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Animal Spatial Cognition:

Comparative, Neural & Computational Approaches

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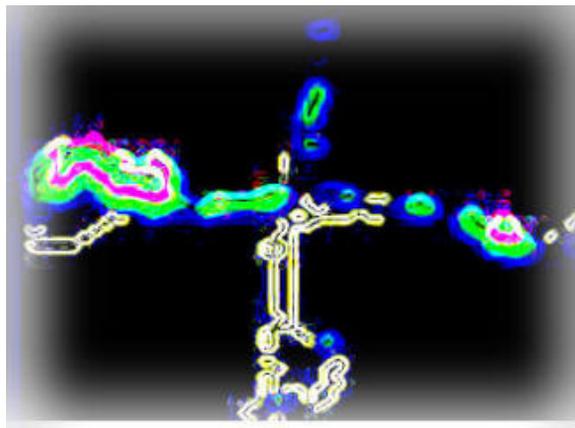
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In cooperation with Comparative Cognition Press
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October, 2006

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Directing Neural Representations of Space

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Abstract

The study of the neurobiology of spatial navigation provides a neural model for a complex form of learning that is likely to be highly conserved across evolution. Single cell recordings from rats as they forage through spatially extended environments have revealed that salient spatial, movement, and reinforcement information become incorporated into local computational networks across multiple brain structures in a context-specific manner. The hippocampus is thought to evaluate the extent to which the current spatial context is different from the one expected based on past experience. This information may be passed on to update long term memory representational systems. Also, hippocampal contextual information may inform behavioral expression systems of the frontal cortex and striatum such that appropriate behavioral responses and strategies are employed. Together, the continuous evaluation of, and responses to, changes in current sensory and reinforcement conditions allow animals to flexibly adapt to ever changing environmental demands.

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I. Introduction

The ability to accurately navigate one's environment is essential for many aspects of individual and species survival, from the procurement of food and water to the selection of mates and locating safe habitats. Consequently, it might be expected that the fundamental neural mechanisms underlying adaptive navigation have been highly conserved across the evolution of vertebrate animals (Mizumori, Canfield, & Yeshenko, 2005).

This possibility is supported by a wide range of empirical data showing that particular brain structures (e.g. the hippocampus, striatum, or thalamus) appear to make comparable functional contributions to spatial orientation or spatial learning by a variety of animal species (Cain & Malwal, 2002; Healy, 1998; Jeffery, 2003; Krushinskaya, 1966). Thus, efforts to understand the functional organization amongst brain systems during rodent navigation may provide a good model for discovering fundamental principles of

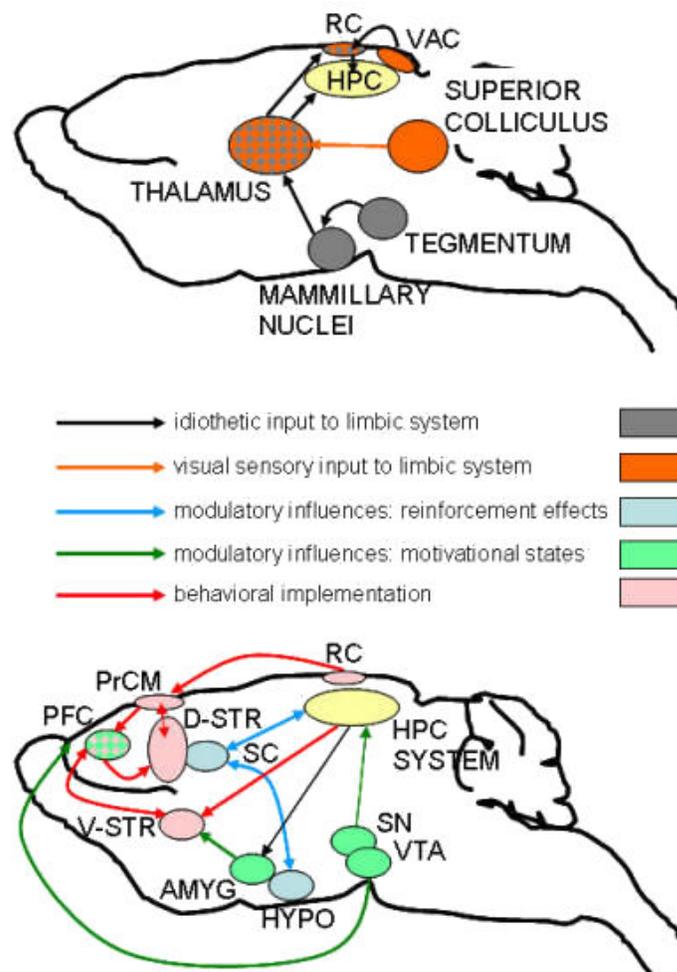


Figure 1. Working model of the neural systems that underlie adaptive navigation (colors = different components).

neural systems interactions in other species, including humans.

In order to study the neural mechanisms of experience-dependent navigation, it is useful to identify the likely essential elements of this complex behavior (Mizumori, Cooper, Leutgeb, & Pratt, 2000a). Functional elements that can be considered essential to adaptive navigation include the evaluation of external and internal sensory information, the integration of this sensory evaluation with past knowledge, the modulation of such spatial mnemonic integration by internal state information (such as motivation, stress, and hormone status) and the determination of the appropriate behavioral output. The evolutionary success of this rather complex navigational system may relate to the fact that each of the above essential functions can be accomplished in different ways. For example, multiple types of sensory information can be analyzed in parallel, thereby allowing animals to use different kinds of environmental information in an opportunistic and adaptive manner (Cain & Malwal, 2002; Healy, 1998; Jeffery, 2003; Krushinskaya, 1966) when environmental or task conditions change. This allows animals to readily switch to alternate sensory modalities to guide accurate navigation with minimal disruption (see [Bingman](#), this volume). As another example of the flexible operation of a functional element of the navigational system, response selection neural circuitry may engage different behaviors or behavioral strategies depending upon task requirements.

Early behavioral evidence demonstrated a crucial role for the limbic system (especially the hippocampus) in adaptive navigation. For example, hippocampal lesions consistently produce spatial learning deficits in rodents and monkeys, while nonspatial forms of learning remain intact (O'Keefe & Conway, 1978). More recent neurophysiological evidence supports the view that the essential functions underlying adaptive navigation require specific patterns of neural activation across a broad network of brain structures that extends beyond the hippocampus (see Figure 1). Therefore, in what follows, our focus on the neural mechanisms of rodent navigation begins with a discussion of hippocampal contributions, then a description of the broader neural circuitry underlying adaptive navigation. We also include a demonstration of spatial representation by fish telencephalon to demonstrate that the mechanisms underlying rodent navigation may reflect evolutionarily conserved processes.

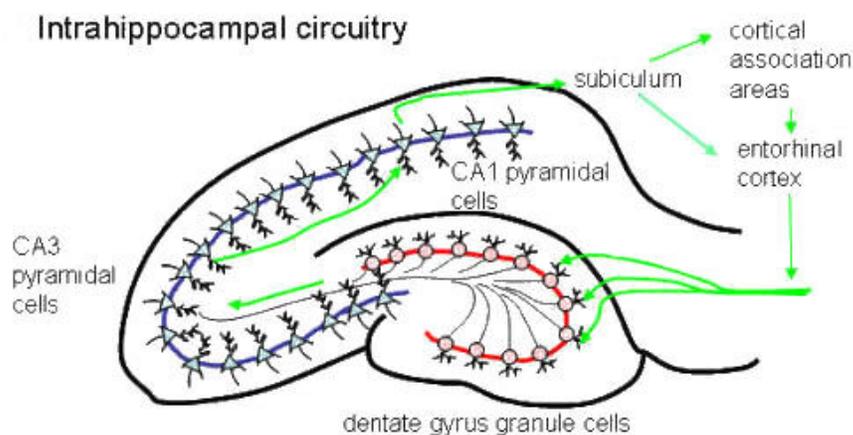


Figure 2. Hippocampal circuitry of spatial processing.

The first evidence for navigation-related neural representations came in the early 1970's with the descriptions of location-specific firing by hippocampal pyramidal neurons (O'Keefe & Dostrovsky, 1971; Ranck, 1973, Figures 2 and 3). These cells, referred to as place cells, showed dramatically elevated discharge rates when a rat passed through circumscribed locations, or place fields, in a fixed environment. Studies of the properties of hippocampal place fields have provided new insights relevant to the issue of the integration of internal and external sensory information, as well

as to the issue of how past knowledge impacts sensory processing that defines the current spatial context. These studies will be reviewed in [Part II: Spatial Context-Dependent Coding by Hippocampal Place Cells](#). [Part III Modulatory Influences on Spatial Mnemonic Processing](#) describes mechanisms by which hippocampal spatial context analysis may be modulated by internal state information. [Part IV: Spatial Context and Internal State Information Impact Ongoing Behaviors](#) will discuss possible ways in which behavioral output may be influenced by the neural processing of spatial context and internal state information. The results of this neural systems analysis of rodent navigation have revealed new fundamental principles of operation relevant to the issue of how neural systems of the brain mediate complex forms of learning. These insights are discussed in the final section.

II. Spatial Context-Dependent Coding by Hippocampal Place Cells

The discovery of place cells sparked intense electrophysiological investigations of spatial navigation. Consequently, this area of research has become one of the most prolific fields of study in the cognitive and behavioral neurosciences. It is now commonly reported in the literature that, depending upon the behavioral task, a majority of hippocampal pyramidal neurons recorded in a given test session will exhibit a place field. These place fields are considered to be quite reliable in that the same field is consistently demonstrated by a cell when it is recorded across multiple sessions within a constant environment. A population of place cells, then, could serve to generate a mental representation of the spatial layout of an environment, known as a cognitive map (O'Keefe & Conway, 1978; Tolman, 1948). Place fields have been recorded in different species, including the rat (Figure 3A), mouse, and most recently, the fish (Figure 3B; Canfield & Mizumori, 2004). Extensive work has been published on the sensory and mnemonic properties of hippocampal place fields, as well as their molecular and neurocomputational foundations (for reviews, see Best & White, 1999; Best, White, & Minai, 2001; Blum & Abbott, 1996; Hasselmo, Hay, Ilyn, & Gorchetchnikov, 2002; Jeffery, 2003; Lorincz & Buzsaki, 2000; McNaughton, Barnes, Gerrard, Gothard, Jung, Knierim, Kudrimoti, Qin, Skaggs, Suster, & Weaver, 1996; Muller & Stead, 1996; O'Mara, 1995; Poucet, Save, & Lenck-Santini, 2000; Redish, 2001; Sharp, 2002).

Place fields are controlled by visual information.

Because hippocampal place cells have been so extensively studied, a great deal is known about the factors that govern their firing. For example, the firing of place cells is not controlled by magnetic north or any other geomagnetic referent. Rather, place cells fire when subjects occupy a particular location relative to the arrangement of objects within an environment (i.e., allocentric space). This is perhaps best illustrated in experiments in which rats are trained to retrieve rewards from particular locations in an environment that contains a number of distinct visual cues distributed around the periphery (e.g., Lenck-Santini, Save, & Poucet, 2001; O'Keefe & Conway, 1978). The rat is then removed from the environment and the distal cues are rotated (e.g., 90 degrees clockwise). Remarkably, when the rat is returned to the rotated environment, the place fields are shifted 90 degrees in the same direction and rats approach a location shifted 90 degrees clockwise from the original position. Experiments such as these illustrate the powerful control distal visual objects exert over place cell firing.

In contrast, place fields recorded from intact rats are less likely to be controlled by local intramaze cues. For example, place fields remain fixed with respect to distal cues when the maze, and any intramaze cues, are rotated (Miller & Best, 1980; Olton, Branch, & Best, 1978). Consistent with this, rats need to see the distal cues of a familiar environment to reproduce the previously seen place fields. Place fields may disappear or shift to new locations if rats are brought into the room in darkness (Mizumori, Ragozzino, Cooper, & Leutgeb, 1999b; Quirk, Muller, & Kubie, 1990).

Place cells also encode self-motion information.

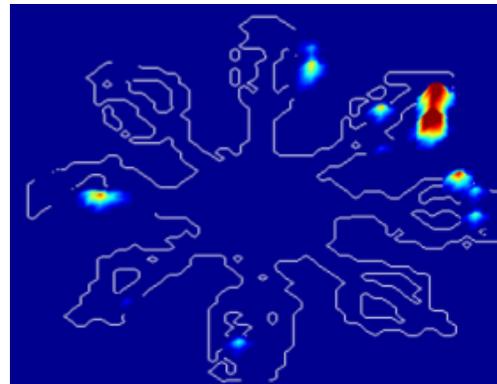
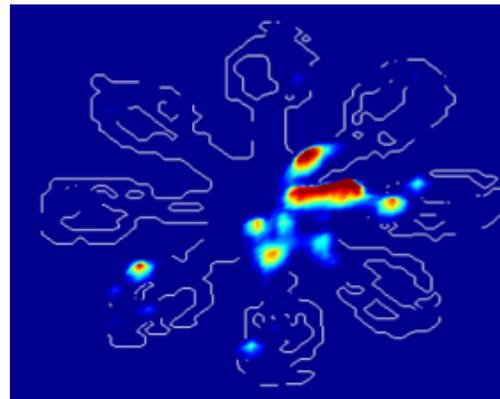
Although visual input provides strong control over place fields, this control does not appear exclusive. That is, it has been demonstrated that place fields can remain stable without visual

input. Although rats need to see distal cues upon initial entry into a familiar environment to generate the same place fields observed in prior recording sessions, place fields remain stable if the lights are extinguished after the rats have seen the environment (Markus, Barnes, McNaughton, Gladden, & Skaggs, 1994; Muller, Kubie, & Sappoff, 1991; Quirk et al., 1990). Blind and deaf rats exhibit place fields (Hill & Best, 1981; Save, Cressant, Thinus-Blanc, & Poucet, 1998). These results have led to the suggestion that the hippocampus may play a role in calculating the present position by keeping track of the previous movements through the environment, a process called path integration or dead reckoning (McNaughton et al., 1996; Mittelstaedt & Mittelstaedt, 1982; Whishaw & Gorny, 1999). The present location can be calculated by accounting for velocity and direction of movement, as well as the distance traveled from a known start position. Indeed, studies have shown that subjects are able to navigate using path integration, and that the navigational systems of the brain receive self-motion information such as proprioception (limb position), vestibular input and motor efference copy (for review, see Etienne & Jeffery, 2004).

Some of the directional and angular velocity information needed for path integration appears to be encoded in the anterior thalamus, subiculum, retrosplenial cortex (Mizumori & Williams, 1993; Taube & Muller, 1998; Sharp, Blair, & Cho, 2001). This circuitry is anatomically connected with the hippocampus and may provide self motion information to hippocampal neurons (Leutgeb et al., 2000). Indeed, the firing of many place cells depends on the rat's velocity and direction of movement through the place field (McNaughton, Barnes, & O'Keefe, 1983; Mizumori, McNaughton, Barnes, & Fox, 1989b). The firing patterns of inhibitory interneurons of the hippocampus, commonly referred to as theta cells because many of them fire synchronously with the theta rhythm, are also sensitive to the velocity and acceleration of translational movements by the animal (Buzsaki, 2002; Fox & Ranck, 1981; Ranck, 1973; Vanderwolf, 1969).

The use of external sensory information and path integration are not mutually exclusive. Without external sensory information, small errors accumulate over time and positional information derived by path integration alone becomes increasingly erroneous as subjects move through their environment. Consistent with this idea, spatial coding including location and directional information becomes disrupted over time in the absence of external sensory information, such as when the room lights are extinguished. Interestingly, the spatial coding of place cells and cells that code directional heading (so called head direction cells) is restored when subjects are allowed to view cues that can be used to determine the current location and orientation, suggesting that landmarks are

A. Rat Hippocampal Place Fields in Eight-arm Radial Maze



B. Fish Telencephalic Place Fields

used periodically to update path integration information. Thus, both idiothetic and sensory information contribute to efficient navigation (Etienne & Jeffery, 2004; Knierim, Kudrimoti, & McNaughton, 1998; McNaughton et al., 1996; also see [Brown](#)). In spite of these findings, the hippocampal role in path integration remains uncertain. Whereas some studies have found hippocampal lesions impair path integration (Maaswinkel, Jarrard, & Whishaw, 1999; Whishaw, McKenna, & Maaswinkel, 1997; Whishaw, Hines, & Wallace, 2001), other studies have found evidence for only an indirect hippocampal involvement in path integration (Alyan & McNaughton, 1999; Save, Guazzelli, & Poucet, 2001).



Figure 3. Place fields are a common type of spatial representation across vertebrate species. Click cursor on bottom panel to play video of recording from fish place cells.

Sensory encoding by place cells is guided by experience.

Memory processes appear to exert some degree of control over the sensory coding by place cells. As mentioned above, place fields persist in darkness after a rat views a familiar environment (Mizumori et al., 1999b; Quirk et al., 1990). In contrast, the place fields were disrupted when rats were introduced into the same environment in darkness. This pattern of responses suggests that the fields can be maintained by mnemonic representation of the visual environment rather than local intramaze cues. Also consistent with the view that memory guides sensory processing by place cells, place fields can remain stable after some or all of the cues have been removed (e.g., Markus et al., 1994; Mizumori et al., 1999b; O'Keefe & Conway, 1978).

Other studies have also shown that experience can alter place cell firing (Lever, Wills, Caccucci, Burgess, & O'Keefe, 2002; Shapiro & Eichenbaum, 1999; Wilson & McNaughton, 1993). For example, hippocampal neurons showed an experience-dependent expansion of their place fields with repeated passes through an environment (Mehta, Barnes, & McNaughton, 1997). Also, the location of place fields can change with learning. For example, shifting the location where rewards could be obtained to a new location in an environment was associated with a migration of the place fields toward the new goal location (Breese et al., 1989). Other studies have found similar experience-dependent migration of place fields with changes in goal locations (Hollup, Molden, Donnett, Moser, & Moser, 2001; Kobayashi, Tran, Nishijo, Ono, & Matsumoto, 2003; Markus, Qin, Leonard, Skaggs, McNaughton, & Barnes, 1995). The influence of prior experience on place fields illustrates the convergence of navigation studies with the well documented role of the hippocampus in learning and memory processes (Cohen & Eichenbaum, 1994; Eichenbaum & Cohen, 2001; Scoville & Milner, 1957; Squire & Zola-Morgan, 1991).

Hippocampal place cells encode more than visual spatial information.

Despite the remarkable correlation between neuronal firing and processing relevant to spatial navigation, it has become increasingly apparent that hippocampal function is not limited to spatial navigation. For example, hippocampal neurons exhibit robust responses to non-spatial stimuli such as tones, odors, and other task relevant stimuli (Eichenbaum, Kuperstein, Fagan, & Nagode, 1987; Freeman, Cuppernell, Flannery, & Gabriel, 1996; Kang & Gabriel, 1998). Within the hippocampus, the phenomenon of representational reorganization, often referred to as remapping, is often observed following spatial *and* nonspatial experimental manipulations. When subjects are placed in a novel environment, stable place fields exhibited in a previous environment suddenly shift to new and unpredictable (but stable) locations (Muller & Kubie, 1987). That is, the pattern of spatial representation across populations of cells undergoes reorganization. This phenomenon was originally labeled remapping because it appeared as though subjects were generating a new map for the new environment (Bostock, Muller, & Kubie, 1991; Kubie & Muller, 1991; Muller & Kubie, 1987; Wilson & McNaughton, 1993). However, this representational reorganization can occur

when the sensory environment has not changed and there is no obvious need for a new environment-based map. For example, Skaggs and McNaughton (1998) found that rats generated two different representations for separate, but visually identical environments. Representational reorganization can also be induced within a single test session by a change in behavioral requirements (Markus et al., 1995), strategy (Yeshenko, Guazzelli, & Mizumori, 2001), reward location (Smith & Mizumori, 2006), and even past or future behavioral trajectories (Ferbinteanu & Shapiro, 2003; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000).

Hippocampal place fields represent spatial context.

The notion of a hippocampal role in context processing is supported by an extensive literature indicating that hippocampal damage renders subjects insensitive to background contextual stimuli present in a conditioning environment (for reviews, see Anagnostaras, Gale, & Fanselow, 2001; Maren, 2001; Myers & Gluck, 1994). For example, subjects with hippocampal damage do not exhibit conditioned fear responses to contextual stimuli (e.g., Kim & Fanselow, 1992; Phillips & LeDoux, 1994). Moreover, when the contextual stimuli (e.g., odor, illumination, or visual background) are altered, intact subjects show a decline in conditioned responding, while subjects with hippocampal lesions exhibit no such decline. Instead, they continue responding as if the context had not changed (Freeman, Weible, Rossi, & Gabriel, 1997; Holt & Maren, 1999; Penick & Solomon, 1991).

Historically, 'context' has been thought of as the continuously present background stimuli present in any learning situation. However, several recent studies have shown that factors other than these background cues can influence place fields. For example, many hippocampal neurons exhibited dramatically different place fields when rats shifted from a random foraging task to a guided foraging task in the same environment (Markus et al., 1995). Hippocampal neurons have also been shown to respond differentially depending on past or future behavioral responses (Ferbinteanu & Shapiro, 2003; Wood et al., 2000). In these studies, rats were trained on a T-maze task. Remarkably, the same neurons exhibited different place fields, depending on which goal arm the rat was about to approach or which arm the rat previously had visited. Thus, the firing patterns underwent representational reorganization even though the physical environment had not changed. Findings such as these suggest that, as far as hippocampal coding is concerned, a 'context' can incorporate not only the physical environment, but also the cognitive and behavioral features of a given situation.

The finding that some of the neuronal firing patterns cannot be attributed to the spatial properties of the environment per se suggests that hippocampal function is not limited to spatial processing. Consistent with the suggestions of others (e.g., Nadel, Willner, & Kurz, 1985), it is hypothesized here that the hippocampus importantly contributes to a broader conceptualization of context processing. However, spatial knowledge may be a critical element of context processing since the spatial layout of an environment is an essential defining feature of any context; it may provide the framework within which detailed spatial and nonspatial information is processed. Perhaps the spatial referent is provided to the hippocampus via entorhinal cortical 'grid cells.' These cells show multiple place fields that appear as vertices of a tessellating triangular patterned array (Hafting, Fyhn, Molden, Moser, & Moser, 2005). The hippocampus, then, can be thought of as processing *spatial context* information during navigation (Mizumori et al., 1999b; Nadel et al., 1985).

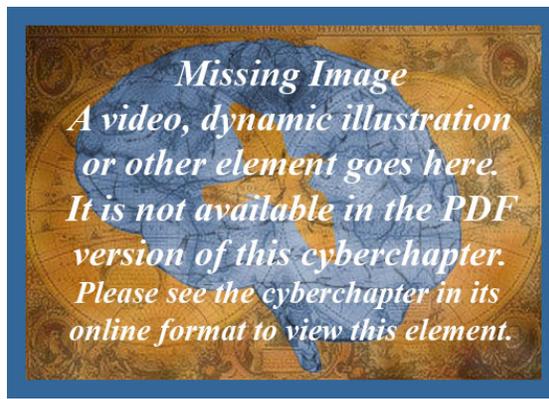


Figure 4 (Above). Place fields reorganize after a switch in cognitive strategy.
A) Place Strategy (Left); B) Response Strategy (Right): Hippocampal Cell 90705. Place mouse cursor on image to play video. These videos as well as Figure 5 videos may require MS Internet Explorer. You may need to download and install a video codec file from Techsmith.com before you will be able to see these videos. [Download and install this codec](#), and then reload the page if necessary.

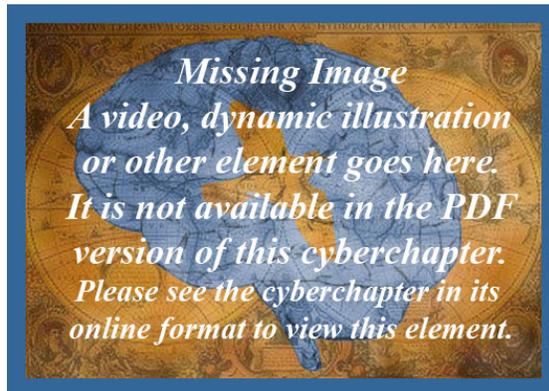
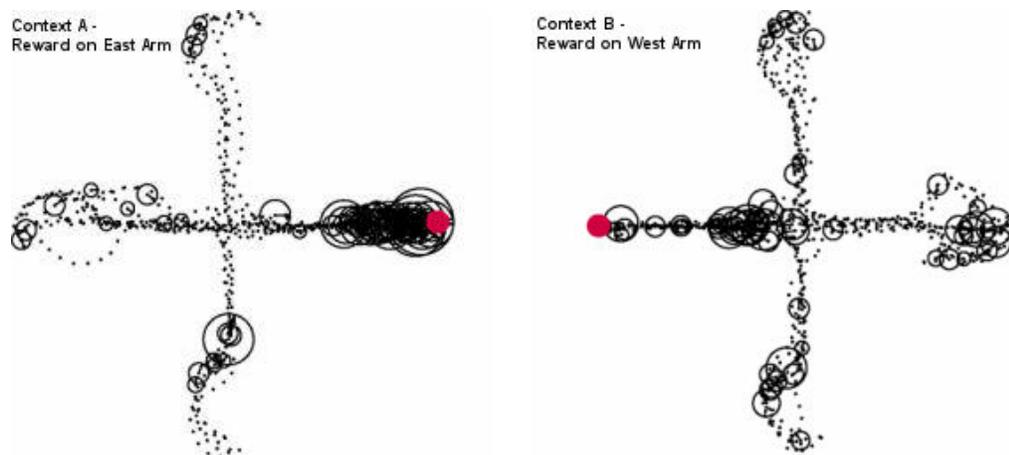


Figure 5. Place field differentially responds to changes in reward location during asymptotic maze performance. Place mouse cursor on each image to play video. (Please refer to the technical information in Figure 4 if you need help.)

Different places are frequently associated with different behaviors (e.g., foraging or predator avoidance). Therefore, it is particularly important to be able to determine that a given sensory environment is the appropriate context for a particular set of behaviors, whereas a different environment may be the appropriate context for different behaviors. Consistent with this idea is the fact that hippocampal neurons generate a new firing pattern (i.e., a new representational organization) when subjects encounter a new environment or when the behavioral demands (e.g., strategy, motivational state or reward location) change within the same environment.

Recent studies in our laboratory have provided considerable support for the idea that cognitive

and behavioral features of a situation shape the representation organization of hippocampal neurons. In one study, rats were trained on a T-maze to use a place strategy (i.e., go to a particular location) during the first part of a training session and they were trained to use a response strategy (e.g., turn right) during the second part of the session (Yeshenko et al., 2001). The place fields of many hippocampal neurons shifted to new locations when the rat switched strategies. This reorganization occurred even when the rat was engaged in the identical sequences of motor behaviors in the 'place' and 'response' trials (see Figure 4). Thus, hippocampal processing was not modulated by the subjects' behavior per se. Rather, it was modulated by the subjects' application of a particular behavioral strategy.

Another recent study found that the same kind of representational reorganization could occur across spatial contexts differentiated only by the locations where rewards could be found (Smith & Mizumori, 2006, Figure 5). In this study rats were trained to go to one location on a plus maze for a reward during the first half of a training session and to a different location during the second half of the session. As was the case in the previous study, the physical environment and the behavioral responses (turn right, go straight, turn left) were similar in the two session halves (i.e., contexts). Additionally, the appropriate behavioral strategy (i.e., to approach a given location for reward) was the same. Again, hippocampal neurons exhibited markedly different place fields depending on the spatial context. In this case, the spatial contexts were distinguished by the rats' knowledge of where rewards could be obtained.

Spatial context-dependent movement and other nonspatial firing.

The movement-related firing of hippocampal neurons has been interpreted as suggesting a hippocampal role in path integration (see above). However, the fact that hippocampal lesions have not consistently yielded impairments in path integration (Alyan & McNaughton, 1999) indicates that the role of the hippocampus in path integration remains uncertain. One possibility is that, as was the case with spatial firing, the movement-related firing of hippocampal neurons may reflect context processing. For example, neuronal firing may be positively correlated with the subjects' velocity in one situation (i.e., during the use of a response strategy) but uncorrelated or negatively correlated with velocity in another situation (i.e., during the use of a place strategy in the same physical environment; Figure 6). Importantly, in studies such as this one, the critical comparison takes place when the same rat is exhibiting the same pattern of locomotion. In this way, differential behavioral activity cannot account for the changed fields. An intriguing interpretation of this finding is that the hippocampal movement-sensitive coding does not reflect ongoing behavior per se, but it may include the learned behaviors (e.g., movements) relevant to a given spatial context.

The hippocampal role in evaluation of the spatial context.

The findings discussed thus far indicate that neural coding within the hippocampus involves more than just the spatial layout of the environment: the *spatial* firing properties of hippocampal neurons undergo reorganization when the behavioral or strategic requirements change. We have also found that neuronal responses to the reward and other task relevant stimuli depend on the context (Smith & Mizumori, 2006). Such spatial context-dependent coding may provide a means of binding together a location with the events, behaviors, and strategies that are relevant to that location. This kind of binding together of items, events, and places as part of an episodic memory has been proposed as a key feature of hippocampal function (Aggleton & Brown, 1999; Cohen & Eichenbaum, 1994; Eichenbaum & Cohen, 2001).

The involvement of the hippocampus in navigation, memory and context processing suggests that a critical function of the hippocampus may be the ongoing evaluation of the spatial context. It is suggested here that a new hippocampal context code is generated whenever subjects are exposed to a novel situation. With experience, the context code could become associated with the relevant memories, behaviors, and strategies that are appropriate for that context. When subjects are reintroduced to the environment, the context code is reactivated and the subject is able to retrieve the appropriate information and behaviors.

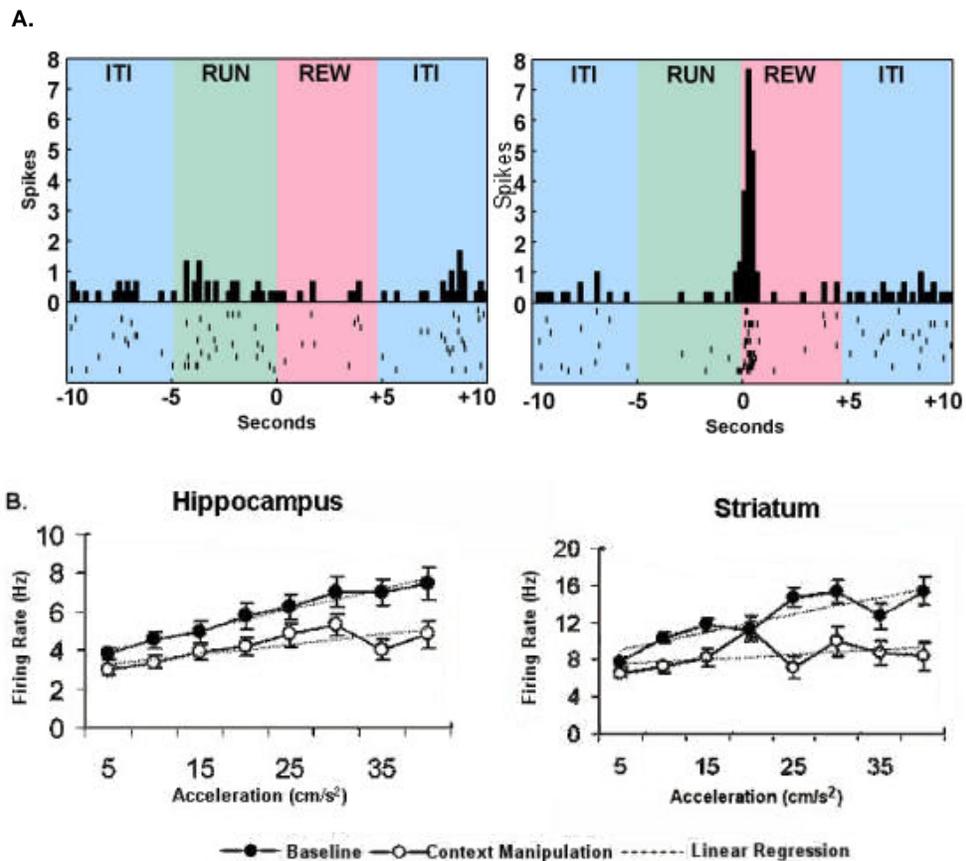


Figure 6. Egocentric neural codes may reflect learned behavioral responses. A. Reward-related firing before (left) and after (right) context change. B. Velocity and acceleration correlates vary with spatial context (Hippocampus and Striatum).

Reactivation of a learned spatial context code each time the subject enters a familiar environment would serve to further strengthen the connections, presumably in the neocortex, that represent long term memory of that context. Relatively small changes in the environment lead to partial reorganization of the hippocampal neural representations in that only a portion of the cells recorded show responses to the experimental manipulation (Knierim et al., 1998). However, when key aspects of the context change, such as the appropriate strategy or the reward locations, massive reorganization of the hippocampal code occurs and an entirely new code is generated. In effect, the hippocampus treats the altered situation as a new context. Perhaps hippocampus compares the learned code with the reorganized pattern to determine the extent to which a spatial context has changed (Mizumori et al., 1999b). A detected change could lead to the modification or updating of the cortical long term memory representations. This form of context coding would provide a flexible means of distinguishing the myriad of situations one could experience and then efficiently retrieving the information relevant to each one.

III. Modulatory Influences on Spatial Mnemonic Processing

An animal's interpretation of its current internal and external sensory environments depends not only on how it interacts with or behaves in the environment, but also on the current motivational state. When one is hungry, preferential attention will be directed towards cues and behaviors that might otherwise be ignored if one is in the same environment but is searching for an escape route. Traditionally, the effects of motivational states on behavior have been studied either by considering the consequences of varying hunger or thirst, or by studying the effects of appetitive or aversive events (e.g., most recently, Kennedy & Shapiro, 2004). The hypothalamus has long been considered central to the regulation of homeostatic systems such as hunger and thirst. The amygdala-prefrontal cortical circuitry has been strongly implicated in learning the association

between specific environmental cues and their reinforcement consequences (Alheid, de Olmos, & Beltramino, 1995), as has been the striatal-prefrontal circuit (Cardinal, Winstanley, Robbins, Everitt, 2004).

Homeostatic modulation of hippocampal processing.

There is substantial evidence that several subcortical structures exert powerful control over the excitability of limbic system neurons. The traditional interpretation of these subcortical influences has been that they somehow gate, or filter, cortical information arriving in the hippocampus (e.g., Winson, 1984). The gating hypothesis is supported by findings that electrical stimulation of numerous subcortical structures facilitates synaptic transmission through the hippocampus (Alvarez-Leefmans & Gardiner-Medwin, 1975; Assaf & Miller, 1978; Bilkey & Goddard, 1985; Dahl & Winson, 1985; Mizumori, McNaughton, & Barnes, 1989a; Segal, 1979). Of these, the medial septum appears to be strategically located to provide the navigation circuit with information concerning the animal's motivational state since the septum receives direct input from hypothalamic nuclei (Jakab & Leranth, 1995; Swanson & Cowan, 1979) and projects directly to the hippocampus (Figure 7). The hippocampal effects (see below) are mediated by powerful GABAergic and cholinergic septal afferents onto both pyramidal and nonpyramidal neurons within multiple subregions of the hippocampus (Freund & Antal, 1988; Freund & Buzsaki, 1996; Risold & Swanson, 1995).

Disruption of septal function, either by permanent lesions or reversible inactivation, impairs hippocampal-dependent learning (Harzi & Jarrard, 1992; Mizumori et al., 1989a; Winson, 1978) and the patterned activity of hippocampal neurons. In an intact, behaving animal, recordings of the hippocampal EEG show a rhythmic oscillation around the theta frequency (about 7-9 Hz). Compromising the integrity of the medial septum significantly attenuates the hippocampal theta rhythm (Mizumori et al., 1989a; Winson, 1978). Studies that record hippocampal single neuron activity during active navigation show that septal lesions or reversible inactivation prevent hippocampal place fields from responding appropriately to changing environments (Ikonen, McMahan, Gallagher, Eichenbaum, & Tanila, 2002; Leutgeb & Mizumori, 1999; Mizumori et al., 1989a). Other evidence shows that cholinergic input (presumably from the septum) significantly modulates hippocampal long-term potentiation (LTP; a synaptic model of plasticity). Also, it appears that there is an increase in acetylcholine release during new learning (Gold, 2003; Ragozzino, Pal, Unick, Stefani, & Gold, 1998). Together, these data indicate that the septum is in a key position to regulate hippocampal processing of cortical (i.e., sensory and/or mnemonic) information as well as the efficiency of intrahippocampal network functions.

One theoretical interpretation of the septal influence is that it identifies for hippocampus the appropriate internal state (or motivational state; Mizumori et al., 2000a). Relevant spatial context information could arrive in septum via the hippocampal CA3 efferent projection system (Fig. 7). Indeed, it has been shown that the lateral septum (the main cortical input area of the septal region)

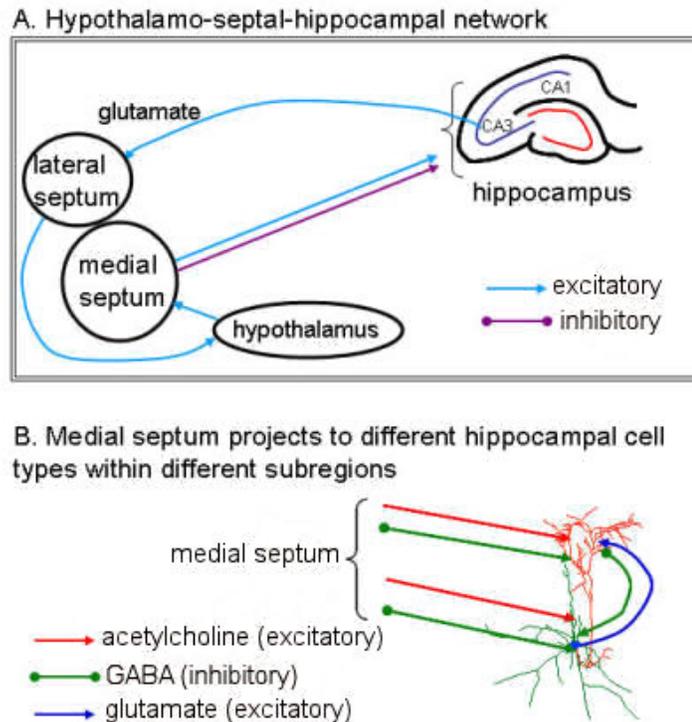


Figure 7. Septal regulation of hippocampal neural representation

contains neurons whose firing is correlated with the location of animals within their environment (Leutgeb & Mizumori, 1999; Zhou, Tamura, Kuriwaki, & Ono, 1999). That is, lateral septal neurons show place fields and, similar to hippocampal place fields, they respond to changes in the spatial context. Our current working hypothesis (Mizumori et al., 2000a) is that the lateral septum, via its extensive projection to various hypothalamic and mammillary nuclei, informs the motivational system of the brain about the current spatial context. In doing so, it may bias the firing properties of hypothalamic neurons to reflect the appropriate motivational state. Such a bias, in turn, could dramatically alter hypothalamic influences over efferent structures, such as the medial septum. Changes in medial septal activity, in turn, could have consequences for hippocampal neural plasticity. As a result, the hypothalamo-septal informational system could be thought of as reflecting the motivational perspective within which hippocampus should interpret sensory information. Effectively, such an operation may disambiguate, or selectively filter, current sensory input according to the current motivational state. Consistent with this view, it has been shown recently that the motivational state of an animal can importantly impact hippocampal-dependent learning (Kennedy & Shapiro, 2004).

Reinforcement-based modulation of hippocampal processing.

The effects of motivational states on limbic function have also been studied in terms of the role of reinforcement or incentive values of sensory cues in learning. Basolateral amygdala lesions impair fear conditioning (Kapp, Frysinger, Gallagher, & Haselton, 1979; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990), second-order conditioning (Hatfield, Han, Conley, Gallagher, & Holland, 1996), and conditioned place preferences (McDonald & White, 1993). The amygdala, then, may contribute to adaptive navigation by contributing knowledge about the incentive value of reward (Pratt & Mizumori, 1998). To test this hypothesis, rats were trained to discriminate locations on a maze that predicted the presence of large or small amounts of reward (chocolate milk). Some basolateral amygdala neurons showed elevated or reduced firing rates in anticipation of encounters with a large reward, while others showed elevated or reduced firing in anticipation of small amounts of reward. Control procedures demonstrated that movement or gustatory aspects of reward consumption could not account for the anticipatory firing. Given that the basolateral amygdala receives hippocampal information via the subiculum and entorhinal cortex, structures that show rather diffuse spatial codes (Mizumori, Ward, & Lavoie, 1992; Quirk, Muller, Kubie, & Ranck, 1992; Sharp & Green, 1994), it is likely that the amygdala does not receive a precise spatial context code. Also, since amygdala lesions do not result in consistent spatial learning deficits (Kesner & Williams, 1995; McDonald & White, 1993), the contribution of the amygdala may be conditional depending on the extent to which distinguishing incentive values is a salient feature of spatial context.

The prefrontal cortex may make a more direct contribution than the amygdala toward the evaluation of incentive values within a given spatial context. Permanent prefrontal cortical lesions in rats result in reliable deficits on tasks that require the flexible use of location information (Gemmell & O'Mara, 1999; Grannon, Save, Buhot, & Poucet, 1996; Poucet & Herrmann, 1990). Also, reversible inactivation of the prefrontal cortex impairs spatial working memory (Ragozzino et al., 1998; Seamans, Floresco, & Phillips, 1995). Attempts to identify the neural codes of the prefrontal cortex have led to the surprising finding of a paucity of spatial representation (Jung, Qin, McNaughton, Barnes, 1998; Poucet, 1997; Pratt & Mizumori, 2001). This result was unexpected because of the reported effects of prefrontal cortical lesions and because of the known direct connection from the CA1 region of the hippocampus to the prefrontal cortex (Jay & Witter, 1991). Instead, the most consistent behavioral correlate identified for prefrontal cortex neurons was reward-related discharge. Similar to amygdala neurons, prefrontal neurons changed firing rates in anticipation of encounters with rewards of different magnitudes (Pratt & Mizumori, 2001). The combined results of the lesion and neural recording studies are consistent with the view that prefrontal cortex may provide a prospective representation of the incentive value associated with different locations in a context-specific manner. This function contrasts slightly with that of the amygdala, which is considered to associate the incentive values with specific cues in a context-independent way. The prospective coding by prefrontal cortex neurons may impact neural response patterns in efferent structures, such as the striatum and motor cortex, structures traditionally thought to control ongoing voluntary movements.

IV. Spatial Context and Internal State Information Impact Ongoing Behaviors

The memory-guided evaluation of internal and external sensory information, and its subsequent modulation by internal state information, must ultimately come to impact processes involved in the evaluation of the consequences of behavior, and the selection of future responses. The latter two processes may exist as a functional unit since it is highly adaptive to be able to quickly modify one's action depending on the consequences of a previous act. The striatum and frontal cortex may work in concert for this purpose. It has been suggested that the striatum generates signals that allow animals to assess the extent to which behavioral errors are made. Such signals could be used by the cortex to modify ongoing behaviors, or select new behaviors, as needed (Houk, 1995; Schultz, 2002; Schultz, Tremblay, & Hollerman, 2003).

Striatal evaluation of response outcomes.

With specific reference to the case of adaptive navigation, Mizumori, Pratt, & Ragozzino (1999a), Mizumori et al. (20001), and Mizumori, Ragozzino, & Cooper (2000b) proposed that the striatum compares the extent to which the outcome of a recent behavioral response is consistent with that expected based on past experience within the same spatial context. The striatum may send different signals to the cortex depending upon whether a match or mismatch to the expected reinforcement outcome is detected. Such a 'response-reference system' should be useful for many forms of learning. The response-reference system interpretation of striatal function appears consistent with the findings of lesion studies and the pattern of striatal afferent and efferent connections.

Behavioral studies show an important role for the striatum in adaptive navigation. Striatal lesions have been shown to produce selective spatial deficits especially during new learning (Annett, McGregor, & Robbins, 1989; Floresco, Seamans, & Phillips, 1996; Gal, Joel, Gusak, Feldon, & Weiner, 1997; Ploeger, Spruijt, & Cools, 1994). There may be specialization for spatial processing within specific regions of the striatum, such as the ventral and the dorsomedial striatum. In contrast, the lateral striatum may selectively contribute to a different sort of learning, one that occurs more slowly (e.g. stimulus-response or response-response learning, e.g., Devan & White, 1999). The anatomical separation of different learning functions is likely related to the different patterns of afferent and efferent connections found in these areas. For example, the ventral and dorsomedial striatum receive extensive convergent input from multiple sensory and association areas of the neocortex and the limbic system (McGeorge & Faull, 1989). The lateral striatum, in contrast, has a distinct pattern of connections with sensory and motor areas of the neocortex (Flaherty & Graybiel, 1993). Computationally speaking, this topographically constrained pattern of input into lateral striatum places a restriction on the number of combinatorial patterns that can be produced, resulting in well-defined stimulus-response relationships. In contrast, the highly convergent pattern of input to ventral and dorsomedial striatum endows these regions with tremendous combinatorial power to produce the high degree of flexible (or contextual) processing needed to evaluate the reinforcement outcomes of ever changing spatial contexts (Mizumori et al., 2000b).

Although there is a clear and distinct topographical organization to the striatal afferent patterns, the intrastriatal computations appear relatively consistent across the structure. That is, the distribution of striatal GABAergic medium spiny projection neurons and cholinergic interneurons is rather homogeneous across the striatum. Further, these medium spiny neurons similarly possess a bistable membrane property that permits selective filtering of incoming information (Stern, Jaeger, & Wilson, 1998; Wilson, 1995). The synaptic efficiency of the spiny neurons is modulated by dopamine signals that are thought to reflect current reinforcement conditions (Houk, 1995; Schultz, Apicella, Romo, & Scarnati, 1995; Schultz, Dayan, & Montague, 1997). Thus, the different regions within the striatum may perform similar response-reference system computations on distinct types of information.

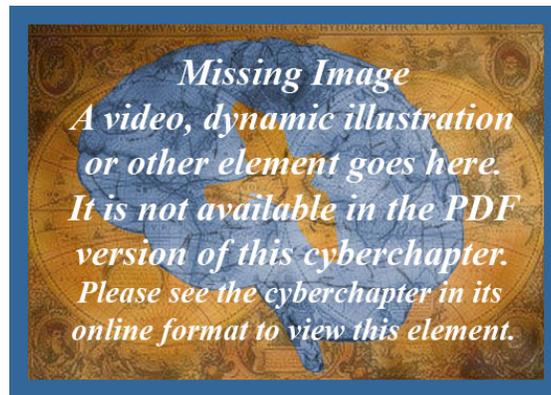
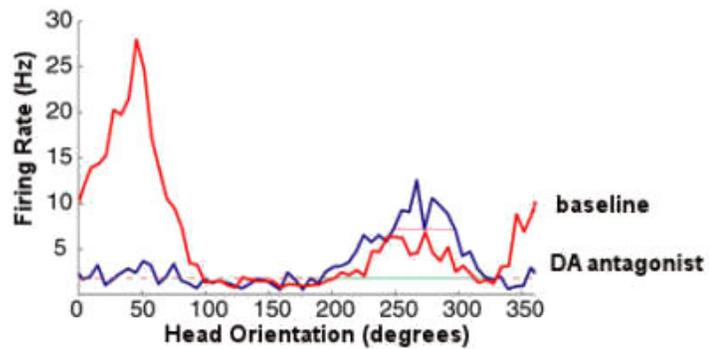


Figure 8. Dopamine regulation of striatal neural representation of directional heading.

A.) Animation of dopamine antagonism disrupting striatal head direction codes.
 B.) Animation of dopamine antagonism effects on striatal head direction codes.
 Place mouse cursor on images in Panel B to play videos.

Neurophysiological data are also consistent with the response-reference theory of striatal function. In behaving animals, dorsal and ventral striatal neurons exhibit changes in firing relative to specific egocentric movements (e.g., right turns or forward movement), reward acquisition, as well as an animal's location and directional heading within an environment (Lavoie & Mizumori, 1994; Mizumori et al., 1999a, 2000b; Wiener, 1993). The striatal place fields appear similar to hippocampal place fields (when tested in a familiar environment) in terms of field reliability and firing rates. However, striatal place fields tend to be larger than hippocampal fields. In addition to place cells, another type of spatial correlate of striatal cells is reflected by increased firing (by as much as ten times the baseline rate) when a rat's head is aligned with certain orientations in space. The preferred orientation of these 'head direction cells' remains constant regardless of the location of the animal in a fixed environment (for an example, see Figure 8). Striatal head direction cells show many of the same features as place cells in that the preferred orientations (e.g. north) can be shown to shift by an amount that corresponds with a shift in the visual environment, or the preference can shift randomly if the visual cues are changed sufficiently (Mizumori et al., 2000b). Thus, these cells are thought to signal context-dependent directional orientation, and not orientation relative to geomagnetic conditions or to a specific visual cue. One mechanism by which dopamine may contribute to reinforcement coding by striatum is to stabilize striatal neural representations. Consistent with this hypothesis, the stability of the directional selectivity of the head direction signal has been shown to be disrupted following injection of a dopamine receptor antagonist

(Figure 8). All of the behaviorally correlated striatal neuron types exhibit partial reorganization after a change in spatial context. That is, only a portion of the movement-correlated cells, for example, show a change in the movement correlate after the context change. In sum, then, the particular combination of neural representations found in striatum (e.g., movement, reward, place, or orientation), and the finding that all of these representation types appear context-dependent (Mizumori et al., 1999a, 2000b; Yeshenko, Guazzelli, & Mizumori, 2004) and exhibit partial reorganization were consistent with the response reference theory.

The PrCM of frontal cortex may direct hippocampal effects on ongoing behavior.

The evaluation of reinforcement outcome by the striatum is critically important for modifying future behaviors. The circuitry involved in the latter function likely involves neocortical operations that ultimately impact the output of the primary motor cortex. Recently, efforts have focused on arguably one of the more direct routes whereby limbic output may become integrated with the basal ganglia (i.e., striatal) and movement control areas of the cortex (Mizumori, Pratt, Cooper, & Guazzelli, 2002; Mizumori, Puryear, Gill, & Guazzelli, 2004a). This route extends from the hippocampus, to a posterior region of the cortex (the retrosplenial cortex), and then to the medial precentral cortex (Figure 1; variously referred to as PrCM, FR 2 or AGm, van Groen & Wyss, 1990; Reep, Goodwin, & Corwin, 1990; Swanson & Kohler, 1986; Vogt & Miller, 1983; Zilles & Wree, 1995). From the PrCM, information can move directly to the primary motor cortex (or FR1, Donoghue & Parham, 1983; Reep, Corwin, & Hashimoto, 1997; Zilles & Wree, 1995). The PrCM also projects directly to the dorsal striatum (Reep, Corwin, Hashimoto, & Watson, 1984; Reep & Corwin, 1999; Sesack, Deutch, Roth, & Bunney, 1989; Zheng & Wilson, 2002). Thus, the PrCM appears to be strategically located to contribute to the integration of the basal ganglia and frontal cortical movement control systems in a hippocampal (or context)-dependent way.

Initial investigation of the relevance of PrCM function to experience-dependent navigation included characterizing the behavioral correlates of PrCM neurons in rats performing a spatial maze task, testing the spatial context-dependency of these neural representations, and then testing whether PrCM neural representations are affected by the removal of limbic input from the retrosplenial cortex. It was found that the PrCM contains neural codes for directional heading, a variety of egocentric movements, and different reward conditions. These codes were demonstrated to be context-sensitive in that the behavioral correlates were significantly altered by changes in the visual spatial environment. For example, head direction cells appeared to shift directional preferences, or lose their directional firing property altogether, when the lights were turned off during the performance of a familiar spatial working memory task. Comparable alterations in firing correlates were observed for egocentric and reward PrCM neurons after changes in the visual environment. Thus, PrCM neural representations appear to be sensitive to the same kind of context information as hippocampal neural representations. Finally, a significant number of PrCM head direction and egocentric movement cells showed dramatic changes in their behavioral correlates after the retrosplenial cortex was temporarily inactivated by microinjection of a local anesthetic (tetracaine). It appears, then, that even though the PrCM can be defined anatomically as a motor system structure, it is functionally connected with the hippocampal system. As such, it may play a pivotal role in mediating hippocampal effects on ongoing behavior.

One interpretation of PrCM function is that it contributes to the determination of future behaviors, perhaps by computing response intentions, in a context-dependent way. The fact that the PrCM is rather uniquely situated to pass on movement intention information to both the basal ganglia and motor cortex suggests that it is in a position to gate relevant information depending on whether or not the spatial context has changed. If a context change has been detected by the hippocampus, there may be preferential output by the PrCM to the striatum that facilitates the evaluation of new reinforcement contingencies before behaviors are changed. If the context is unchanged, then direct messages from the PrCM to the motor cortex could result in rapid response outcomes; such a gating mechanism may contribute to the development of automatic responses in unchanging environments.

V. Summary and Implications

The study of adaptive navigation from a neural systems perspective has provided much evidence to support the view that this complex behavior involves the integration of numerous fundamental processes, the first of which allows for the detection of changes in the expected sensory environment. This information may interact with, or be regulated by, other processes that reflect the internal (or motivational) state. Such evaluation of sensory and motivational states are likely guided by one's past experience, and they involve hippocampal-cortical and septal-hippocampal interactions. Animals must also continuously evaluate the consequences of their behaviors in order to select appropriate future behavioral responses. The striatal-frontal cortex circuit is proposed to serve this function. When functioning optimally, then, the coordinated actions of these different neural circuits continuously determine the appropriate navigational behaviors in ever changing environments.

Several patterns of neural responsiveness become clear upon consideration of the vast amount of neurophysiological data accumulated during the many investigations of adaptive navigation. Each pattern provides new insight into the fundamental nature of the processing within and between neural systems. For example, representation of egocentric movement was the most common correlate type found across the different neural systems studied. Also, within each neural system, movement-correlated cells represent one of the largest categories of functionally correlated cells. Different interpretations could be offered to account for the parallel coding of egocentric movement. One possibility is that information about the current behavioral state needs to be incorporated by the local neurocomputational architecture. In this way, the behaviors relevant to a particular association (stimulus-stimulus, or stimulus-reward) or a specific stimulus can be encoded. Another possibility relates to the finding that hippocampal and striatal egocentric movement correlates often change if the expected spatial context is changed. This result suggests that the egocentric code may also reflect a learned association between expected contextual information and the relevant behavior. The term 'behavior' here refers not only to the broad category of behavior exhibited (e.g., a turn correlate), but also to the details of the behavior such as the velocity and acceleration of the actual movement. Such an integrated representation could be useful to provide information to the local computational network about the expected behavioral context of a task, a variable known to impact movement-related responses of parietal cortex neurons in primates (Colby & Goldberg, 1999). The fact that many brain structures contain such movement codes that are sensitive to changes in the sensory environment suggests that the behavioral context (i.e., the behaviors appropriate to a given situation) in which learning occurs is a fundamental unit of information that is useful for multiple forms of learning. Also, the broad presence of behavioral context information may provide one (of many?) functional architectures through which different neural processing systems can be orchestrated. If the behavioral context changes (resulting in altered firing patterns of the context-sensitive movement cells), information is fed back to a neural network that represents a functional architecture, or global domain, of behavioral expression (Figure 9). The behavioral expression domain, then, refers to a processing network that is responsible for behavioral selection, planning of actions, and the memory of behavioral acts (Mizumori, Yeshenko, Gill, & Davis, 2004b). Frontal and parietal cortices are likely to be centrally involved in the operations of this functional domain. Feedback indicating a change in behavioral context may cause the neural activity landscape within the behavioral expression domain to reconfigure, which in turn provides adaptive feedback that updates movement-sensitive representations in multiple neural systems.

Similar to the operation of the behavioral expression functional domain, we postulate the existence of a distributed network that corresponds to the functional domain of spatial context memory (perhaps involving parietal and temporal cortices; Figure 9). This network may serve to coordinate spatial context codes within different neural systems, such as the hippocampus and the striatum. That is, the spatial context memory network could define, for different neural systems, an expectation of sensory, behavioral, and reward elements of a learning situation. As noted above, this information could be used in different ways to support local network functions. Feedback to the spatial context memory network from individual neural systems may be required to update memory as the learning situation changes. The consequence of such updates may in turn update memory representations within other functional domains such as the behavioral expression system. There may be other functional domains that interact with the spatial context and behavioral control

domains.

Another common observation across different categories of correlated neurons that were recorded within different neural systems is that changes in context produced only partial reorganization

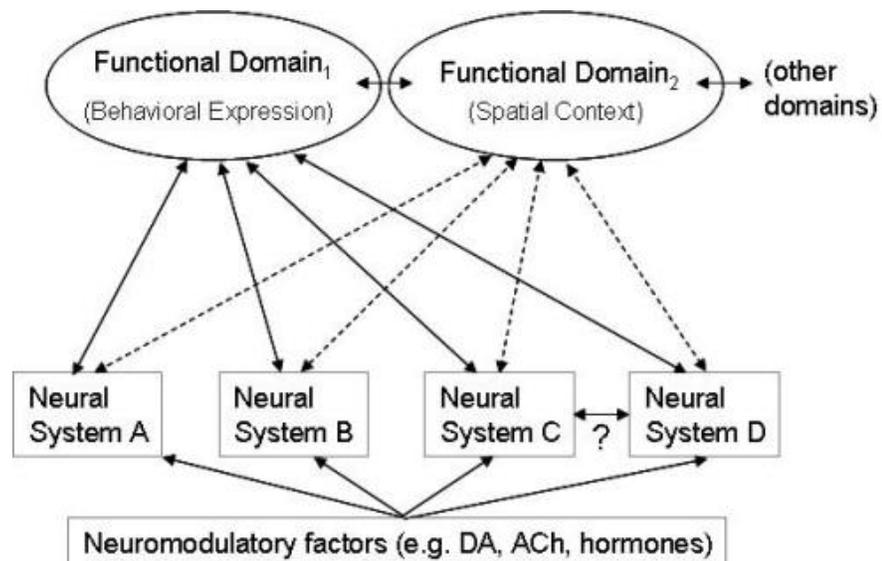


Figure 9. Theoretical model of neural systems interactions.

of firing patterns. That is, only a portion of place, movement, and reward-related cells responded to context change. If we assume that context-independent firing reflects expected information based on past experience (e.g., expected spatial contexts, learned responses, or reinforcement outcomes), and if we assume that context-dependent neural codes reflect ongoing features of a current situation, then a fundamental operating principle that applies to diverse neural systems could be the engagement in error-driven (match-mismatch) computations. Such a conclusion is consistent with the prediction of computational models of striatal and hippocampal function (e.g. Houk, 1995). Such computations would be highly adaptive for they provide a mechanism by which past experience can impact the processing of different forms of incoming information.

Finally, it is noted that not only are similar representation types found in different neural systems during the performance of a single task (and presumably during learning), but similar representations are found across different learning situations. This suggests that different neural systems continuously engage in their distinct learning-related computations, regardless of task demands. Their relative influences on behavioral expression systems may vary depending upon a number of factors such as experience and motivation. A challenge for this field is to determine more specifically how neural systems appear to compete for control over behavioral expression systems, and how other factors such as hormone status, stress, and age impact this competition.

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Acknowledgements

Over the years, many students have made significant contributions to the generation of data and to the development of key concepts described in this chapter. In particular, we would like to thank many of the past graduate students and postdocs in the lab: Brent Cooper, Katy Gill, Alex Guazzelli, Stefan Leutgeb, Wayne Pratt, Corey Puryear, Kay Ragozzino, and Oxana Yeshenko. Also, a large number of talented undergraduate students provided invaluable assistance with this work. An NIMH grant (#58755 to S. J. Y. Mizumori) supported our work over many years.



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