual cue (Sharp, Blair, Etkin, & Tzanetos, 1995; see reviews Redish, 1999 and Muller, 1996) or during different subparts of spatial alternation tasks (Wood, Dudchenko, Robitsek, & Eichenbaum, 2000). Some studies reported changes in firing that occurred in response

to changes in task within an environment (Markus et al., 1995), but the organization of these different firing patterns was rarely systematically studied on a the time scale of seconds, largely because of the emphasis on single cell firing fields as the unit of study. Notable exceptions are a set of investigations that pioneered studies of the representational dynamics of positional information in the discharge of place cell ensembles (Gothard, Skaggs, & McNaughton, 1996b; Gothard, Skaggs, Moore, & McNaughton, 1996a; Redish, Rosenzweig, Bohanick, McNaughton, & Barnes, 2000; Rosenzweig, Redish, McNaughton, & Barnes, 2003). Relatively few other studies reported changes in place cell firing within a session (Knierim, 2002; Knierim, Kudrimoti, & McNaughton, 1995; Tanila, Shapiro, Gallagher, & Eichenbaum, 1997), but again, with a focus on the session-averaged properties of the phenomena, rather than the dynamics of the potential changes.

Early studies that aimed at the question of how multiple representations are processed within the hippocampus were designed, performed and interpreted in the analytical framework that was established by session-averaged firing rate maps. A number of these early studies used a “double rotation” experimental design (Fig. 1A): To probe how the hippocampal representation reacts when two different interpretations of environmental landmarks are possible, the same set of place cells was compared in two recording sessions: in a standard session with two sets of landmarks present, and then again in a double rotation session with one set of landmarks rotated in one direction, and the other set of landmarks rotated in the opposite direction (Fenton, Csizmadia, & Muller, 2000a; Tanila, Shapiro, & Eichenbaum, 1997; Tanila, Shapiro, Gallagher, et al., 1997; Brown & Skaggs, 2002; Knierim 2002; Lee et al., 2004). The results somewhat varied depending on the details of a particular experiment, but they allow general conclusions. In the hands of Fenton, Csizmadia, and Muller (2000a), Fenton, Csizmadia, and Muller (2000b), who performed the smallest perturbation-like changes in the landmark composition, the place cell representation was distorted but remained cohesive, so that each cell's firing rate map responded to the position of both displaced landmarks. In most other experiments, the majority of CA1 place cells responded consistently, following one set of landmarks (Brown & Skaggs, 2002; Tanila, Shapiro, & Eichenbaum, 1997). But some of the CA1 cells responded independently of the majority (Shapiro, Tanila, & Eichenbaum, 1997; Tanila, Shapiro, & Eichenbaum, 1997) and a significant proportion followed the other (non-dominant) set of landmarks (Knierim, 2002, Fig. 1B). A stronger tendency for a consistent response across the population of cells was observed in CA3 than in the CA1 hippocampal subfield (Lee et al., 2004).

The question of multiple representations in hippocampal discharge was investigated by Gothard et al. (1996a) using a different strategy. They used a spatial task in which a rat in an open field started a trial in a box, looked for food located relative to two local landmarks, and then returned to the box at the end of the trial. The positions of the box at the beginning of the trial, the positions of the box at the end of the trial, as well as the position of landmarks marking the reward location were changed from trial to trial. This allowed the authors to study place cell representations of the rat's position in different reference frames: relative to the box's variable start location, relative to the box's variable end location, relative to the variable reward location, as well as relative to the rat's position in the stationary room. The authors observed hippocampal place cells responding to the room location, as well as cells discharging in relationship to the start-box, end-box and reward locations. Similarly, Muller and Kubie (1987) and Rivard, Li, Lenck-Santini, Poucet, and Muller (2004), observed cells responding to the rat's position relative to distal landmarks as well as cells responding in the vicinity of locally placed barriers. Overall these results show that in addition to the general tendency for a uniform across-cell

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