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Parallel processing across neural systems: Implications for a multiple memory system hypothesis

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Abstract

A common conceptualization of the organization of memory systems in brain is that different types of memory are mediated by distinct neural systems. Strong support for this view comes from studies that show double (or triple) dissociations between spatial, response, and emotional memories following selective lesions of hippocampus, striatum, and the amygdala. Here, we examine the extent to which hippocampal and striatal neural activity patterns support the multiple memory systems view. A comparison is made between hippocampal and striatal neural correlates with behavior during asymptotic performance of spatial and response maze tasks. Location- (or place), movement, and reward-specific firing patterns were found in both structures regardless of the task demands. Many, but not all, place fields of hippocampal and striatal neurons were similarly affected by changes in the visual and reward context regardless of the cognitive demands. Also, many, but not all, hippocampal and striatal movement-sensitive neurons showed significant changes in their behavioral correlates after a change in visual context, irrespective of cognitive strategy. Similar partial reorganization was observed following manipulations of the reward condition for cells recorded from both structures, again regardless of task. Assuming that representations that persist across context changes reflect learned information, we make the following conclusions. First, the consistent pattern of partial reorganization supports a view that the analysis of spatial, response, and reinforcement information is accomplished via an error-driven, or match–mismatch, algorithm across neural systems. Second, task-relevant processing occurs continuously within hippocampus and striatum regardless of the cognitive demands of the task. Third, given the high degree of parallel processing across allegedly different memory systems, we propose that different neural systems may effectively compete for control of a behavioral expression system. The strength of the influence of any one neural system on behavioral output is likely modulated by factors such as motivation, experience, or hormone status.

Keywords: Spatial learning; Response learning; Hippocampus; Striatum; Single unit activity; Place cells; Egocentric movement

1. Introduction

For many decades it has been generally accepted that neuroanatomically separate brain regions subserve different memory functions. Much of the early support for this view came from the neuropsychological literature. The first clear example was provided by patient H.M. who underwent bilateral removal of the temporal lobes (including hippocampus). This resulted in severe anterograde amnesia for episodic information while non-episodic memory systems remained intact (Milner, Corkin, & Teuber, 1968). Since then, numerous cases have been reported in which different forms of brain dysfunction result in selective memory loss (see review in Eichenbaum & Cohen, 2001; Knowlton, Mangels, & Squire, 1996). Generally speaking, patients suffering from hippocampal system damage tend to show selective deficits in episodic, declarative, contextual and/or spatial processing, while patients suffering from damage to other neural systems such as the basal ganglia tend to experience selective impairments in response learning

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that is independent of episodic information. Consistent with these findings are the results of numerous studies testing the effects of hippocampal or striatal lesions in rodents (e.g., Kesner, Bolland, & Dakis, 1993; McDonald & White, 1993; Packard & McGaugh, 1996). Based on the combined results of human clinical and animal work, as well as neurocomputational models, the hippocampus is thought to have the capacity for flexible, memory guided processing necessary for rapidly associating a complex array of stimuli. In contrast, based on similar kinds of data, the striatum appears specialized for a slower form of learning, one that seems ideally suited for linking reinforcement outcomes with specific stimuli or responses. These dissociations provide strong evidence to support a multiple memory systems interpretation of the mnemonic organization of the brain.

Confirming the differential contribution of relevant brain structures using methods other than lesions is an important first step toward validating the multiple memory systems hypothesis. Therefore, a major goal of this paper is to evaluate the extent to which this hypothesis is supported by neurophysiological data. Specifically, the goal of the first study (described below) was to search for the neural instantiation of the multiple memory systems hypothesis. Specifically, we tested the hypothesis that hippocampus and striatum mediate different forms of learning because they represent different kinds of information. Supporting this view, hippocampus contains many 'place cells' that discharge when animals occupy circumscribed locations with an environment (O'Keefe & Dostrovsky, 1971). The 'place fields' of these cells may reflect neural codes specific to a given spatial context (e.g., Anderson & Jeffery, 2003; Hayman, Chakraborty, Anderson, & Jeffery, 2003; Mizumori, Ragozzino, Cooper, & Leutgeb, 1999; Nadel & Wilner, 1980). As such, they may provide a fundamental code for the development of episodic memories. Striatum, on the other hand, is known to contain response and reward related neural representations (Hikosaka, Sakamoto, & Usui, 1989; Jog, Kubota, Connolley, Hillegaart, & Graybiel, 1999; Mizumori, Ragozzino, & Cooper, 2000; Schultz & Dickinson, 2000; Schultz, Tremblay, & Hollerman, 2003), and these may contribute to response learning. Other evidence, however, suggests that simply considering the type of neural representation in hippocampus and striatum does not fully account for their allegedly different contributions to learning. For example, the predominant behavioral correlate of hippocampal theta cell (i.e., interneuron) firing is an animal's movement within an environment (McNaughton, Barnes, & O'Keefe, 1983; Ranck, 1973; Rose, 1983), and many medial and lateral striatal neurons exhibit location-specific firing that is independent of movement and reward conditions (Mizumori, Ragozzino et al., 2000; Weiner, 1993). At present, then, there is no clear answer to the question of whether neural response patterns support the multiple memory systems hypothesis. Sections 3 and 4 present a comparison of simultaneously recorded hippocampal and striatal neural correlates as rats perform learning tasks that have been used to dissociate hippocampal or striatal mnemonic processing following lesions.

Another possible explanation for differential hippocampal and striatal contributions to learning is that their neurons are differentially sensitive to changes in spatial context. Therefore, Sections 5 and 6 describe a second study in which we compare the responses of spatial and movement-correlated hippocampal and striatal neurons following alterations of the visual environment. In particular, neurons were recorded during the performance of either spatial or response tasks, both before and after changes in the visual environment.

In addition to an examination of the nature of neural representations by different memory systems, is imperative that we understand possible neural mechanisms by which different neural systems relate to one another to result in adaptive behavior. One model of such an interaction is that there is direct competition for processing resources such that when one structure is actively engaged, other structures are not. As shown below, a single unit analysis of the nature of information coding by hippocampal and striatal neurons during spatial and response learning reveal that in most respects, both structures are similarly engaged regardless of whether the rat is performing a hippocampal-dependent or striatal-dependent task. Therefore, an alternative explanation of memory systems interaction is proposed (Section 7). According to this model, neuromodulatory systems (e.g., the dopamine system) might regulate the relative effectiveness of the efferent codes by hippocampal and striatal neurons during a given task. In one sense, then, memory systems interactions may take place in the form of competition for greater control over behavioral expression systems. This model complements the recent proposal by Gold and colleagues (in this issue) that acetylcholine is an important neuromodulatory factor that regulates the relative efficiency of hippocampal and striatal processing during spatial and response learning.

The remaining segments of this paper discuss two broad issues. Section 8 summarizes how the data presented can be incorporated into a neural systems view of a model of complex learning, adaptive navigation. The second issue (Section 9) concerns the implications of this work for multiple memory systems theory.

2. General method

2.1. Animals and apparatus

Long-Evans rats (5–7 month old) were obtained from Charles River Laboratory. Rats were housed singly and

maintained at about 80% of their free feeding weight throughout behavioral and single unit testing. Tap water was provided ad libitum. For plus maze training, only four arms of an eight-arm radial maze were used. Each maze arm (58 cm × 5.5 cm) and the center platform (19.5 cm diameter) were elevated 79 cm off of the floor. Radial maze training involved seven of the eight possible maze arms. For both forms of training, access to the distal segment of each maze arm from the central platform was allowed by raising the proximal portion of the maze arm so that it was flush with the central platform. Drops of chocolate milk served as rewards, and these were placed at the ends of goal arms. Black curtains surrounded the entire maze, and distinct visual cues were provided within the curtained area. Four 15 W light bulbs were spaced equally near the ceiling above the maze. Unit and video recording hardware were located in an adjacent room (see Fig. 1).

2.2. Behavioral procedures

During pretraining, rats collected the rewards at the ends of maze arms while traversing a maze that was configured differently from the experimental one (e.g., a linear track arrangement). Afterwards, rats were trained on either a place or response version of the *plus maze task* (Yeshenko, Guazzelli, & Mizumori, 2004). Both versions included start locations that were opposite of each other (e.g., west and east maze arms), and the start locations were randomly sequenced. At the start of a trial, a rat was removed from a holding bin next to the maze, and then placed on a start arm facing the curtain that surrounded the maze. For the place task, the reward location was fixed. Thus, depending on the start location, a rat had to make either a left or right turn on the center platform to enter the goal arm. For the response task, the start and reward locations were paired such that a rat had to make the same turn (i.e., always a right or left turn) on the center platform to enter the goal arm. During training, 10 trials (five from each start location selected in a pseudo-random order; intertrial interval of about 15 s) were presented each day until criterion performance was achieved (90% correct choices). Next, rats were implanted with recording electrodes in dorsal striatum and hippocampus.

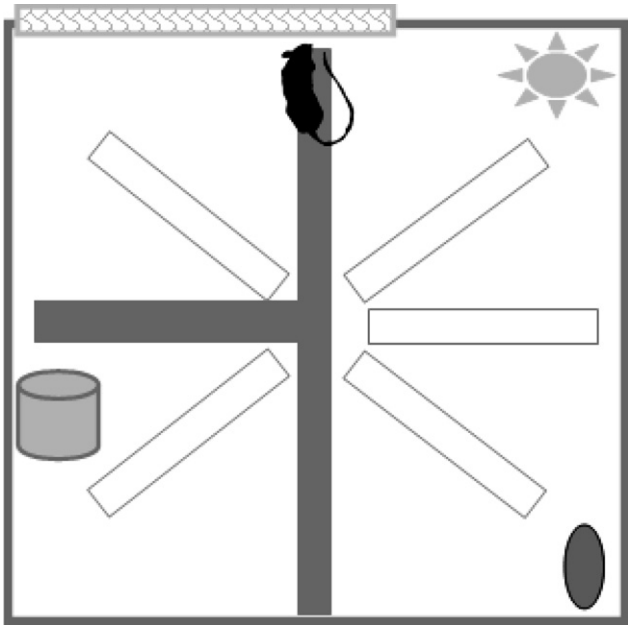


Fig. 1. Schematic diagram of the maze and training environment. This top–down view of an 8-arm radial maze illustrates the actual maze arms used in a given trial (filled arms) and maze arms that were made inaccessible to the rat during a trial (open arms). The precise configuration of maze arms used varied across training trials. Several objects were placed within a black curtain that surrounded the maze.

Following recovery from surgery, the rats were trained to perform 20 trials daily. Baseline unit-behavioral correlates were recorded during trials 1–10. During the intertrial interval between trials 10 and 11, the distal visual cues were changed (e.g., scrambled or rearranged, rotated by 90° or 180°, or removed altogether). Then, the rats performed 10 additional trials to test whether a change in visual context differentially affected hippocampal and striatal neural codes. For place trained rats, the significance of the goal location was also tested by moving the reward location to the opposite arm of the maze during the second block of 10 trials (e.g., moved to the north arm if the reward was originally on the south arm). After the unit responses to context changes were recorded, initially place-trained rats were trained according to the response procedure, and initially response trained rats were trained according to the place procedure. Upon achieving criterion performance with the alternate strategy, the responses of a different group of neurons were recorded before and after cue or reward location changes. After the second set of cells was tested, the rat was retrained according to the original strategy. A third set of cells was then tested for their response to cue changes, and so on.

A different group of rats underwent training on a *radial maze task* in which seven maze arms were used. The distal end of the eighth maze arm served as a holding platform for the rat during the intertrial interval. During phase 1 of training, the reward was consistently located on one maze arm (e.g., arm 6). For each trial, the start arm varied randomly across the six possible start locations. In addition, there was one constant goal arm, and the remaining five arms served as alternative, but incorrect, choice arms. For each session, each start location was used three times, resulting in 18 trials. Thus, relative to plus maze training, the radial maze procedure made it more likely that the rat solved the task by learning the reward location independent of response trajectories. After rats reached criterion on this task (90% correct choices), recording electrodes were implanted

in hippocampus and dorsal striatum. One week later, the rats were tested to ensure that asymptotic performance levels were maintained across the 18 trials. Then, phase 2 of training began in which the first 18 of 36 trials were identical to phase 1 of training. Trials 19–36 were performed with the goal in a different, but constant location. On each of the following days, a different maze arm served as the goal location during trials 19–36. Thus, as an example, a given rat might have been trained to find food on arm 6 during phase 1 (before surgery). During phase 2, the original goal arm was maintained for trials 1–18 (e.g., arm 6), then the reward arm switched (to say, arm 0) for trials 19–36. On the next day, the goal arm was arm 6 for trials 1–18, then arm 5 for trials 19–36, and so on.

2.3. Surgical procedures and electrode implantation

The method by which recording electrodes were implanted has been described in detail elsewhere (e.g., Cooper & Mizumori, 2001; Leutgeb & Mizumori, 1999, 2002; Mizumori, Ragozzino et al., 2000; Yeshenko et al., 2004). Briefly, rats were anesthetized with 40 mg/kg sodium pentobarbital (i.p.), and given 0.5 ml supplements as needed. Atropine sulfate (0.2 mg/kg) was also administered (i.p.) to relieve respiratory distress. The stereotrode recording electrodes (McNaughton et al., 1983) were made of two lacquer-coated tungsten wires (20 μm diameter) that were threaded through a 30 ga tube mounted on a moveable microdrive. The electrodes were connected to wires that were inserted into a connecting socket mounted on the rat's head. Multiple pairs of stereotrode electrodes were implanted (bilaterally) above the dorsal striatum and dorsal hippocampus of each rat. Rats were also injected with 0.1 Bicillin L-A (600 units/ml, im) to guard against infection. Free access to food and water was allowed for 7 days following surgery.

2.4. Unit and behavioral recording procedures

The electrodes were checked daily for single unit activity. Specifically, rats were connected to a preamplification headstage that transmitted the electrical signals to a DataWave data acquisition system. Neural signals were sampled at a frequency of 26–32 kHz, amplified by 4000–10,000 times, and filtered (600 Hz–6 kHz). Those signals that passed a predetermined amplitude threshold initiated a 1 ms sampling period. Subsequent separation of the multiunit record into single unit sources was accomplished off-line with the aid of a multidimensional cluster-cutting routine. A rat's position on the maze was monitored with the help of an automatic tracking system (Dragon Tracker) that sampled the relative positions of two diode arrays that were attached to the headstage. The position of the front diode array within the X–Y coordinate system of the maze was taken as the current location of the rat. A comparison of the position of the front and back diode arrays revealed the current head orientation of the rat. These diode arrays were sampled at a frequency of 20 Hz, resulting in a resolution of about 1.5–2.0 cm.

2.5. Cell classification and analysis

Spatial and egocentric movement correlates are commonly reported for hippocampal and striatal neurons (e.g., Mizumori, Cooper, Leutgeb, & Pratt, 2000; Mizumori, Ragozzino et al., 2000; Ragozzino, Leutgeb, & Mizumori, 2001; Yeshenko et al., 2004). Therefore, these experiments focused on these types of neural response correlates. To evaluate the spatial distribution of cell discharge, the maze area was divided into pixels (2.8×2.8 cm) and the average firing rate per pixel was calculated. Neurons were classified as place cells if the spatial distribution of firing satisfied the following criteria: (a) there were at least four adjacent pixels that exhibited firing that was at least 20% of the maximum pixel rate, (b) the in-field firing rate exceeded the out-of-field firing rate by more than two times, and (c) above threshold firing occurred during more than 50% of the total number of visits that a rat made to the location of the largest, or principal, field. A spatial (Pearson's) correlation was used to quantify place field reorganization across block 1 (baseline) and block 2 (manipulation) phases of a test session (Cooper & Mizumori, 2001; Leutgeb & Mizumori, 2002; Yeshenko et al., 2004). Only those pixels that were visited in both blocks were considered for this analysis.

Cell firing related to egocentric movement was evaluated for those neurons that did not show location-specific firing. If the firing rate of a given neuron showed a significant (linear) correlation with either velocity or acceleration of movement during baseline or manipulation phases of testing, it was considered to be movement-correlated. A one-sample t test was used to assess whether the degree of movement correlation was significantly affected by task manipulation for those cells that showed significant movement correlations during both baseline and manipulation phases. Analysis of variance was used to test whether the movement or spatial correlation varied as a function of brain area or task manipulation.

3. Is hippocampus unique by having spatial-context sensitive neural codes?

3.1. Hippocampal neural codes for spatial context

In order to establish the extent to which hippocampal place fields are unique, it is relevant to first discuss some

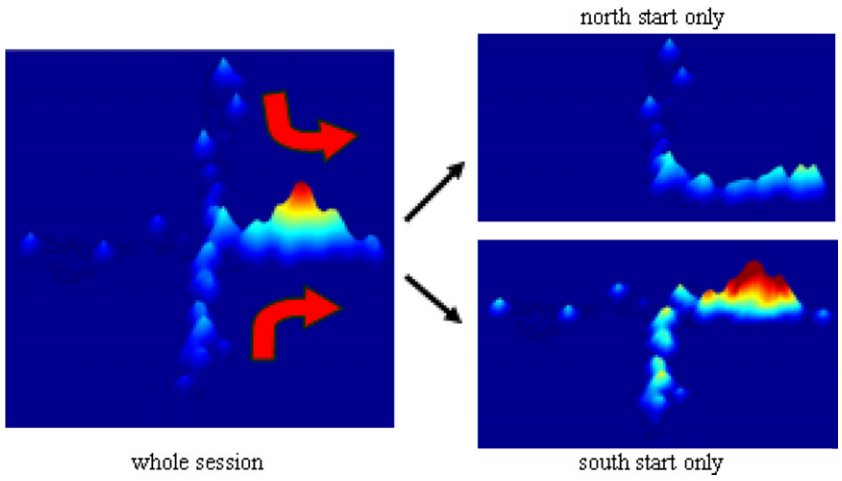
of the key properties of place field representations, and then compare these properties to striatal place fields. Initial research focused on the nature of place field modulation by sensory or movement information (e.g., Huxter, Burgess, & O'Keefe, 2003; Knierim, Kudrimoti, & McNaughton, 1998; Muller & Kubie, 1987; Shapiro, Tanila, & Eichenbaum, 1997). Hippocampal place fields typically changed the location of their fields (i.e., showed complete or partial reorganization) following changes in the visual sensory environment (e.g., Knierim, 2002). Place fields were also found to be sensitive to variables such as the velocity of movement through the field (e.g., Czurko, Hirase, Ssicsvari, & Buzsaki, 1999; McNaughton et al., 1983; Muir & Bilkey, 2003) and place cell firing can be synchronized to the ongoing theta activity (O'Keefe & Recce, 1993). These findings suggested that hippocampal neural discharge reflects complex multimodal associations, perhaps between visual and idiothetic information, that are useful during navigation (e.g., Knierim et al., 1998; O'Keefe & Nadel, 1978).

While more details continue to be revealed about the nature of the integration of landmark and idiothetic information by place cells during navigation, it remains to be determined how place fields contribute to the commonly held view that hippocampus mediates episodic learning (e.g., Eacott & Norman, 2004; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Morris, 2001; Vargha-Khadem et al., 1997). Early evidence that place fields may reflect memory processes include the findings that place fields persist following drastic changes in the visual environment if animals are able to first view a familiar environment (Mizumori et al., 1999; O'Keefe & Speakman, 1987; Quirk et al., 1990). For example, when tested on a standard spatial working memory task on a radial maze, about 40–60% of place fields will persist when darkness is imposed in a familiar environment (Mizumori et al., 1999). This partial reorganization suggests that hippocampus may contain neural representations of the previously learned (or expected) features of a spatial context, and it may monitor changes in the current environment. In this way, hippocampus may compare the current context to what was expected based on past experience to determine whether a context has changed (Mizumori et al., 1999, 2000). This view represents an elaboration on the initial hypothesis by Nadel and Wilner (1980) that place fields represent a spatial context code. Furthermore, it has been argued that this hippocampal neural code may reflect information about the learned significance of particular locations. The learned significance could be operationally defined in terms of the learned rewards or behavioral responses associated with particular locations. This more broad definition of place field representation allows one to argue that place fields comprise elements of a spatial context code that can be used to define meaningful episodes. Recent work (described below) has begun to support this view.

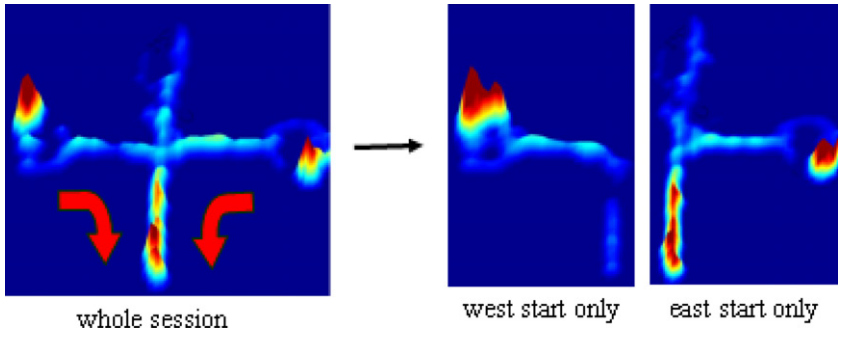
The direction from which a rat moves through a place field dramatically impacts the expression of a place field (Frank, Brown, & Wilson, 2001; McNaughton et al., 1983). Thus, place cells do not code absolute locations in space. The direction-selective firing could have been the result of the different visual experiences associated with different orientations within a field. This variable was controlled for in a recent study (Wood, Dudchenko, & Eichenbaum, 1999). Rats were trained to run through a central corridor of a maze after having made either a right turn or left turn into the corridor. Rats were allowed to exit the corridor at the opposite end by turning left (if it entered by turning right) or by turning right (if it entered by turning left). It was found that the expression of place fields within the central corridor often depended upon whether the rat turned right to enter the corridor (and left to exit) or turned left to enter the corridor (and right to exit). This finding suggested to the authors that place fields represent an animal's position relative to past or future movement trajectories. This is intriguing for it suggests that place fields are in some way linked to retrospective or prospective memories. Indeed, reduced prospective and retrospective coding has been related to increased behavioral errors (Ferbinteanu & Shapiro, 2003). Thus, a place field representation may include information about learned behavioral sequences relevant to a particular location in space.

Using a different behavioral paradigm, we recently replicated the main results of the study by Wood and colleagues (1999). Rats ($n = 6$) were trained to perform the plus maze task (described above) according to a place strategy. The reward was always found on the east arm (or west arm for other rats), but the start location varied between north and south arms. Fig. 2 shows an example of hippocampal place cell firing during the performance of this place task. When viewing the location-selective discharge across the whole session, a place field is clearly observed on the east maze arm. When the data were divided according to trials started from the north arm and trials started from the south arm, one can see that the field was exhibited only when the rat entered the goal arm by turning right (from the south arm), and not when entering the arm by turning left (from the north arm). Thus, the previous movement trajectory determined whether or not the place field would be observed.

Our hypothesis that a place field reflects an information construct that includes the definition of a location and its significance suggest that changes in reinforcement location should influence the expression of place fields. We tested this hypothesis by recording hippocampal place fields during performance of the spatial plus maze task. During the first 10 trials, food was always found on one maze arm (e.g., north arm). During the



A. Hippocampal place cell



B. Striatal place cell

Fig. 2. Color density plots illustrating the sensitivity of hippocampal and striatal place fields to the prior trajectory of the rat (A) The left figure illustrates a place field on the east maze arm during the performance of a spatial plus maze task. When the plots were generated separately for trials in which the rat entered the goal (east) arm from the north or south, it is clear that the place field was selectively expressed when the rat entered from the south (B) A similar trajectory-dependent response was observed for a striatal place cell recorded as a rat performed a spatial plus maze task. A place field was selectively expressed on the south maze arm when arriving from the east, and not west, arm. These data suggest that the neural encoding of location within hippocampus and striatum depends at least in part on the recent behaviors of the animals.

second 10 trials, the reward location was changed to the opposite arm (e.g., south arm). We evaluated place fields located on the maze arms that were common between the blocks of trials and found that place fields observed during block 1 often underwent reorganization during block 2 even though the behavior of the rat was the same on the arms common across blocks. Fig. 3 (top) shows an example of such a response.

It could be argued that the reorganization observed after a change in the reward location was due to the fact that the rat was solving the plus maze task by performing not according to a place strategy, but by a conditional response strategy. That is, when placed on the west maze arm, the rat should make a left turn to find food. When placed on the east arm, the rat should make a right turn. When the reward shifted, perhaps a different set of conditional responses was created, resulting in place field reorganization. To test more rigorously the conclusion that reward shifts during place training reflects a change in place and not response learning, we tested the effects of reward location shift during the performance of a more complex place learning task in which rats were trained to find food on only one maze arm from six possible start locations on a radial maze (described above). During the first block of trials, the reward was found in a familiar and constant location. During the second block of trials, the rat learned to find food at a new location after starting from one of six possible start arms. Fig. 3 (bottom) shows that reorganization of place fields was observed after the goal location shifted even though the rat traversed the same maze arms during both blocks of trials. Fig. 4A presents a summary of spatial correlation scores that reflect the degree to which the spatial distribution of firing changed between blocks 1 and 2 during radial maze and plus maze training. For hippocampal neurons, it can be seen that during place and response plus maze tests, the relatively low correlation scores indicates that the place fields tended to reorganize after the shift in reward location. By comparison, during radial maze performance

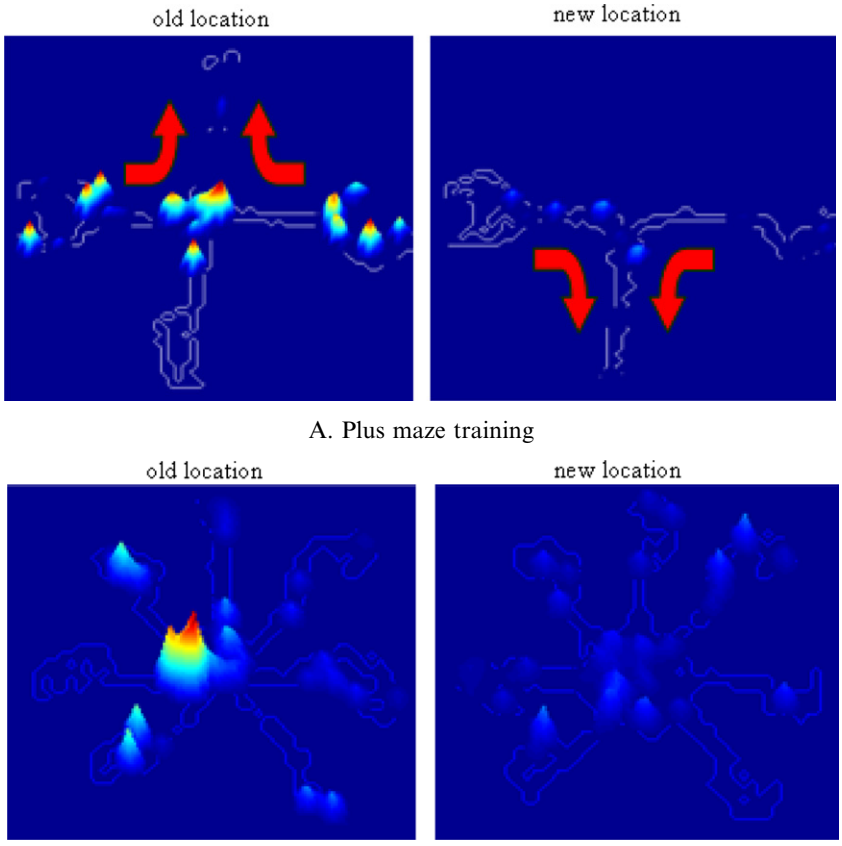


Fig. 3. Hippocampal place fields respond to changes in reward location. After rats achieved asymptotic performance on the spatial plus maze (A) or radial arm maze (B) task, the reward location was changed. It can be seen that dramatic place field reorganization was apparent even though the rat continued to traverse the same maze arms and the sensory environment was unchanged.

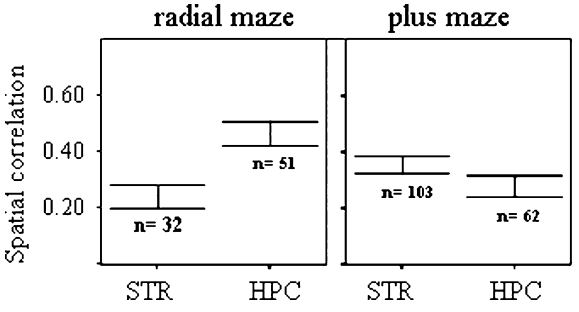


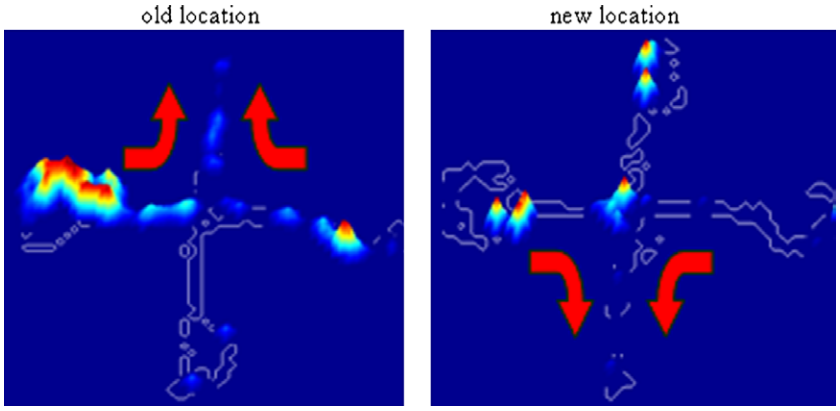
Fig. 4. Summary of the spatial correlation values for hippocampal and striatal neurons recorded during radial maze and plus maze performance. The correlation analyses compared the spatial distribution of cell firing before and after the shift in reward described for Fig. 3. Striatal place fields reorganized to a greater degree than hippocampal place fields during radial maze performance, and not during plus maze performance. The n's correspond to the number of place cells tested.

significantly less reorganization was observed [$F(1,112) = 10.56$, $p < .01$].

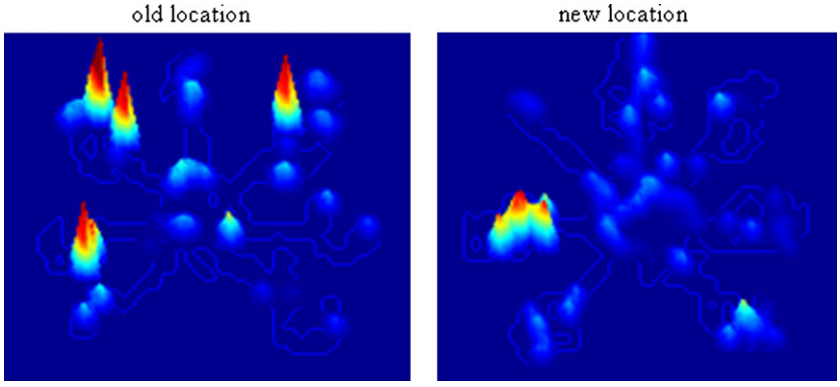
The evidence presented thus far, together with data reported in earlier studies, indicate that hippocampal place fields are sensitive to sensory, movement, and reward information. Thus, place fields may indeed represent information regarding past associations between landmark and idiothetic information, as well as information about the reinforcement and behavioral significance of particular locations. It is tempting to conclude that such neural coding is fundamental to the allegedly unique role that hippocampus may play in episodic learning and memory. However, before one can make such a conclusion, it is necessary to determine the extent to which hippocampus is unique in representing spatial context information. In the following section, we compare striatal place field properties to those just described for hippocampal place cells.

3.2. Striatal neural codes for spatial context

Dorsomedial striatal neurons were recorded simultaneously with the hippocampal units described above. With only a couple of exceptions, the dynamic and complex responses observed for hippocampal place cells were also observed for striatal place cells (Yeshenko et al., 2004). For example, Fig. 2 shows a striatal place field that was differentially expressed depending upon



A. Plus maze training



B. Radial maze training

Fig. 5. When tested under the same conditions described for Fig. 3, striatal place fields showed a similar reorganization response to a shift in the expected reward location. Thus, hippocampal and striatal place fields appear to be similarly sensitive to rewards associated with a particular spatial context.

the direction of movement prior to entering the location of the place field. Such a conditional response has not been described before for striatal neurons. Thus, similar to hippocampus, information about specific movements or movement sequences may guide the expression of striatal place fields.

It was shown above that hippocampal place fields are impacted by changes in reward location. Fig. 5 shows that striatal place fields also reorganize when the reward location shifts in a familiar environment. This was the case during both plus maze and radial maze testing. The degree of reorganization was similar for striatal place cells tested during plus maze and radial maze performance [$F(1,134) = 3.38$, ns; see Fig. 4]. In contrast, hippocampal place cells (described above) showed greater reorganization when the reward was switched during plus maze training. The difference may indicate that when the reward changes are predictable (as in the case of plus maze training), hippocampal fields will reorganize according the expected context change. When the reward location change is less predictable (as in radial maze testing), place fields may be impacted less by input regarding the expected reward location, resulting in apparently less reorganization of place fields. Furthermore, the striatum may be more sensitive to any sort of change in reward information than hippocampus. This conclusion is consistent with other studies suggesting that striatal neurons respond to specific changes in reinforcement conditions, such as reward expectancy and consumption (e.g., Hikosaka et al., 1989).

In summary, striatum contains neurons whose location-selective firing is remarkably similar to that of hippocampal place fields. One notable difference was that hippocampal place fields showed less reorganization after reward shifts on the radial maze task than after reward shifts on the plus maze task. Striatal place fields showed dramatic reorganization after reward shifts during both tasks, suggesting that striatum is more sensitive to changes in reward contingency irrespective of the specific behavioral task. While these differences could in theory be used to explain a different contribution by hippocampus and striatum to learning, it is also possible that these structures differentially impact place and response learning because striatum contains egocentric movement codes that hippocampus does not. The following section evaluates this possibility first by

describing the kind of movement codes found in striatum, then assessing whether similar movement codes are found in hippocampus.

4. Is striatum unique by having response-sensitive neural codes?

4.1. Striatal neural codes for movement

The firing rates of many striatal neurons are significantly modulated by egocentric movement when recorded from freely moving rats performing either a spatial working memory task on a radial maze (e.g., Mizumori, Ragozzino et al., 2000) or the plus maze task described above (Yeshenko et al., 2004). Many striatal neurons increase firing when rats engage in active forward locomotion regardless of the animal's location on the maze. Other neurons selectively fire when rats engage in specific behaviors, such as when they make right or left turns during maze navigation (see Fig. 6 for examples; Jog et al., 1999; Mizumori, Ragozzino et al., 2000). Many of these movement-sensitive striatal neurons are also significantly related to the velocity and acceleration of movement (Yeshenko et al., 2004; see examples in Fig. 7). Another behaviorally regulated pattern of striatal neuronal firing can be seen as an increase in discharge rate relative to the orientation of an animal's head within a given environment (Mizumori, Ragozzino et al., 2000; Weiner, 1993). These so-called head direction cells preferentially discharge when a rat's head is aligned with a particular orientation (irrespective of location within the environment). Many of the properties of striatal head direction cells resemble those of head direction cells reported in other brain structures, such as the anterior and lateral thalamus (Mizumori & Williams, 1993; Taube, 1995) and postsubiculum (Taube, Muller, & Ranck, 1990). It seems, then, that a variety of response-related firing patterns are observed for dorsal striatal neurons.

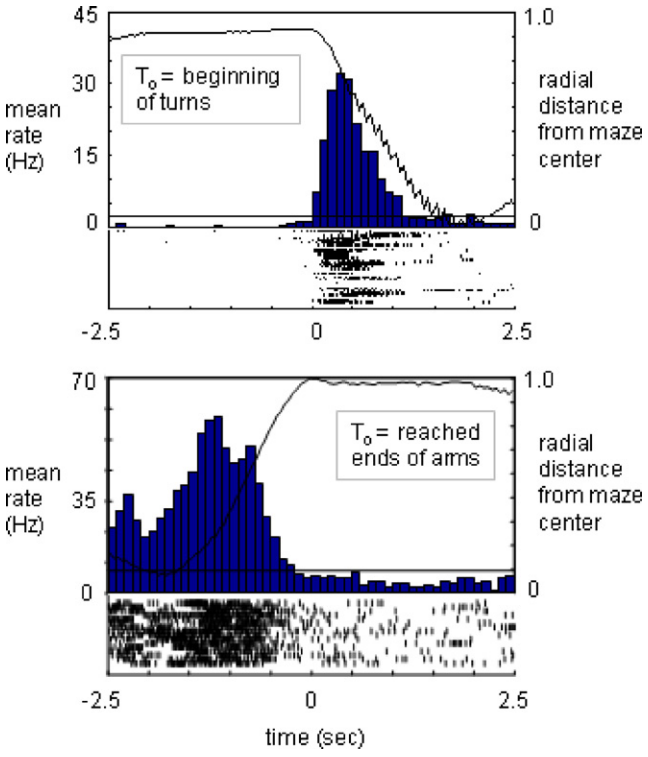


Fig. 6. Peri-event histograms that illustrate the specificity of the egocentric movement modulated firing by dorsal striatal neurons. (Top) This cell was essentially silent until the rat began to make 180° turns at the ends of the maze arms. The gray line indicates the distance of the rat from the maze center. Other egocentric movement-correlated cells increased firing as the rat traversed the maze arms, only to become inhibited from firing when the rat reached the ends of maze arm (and stopped forward movement).

4.2. Hippocampal neural codes for movement

It has been known for some time that a subpopulation of hippocampal neurons (inhibitory interneurons) increase discharge rates when animals engage in translational behaviors associated with a 7–9 Hz theta modulation of the hippocampal EEG (Czurko et al., 1999; Ranck, 1973; Rose, 1983; Vanderwolf, 1969). Similar to striatal movement cells, hippocampal interneurons (or, 'theta cells') typically show higher baseline firing rates than place cells. The firing rates of theta cells can be further refined in accordance with the ongoing velocity and acceleration of movement (Czurko et al., 1999; Yeshenko et al., 2004). Fig. 8 shows examples of such velocity and acceleration tuning for hippocampal theta cells. Another similarity to striatum is that hippocampus contains a small population head direction cells (Leutgeb, Ragozzino, & Mizumori, 2000). Thus, both hippocampal and striatal computations likely incorporate directional heading information. In contrast to striatum, however, hippocampal neurons do not appear to code specific egocentric movements, such as turns.

It appears, then, that there are a surprising number of commonalities in terms of the kinds of information represented by hippocampal and striatal neurons. Both structures contain similar types of location-specific codes, and both structures contain codes for egocentric movement. Amidst these similarities, however, are some potentially important differences that may contribute to their differential roles during learning. First of all, striatum, but not hippocampus, contains neural representations of specific egocentric behaviors. Second, striatum may be more sensitive to changes in reward variables such as reward location or reward consumption. In the following section, we explore an additional possibility: that is, the distinct roles of hippocampus and striatum in learning may also be related to their differential response to changes in

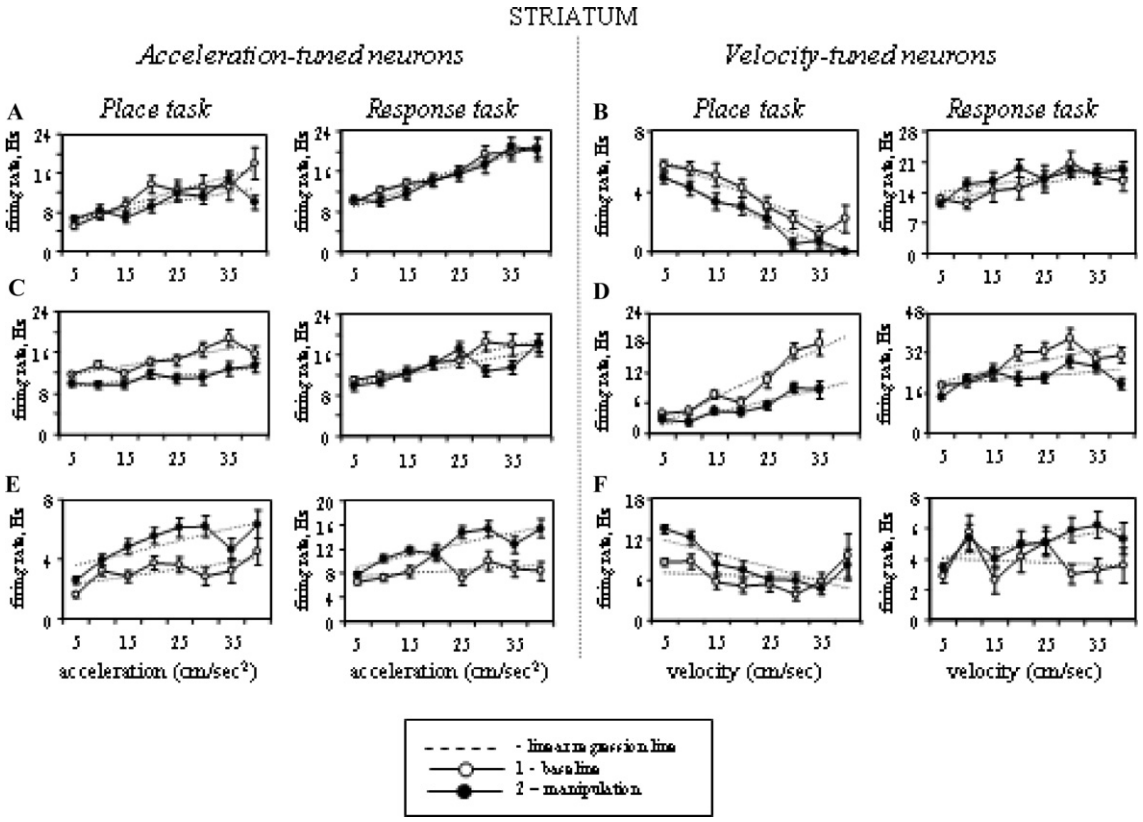


Fig. 7. Context-dependent responses of striatal movement-related firing during place and response training on the plus maze. Each panel presents data for an individual cell. For this analysis, the firing rates are plotted as a function of acceleration (left) or velocity (right) of movement on the maze. It can be seen that during the baseline period of testing, we observed significant relationships between acceleration or velocity and firing rate. For many of the cells, these relationships were observed to change (i.e., made stronger or weaker) following a change in the visual context. These responses demonstrate that egocentric movement cells code more than the current movement state of the animal. It is suggested that such responses may indicate that these cells represent context-dependent learned movement associations.

spatial context. The two types of context change used in these studies were an altered visual environment and different cognitive strategies.

5. Are similar types of hippocampal and striatal neural representations differentially influenced by changes in spatial context?

5.1. Place and movement cell responses to changes in the visual environment

To investigate the relative impact of an altered visual environment on hippocampal and striatal place and movement representation, we compared the responses of neurons in these structures to cue rotation, cue removal, and cue rearrangement (Yeshenko et al., 2004). Rats were trained on either the place or response version of the plus maze task. After achievement of asymptotic performance, one of the cue manipulations (randomly selected) was imposed during a recording session. Thus, trials 1–10 were conducted with familiar cues present, and trials 11–20 took place after the cues had been manipulated. Place fields and movement correlates were compared across the two blocks of ten trials. Individual hippocampal and striatal place cell responses to the various cue manipulations are exemplified in Figs. 9 and 10. Examples of hippocampal and striatal movement-related cell responses to context change are shown in Figs. 7 and 8. Qualitatively speaking, similar types of responses were made by hippocampal and striatal neurons. It can be seen that both groups of neurons showed either increased and decreased correlate specificity following cue manipulations. Since the different cue manipulations produced comparable patterns of neural responses, the data were combined for group summaries. An analysis of variance on the spatial correlation scores comparing blocks 1 and 2 revealed no significant difference between hippocampal and striatal place cell responses. That is, both structures exhibited the same degree of field reorganization following changes in the visual environment.

Figs. 7 and 8 provide examples of responses by movement-related hippocampal and striatal neurons to visual cue manipulation. These illustrate that cell firing became either more or less correlated with velocity and/or

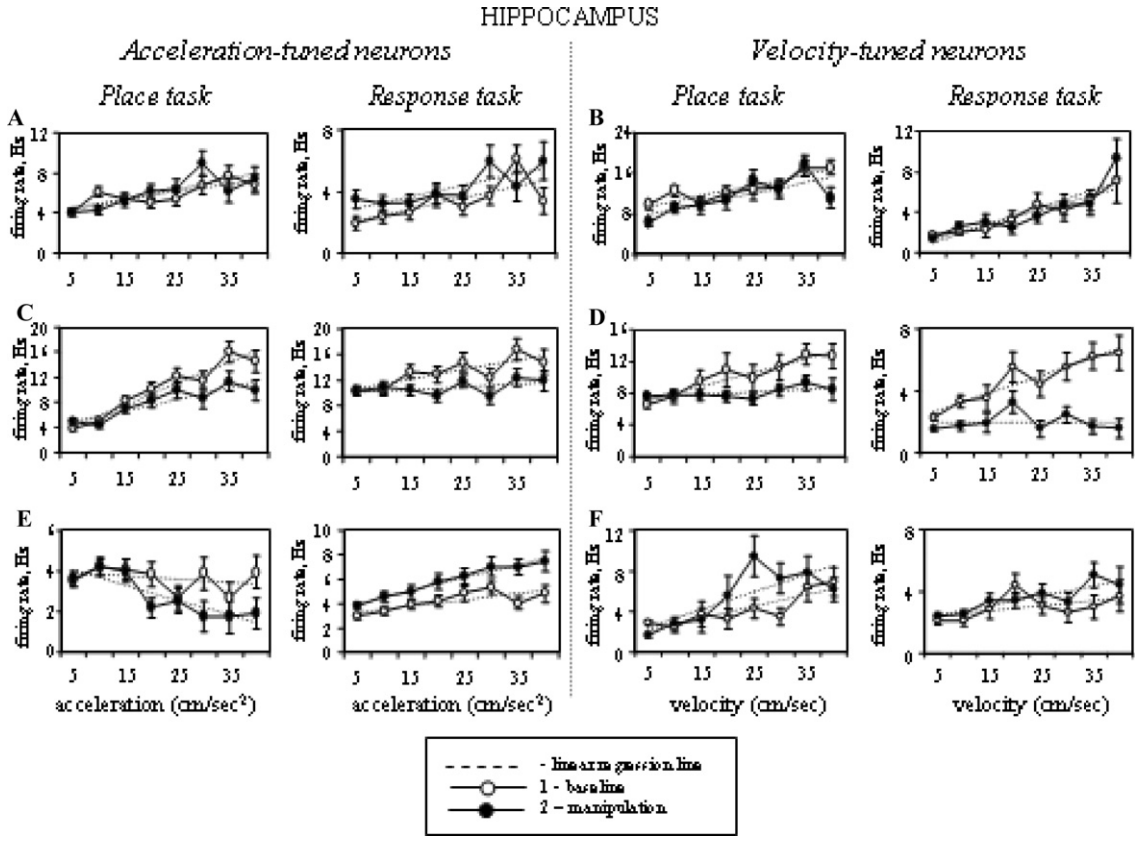


Fig. 8. Context-dependent responses of hippocampal movement-related firing during place and response training on the plus maze. Similar to what was is shown in Fig. 7, hippocampal movement-related firing was strong during the baseline period, and was observed to change significantly after context change.

acceleration. Other cells showed no response. Group summaries (Fig. 11) revealed no significant differences between the overall magnitude of change by hippocampal and striatal neurons following cue manipulation. This was true for both velocity and acceleration measures, regardless of whether the analysis was performed on the resultant correlation score or slope coefficient.

5.2. Place and movement cell responses to changes in cognitive strategy

To test whether hippocampal or striatal place fields might be differentially sensitive to context change depending upon the current cognitive strategy, we compared (within each structure) the degree of place field reorganization after cue manipulation during place and response task performance. Figs. 9 and 10 show examples of the types of place field changes observed. Strong and weak reorganization was observed by both hippocampal and striatal place cells. There was no significant difference between strategy groups in terms of the average spatial correlation value (Yeshenko et al., 2004). That is, both hippocampal and striatal place fields changed by a similar amount during response and place training.

Figs. 7 and 8 provide examples of the variety of responses observed for velocity or acceleration-tuned hippocampal and striatal neurons after cue manipulation. Movement-correlated cells from both structures were surprisingly, and often dramatically, sensitive to cue manipulation. As a group, the average correlation between hippocampal cell firing rate and movement acceleration changed during place training to a greater degree than during response training following a cue manipulation (Fig. 11A). An analysis of the slope coefficient showed that the acceleration correlate of hippocampal neurons was more sensitive to cue manipulations during response training. This pattern suggests that, on the whole, hippocampal, and not striatal, movement cells are differentially sensitive to visual context changes depending upon the cognitive strategy. It appears that hippocampal and striatal movement-correlated cells not only reflect egocentric information, but they may also represent learned behavioral responses (Yeshenko et al., 2004). To the extent that the use of different cognitive strategies reflects the operation of different memory systems, hippocampal movement-related firing may be guided directly by memory more than striatal movement representations.

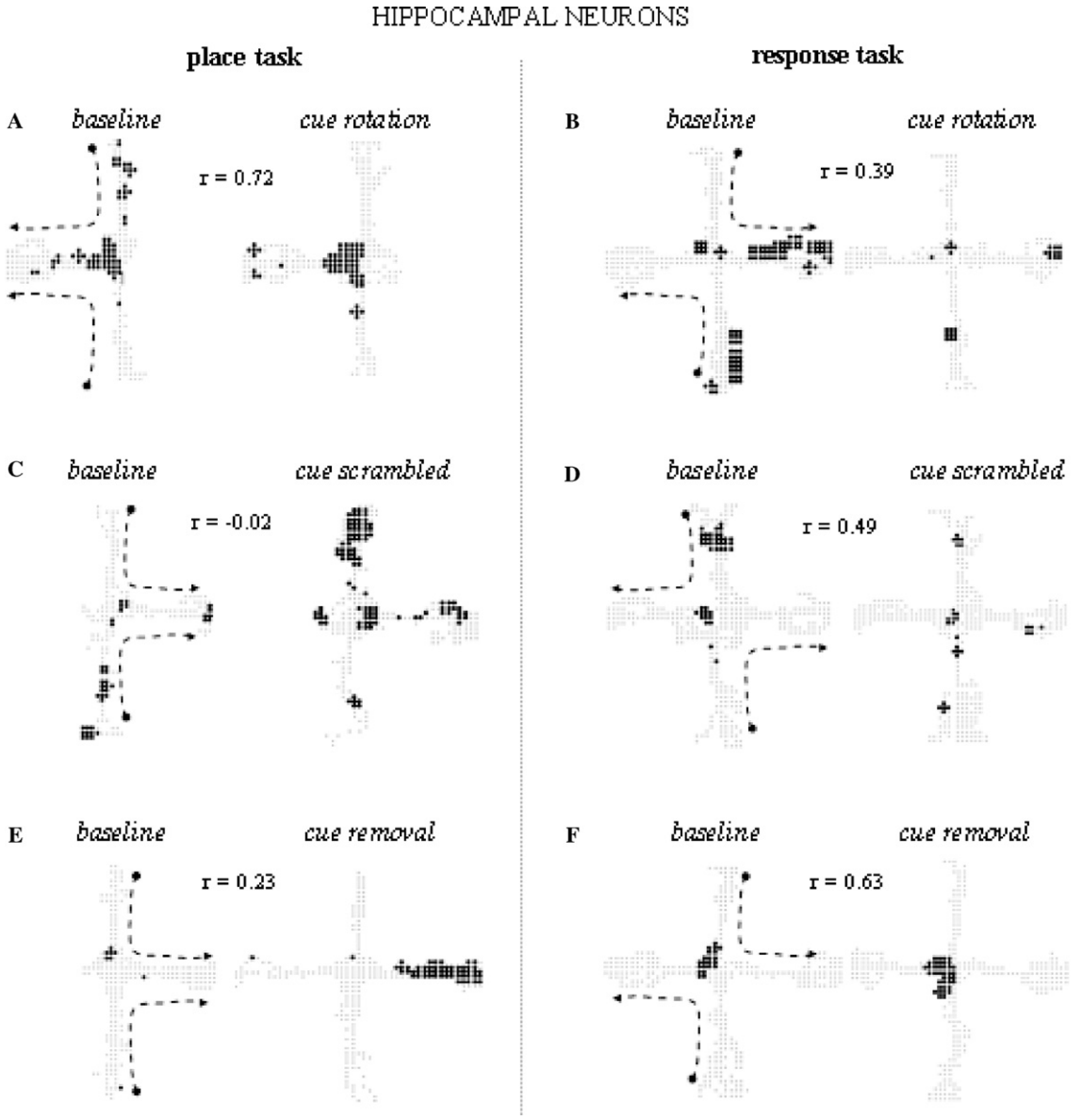


Fig. 9. Context-dependent responses of hippocampal place fields during place (left) and response (right) performance. The spatial distribution of firing is illustrated for cells recorded during the baseline period, and then after the visual cues were manipulated in different ways. All forms of cue manipulation resulted in place field reorganization. The *r* value is the spatial correlation that compares baseline and cue manipulation phases. Bold dots indicates firing rates that were greater than 20% of the maximum firing rate for the cell. Arrows indicate the response trajectories of the animal.

6. Summary of similarities and differences in hippocampal and striatal neural codes

The analyses presented above were directed toward two issues. The first issue was whether a differential contribution of hippocampus and striatum to learning could be accounted for by arguing that different information is represented in these structures. Our findings show that both structures contain neurons whose firing is significantly correlated with an animal's location, directional heading, egocentric movement, and prospective/retrospective behavioral trajectories. Also, both structures contain neurons that are sensitive to changes in the expected reward location. In addition to these striking similarities in neural codes, there are at least three notable differences. Striatum contains neural codes specific to particular behaviors (e.g., turns) while hippocampus movement codes are more broad in scope (i.e., they detect changes in general movement states such as whether translational movements occur or not). Also, we show that striatal neurons are more sensitive to changes in reward location than hippocampal neurons. In addition, it is worth noting that it has been shown that rodent striatum contains neurons that are sensitive to reward consumption and the anticipation of reward encounters (Mizumori, Ragozzino et al., 2000). No such correlate has been observed in hippocampus. Finally, it appears that the movement-related cells of hippocampus are

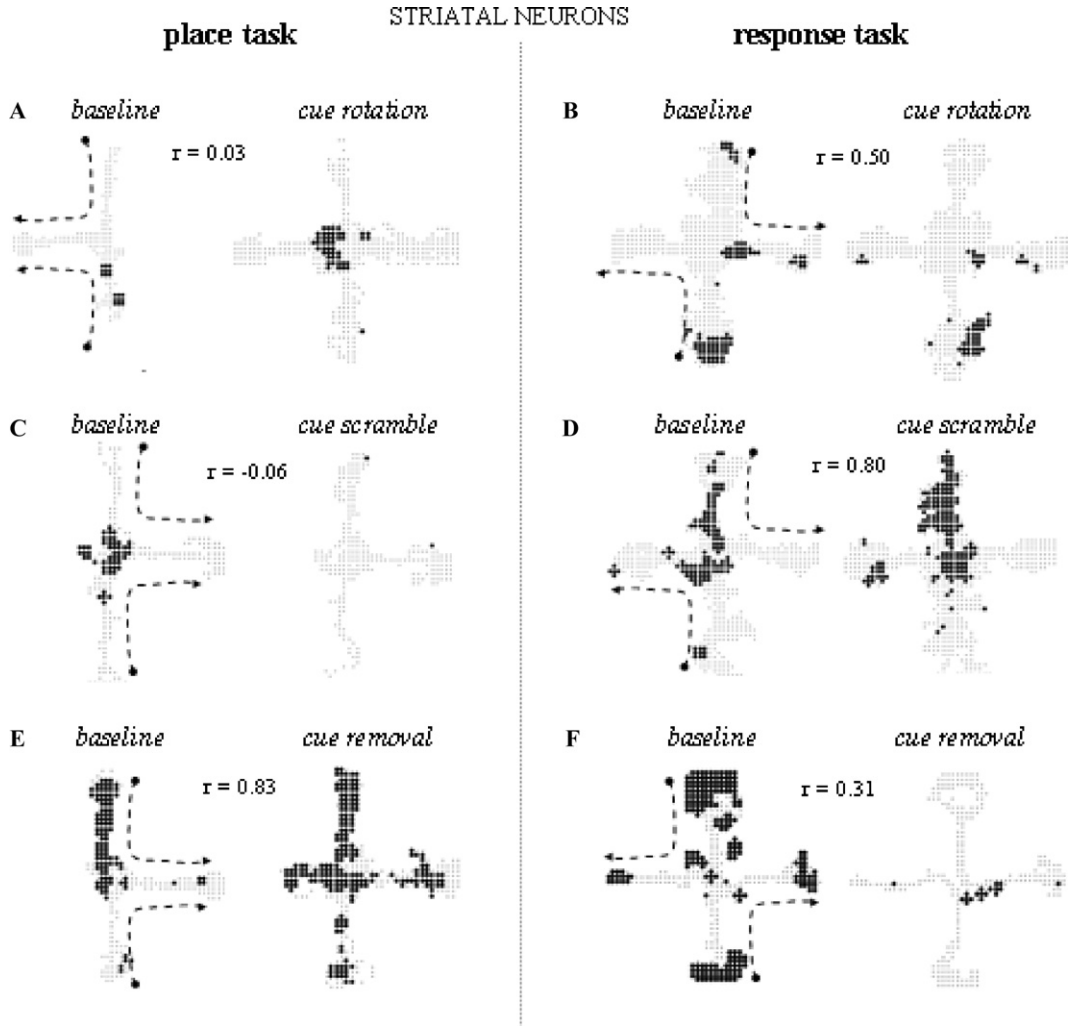


Fig. 10. Context-dependent responses of striatal place fields during place (left) and response (right) performance. Similar to the hippocampal responses shown in Fig. 9, striatal place fields showed reorganization responses following different forms of cue manipulation regardless of the cognitive strategy.

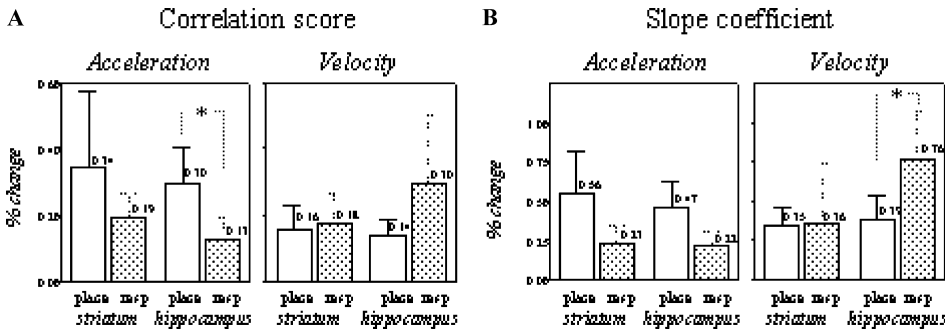


Fig. 11. Summary of context-dependent responses of hippocampal and striatal movement-related cells during place or response testing on a plus maze. (A) The responses are expressed in terms of the percent change in the correlation between acceleration or velocity and firing rate after a change in visual context. Only hippocampal cells showed a strategy-dependent response to context changes: these cells showed a greater change in correlation during place task performance. (B) When comparing the slope coefficient of the correlation function, it appears that hippocampal cells showed a greater response to context change during response performance. While the significance of these individual effects is unclear, hippocampal movement-cells in general appear to be more sensitive to strategy effects.

generally more sensitive to visual and cognitive context (i.e., strategy) changes when compared to striatum. The cumulative effect of the differences observed between hippocampal and striatal neural representational properties may effectively bias the significance or strength of their output such that hippocampus has greater impact on ongoing behavior during spatial context learning despite the fact that striatum continues to process information in parallel with hippocampus. When spatial context learning is not critical, the strength of the hippocampal output may be attenuated such that striatal output gains greater relative influence over behavioral output systems.

Intrinsic factors may regulate the relative strengths of hippocampal and striatal output. Fig. 11 illustrates that cognitive strategy is one such factor. Mizumori, Ragozzino et al. (2000) suggested that motivational factors or hormone status may also influence the relative contribution of hippocampus and striatum during learning. Motivational influences can be assessed in different ways. One method involves testing hippocampal and striatal unit responses during different motivational states, such as hunger vs. thirst. Of interest in this regard is the recent report that hippocampal place cells respond differently to context change depending on whether a rat is hungry or thirsty (Kennedy & Shapiro, 2003). Another approach to the study of motivational influences is to compare hippocampal and striatal responses to neurotransmitters that are thought to mediate signals that reflect the level of motivation, such as dopamine. Dopamine has indeed been implicated in the regulation of feeding and other motivated behaviors (Phillips, Ahn, & Howland, 2003). In the following section, we describe our initial attempts to determine whether intrinsic factors such as dopamine or estrogen status might differentially regulate hippocampal and striatal output in a manner consistent with their allegedly different roles during learning.

7. Are hippocampus and striatum differentially regulated by intrinsic variables?

Dopamine seems to play a central role in regulating different cognitive processes, from attention to behavioral selection to learning (Nieoullon, 2002). Here, we focus on the issue of whether dopamine impacts the relative contribution of hippocampus and striatum to learning by regulating their output strength and clarity. Such a function may be predicted by anatomical and physiological investigations of dopaminergic connections with hippocampus and striatum. For example, dopamine afferents appear to be located strategically to differentially regulate associative mechanisms in hippocampus and striatum. Dopamine neurons within the ventral tegmental area (VTA) project to subiculum, as well as the CA1 and CA3 regions of dorsal and ventral hippocampus (Gasbarri, Introini-Collison, Packard, Pacitti, & McGaugh, 1993; Gasbarri, Packard, Campana, & Pacitti, 1994). Dopamine neurons of the substantia nigra pars compacta (SNc) also project to hippocampus. VTA projects primarily to ventral striatum while SNc projects mainly to dorsal striatum (Gasbarri et al., 1993). Mnemonic and/or spatial context-relevant firing by dopamine neurons may result from the coordinated input of glutamatergic afferents from prefrontal cortex and/or tegmentum (Forster & Blaha, 2000).

In striatum, it has been proposed that dopamine contributes to the evaluation of behavioral contexts, perhaps by contributing to long term plasticity via its regulation of glutamatergic afferents (Calabrese, Pisani, Mercuri, & Bernardi, 1996; Seutin, Johnson, & North, 1993) and its effects on the oscillatory pattern of striatal discharge (Ruskin et al., 1999). Within hippocampus, dopamine may determine the duration of synaptic plasticity since application of D1 and D2 receptor agonists produce long lasting activation and inhibition, respectively, of CA1 pyramidal neuron firing rates (Smialowski & Bijak, 1987). In addition to direct effects on pyramidal neurons, dopamine may have indirect effects in hippocampus by increasing acetylcholine release (Brito, 1992) , which in turn may regulate the stabilization of place representations in new environments (Leutgeb & Mizumori, 1999, 2002). Indeed, recent evidence suggests a possible role for acetylcholine in regulating the relative contributions of hippocampus and striatum during different forms of learning (Chang & Gold, 2003; Gold, 2003).

To begin an examination of a possible regulatory role for dopamine in hippocampal and striatal mnemonic function, we tested the effects of a D1 receptor antagonist (SCH23390) on hippocampal and striatal place fields (Gill & Mizumori, 2002). Rats were trained to perform a standard spatial working memory task on an eight-arm radial maze (Mizumori, McNaughton, Barnes, & Fox, 1989; Mizumori, Ragozzino et al., 2000). During training, the first four choices of a trial were predetermined by the experimenter (study phase) and presented sequentially to the rat. All maze arms were then made available to the rat (test phase), and the rat was trained to select maze arms that were not previously visited that trial. Rats performed five such trials (2 min intertrial interval) while baseline unit data were collected. During the intertrial interval between trials 5 and 6, vehicle or SCH23390 (5 mg/kg) was injected (sc). After 5 min, the rat performed trials 6–10. To test whether dopamine differentially regulates hippocampal and striatal place fields during times of context change, the maze room lights were turned off during trials 6–10 for half of the test sessions (dark trials).

Spatial correlation values were compared across times when vehicle solution was injected prior to trials

performed with the lights on (VEH-LIGHT condition), and times when vehicle solution was injected prior to dark trials (VEH-DARK condition). When compared to the VEH-LIGHT group, striatal place fields tested showed significant reorganization after SCH23390 injection (SCH-LIGHT; Fig. 12; $p < .05$). In contrast, relative to spatial correlation scores obtained during the VEH-LIGHT condition, hippocampal place fields did not show significantly more reorganization during the SCH-LIGHT condition. Consistent with our previous reports (Mizumori, Ragozzino et al., 2000; Yeshenko et al., 2004) , both hippocampal and striatal place fields reorganized when a vehicle solution was injected prior to dark trials. When the vehicle solution or SCH23390 was injected prior to dark trials (VEH-DARK and SCH-DARK, respectively), a different pattern emerged. Hippocampal place fields showed significantly greater reorganization in response to darkness under the influence of SCH23390 when compared to the SCH-LIGHT condition ($p < .01$). In contrast, striatal place fields showed similar amounts of reorganization in both SCH-LIGHT and SCH-DARK conditions. Thus, in familiar test conditions, D1 antagonism had greater effects on striatal place field reorganization than on hippocampal field reorganization. When tested after a change in visual context, D1 antagonism induced greater reorganization by hippocampal place fields than what was observed following D1 antagonisms in a familiar, constant environment. In contrast, striatal fields responded similarly to D1 antagonism regardless of context changes. These preliminary data are consistent with the proposal that the dopamine system differentially regulates hippocampal and striatal neural representation depending on the spatial context. Consequently, dopamine may play an important role in determining the relative contributions of hippocampus and striatum to learning.

Estrogen status may also bias the relative contribution of hippocampus and striatum during learning. Interestingly, estrogen's effects may be tied to the effects that estrogen has on the dopaminergic system, at least in striatum. It has been shown that tyrosine hydroxylase and dopamine turnover are higher during rising or high estrogen states compared to during low estrogen states in naturally cycling female rats (Fernandez-Ruiz, Hernandez, de Miguel, & Ramos, 1991). More recent work confirms that estrogen increases dopamine function, especially within the striatum. Intrastriatal injection of estrogen produces rapid effects on rotational behavior and enhances sensorimotor performance (e.g., Becker, 1990a, 1990b; Becker, Snyder, Miller, Westgate, & Jenuwine, 1987). The mechanism for this effect is thought not to involve classical estrogen receptor mechanisms (McEwen & Alves, 1999) since there are no intracellular estrogen receptors in striatum and since the estrogen effects occur very rapidly. Rather, a membrane-associated

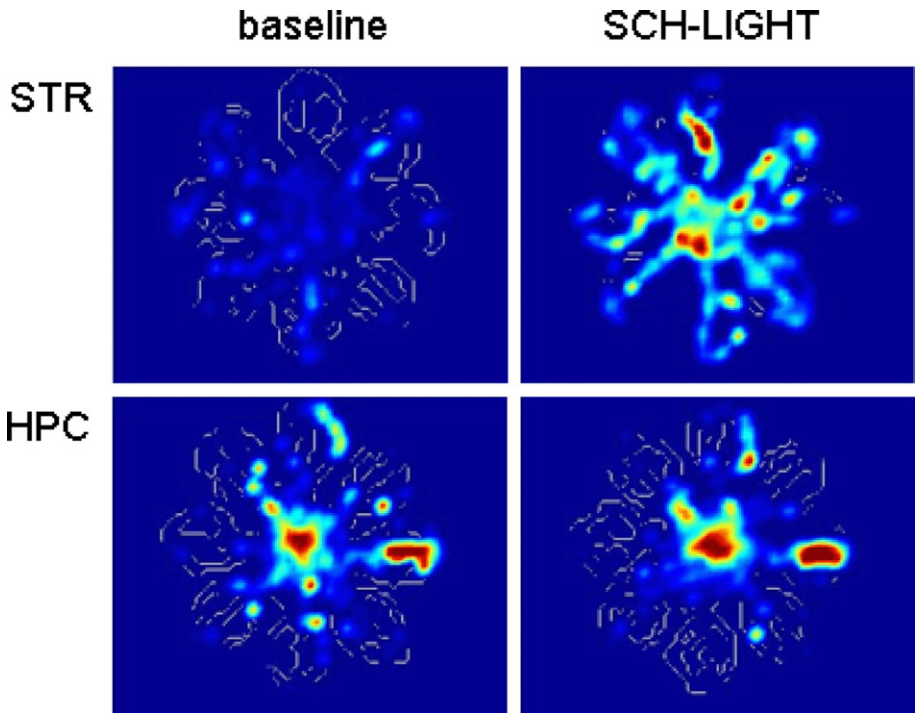


Fig. 12. Color density plots illustrating the effects of a D1 receptor antonist (SCH23390, or SCH) on striatal and hippocampal place fields recorded from rats performing a spatial working memory task on a radial arm maze. Striatal place fields appear to be more sensitive to disruption of dopaminergic function than hippocampal place fields. This pattern is consistent with the view that dopamine may differentially regulate the output of striatum and hippocampus.

receptor mechanism is postulated, perhaps one that interferes with DA autoreceptor/DA transporter coupling (Dluzen, 2000; Thompson, Bridges, & Weirs, 2001) and/or presynaptic potentiation of DA release. Indeed, estrogen pretreatment increases firing by nigrostriatal neurons after dopamine application (Arnaud, Duffy, Pestre, & Vincent, 1981). The functional increase in the availability of DA could ultimately enhance the ability of striatum to evaluate reinforcement consequences. This enhanced efficiency may translate into improved learning, a view consistent with the behavioral literature showing improved learning following administration of DA agonist agents (Nieoullon, 2002).

To begin to examine estrogen's impact on striatal representational stability, we recently assessed striatal neuron responsiveness to estrogen manipulation. Female rats were ovariectomized (OVX), and half of the rats received estrogen replacement by insertion of a 0.5 mg timed release tablet that maintains estrogen levels within the range observed naturally during the proestrous phase (OVX + E; Matsuda, Hirano, & Watanabe, 2002). The rats were also implanted with recording electrodes just above dorsal striatum. Striatal place cells were recorded during the performance of a spatial plus-maze task. Our initial analysis reveals that estrogen did not have an effect on striatal place field specificity. That is, the size and spatial clarity of the location-specific signal was the same for OVX and OVX + E rats. The reliability with which elevated cell firing was observed with each pass through the area of the field, however, was significantly affected by estrogen. OVX + E animals exhibited striatal place fields with greater reliability than the place fields recorded from OVX rats ($p < .05$). This finding suggests that estrogen may facilitate the stability of striatal place fields. If the reliability change is mediated via estrogen-induced dopamine release, then our finding is consistent with the finding that dopamine antagonists change the stability of striatal place fields (see above). Furthermore, estrogen-induced stability of striatal place fields might predict that hippocampal place fields are also more reliable, a prediction consistent with behavioral results that rats preferentially use a spatial strategy when tested during conditions of elevated estrogen levels (Korol & Kolo, 2002). Thus, we are currently examining hippocampal place field responses recorded in an identical test situation to determine whether estrogen, like dopamine, may differentially regulate the plasticity of neural representation in hippocampus and striatum.

8. Implications for selective roles of hippocampus and striatum during navigation

It is clear from the data presented that hippocampus and striatum engage in similar, though not identical, context-dependent task and behavior-related neural processing regardless of the current cognitive strategy. One question, then, is whether these structures as a whole make redundant or distinct contributions to adaptive navigation. It has been argued, based on the results of numerous lesion and behavioral studies as well as the neurophysiological results from primate and rodent studies, that hippocampus and striatum make separate contributions to navigation perhaps by incorporating similar types of information into neurocomputations defined by unique patterns of intrinsic connections (Mizumori, Ragozzino et al., 2000). Specifically, the striatum assists the navigational system by helping to define future actions that are appropriate for the current context, regardless of whether the task to be learned is stimulus–response in nature or involves the more flexible processing of context learning. It does so by engaging a *response reference system* that compares the sensory context-defined, expected success of a learned behavior with the actual success experienced by the animal. Such a function should be important for may forms of learning. Stimulus–response learning may appear as a special (but not sole) function of striatum because of the nature of the learning involved. Stimulus–response learning requires that an association be made between a well-defined, current external stimulus (or motor act) and its immediate consequence. Since, in theory, response flexibility is not required, and is in fact detrimental, for good performance, the most direct way to accomplish such learning is to use the lateral dorsal striatal connections with motor and somatosensory cortex that are direct and somatotopically organized (Crutcher & Alexander, 1990; Crutcher & DeLong, 1984). As a result, the learned responses seem relatively inflexible, habitual in appearance (because the response can be elicited with short latency), and slow to acquire because the process does not take advantage of the more rapid learning that is possible when response outcomes are associated with environmental contexts.

The hippocampus, in contrast, may serve as a *spatial context reference system* that determines the extent to which the expected sensory definition of a context matches the one currently being experienced (Mizumori et al., 1999). In the case of both hippocampus and striatum, output to memory systems should reflect the extent to which a match is detected. Many computational and neurophysiological models suggest that learning is error (or mismatch) driven (Schultz & Dickinson, 2000; Schultz et al., 2003). Signals corresponding to mismatch detection could, in the case of hippocampus, result in the updating of memory representations of the expected or learned spatial context. In the case of striatum, mismatch detection could result in the updating of memory representations regarding the learned reinforcement consequences of context-dependent sensory-motor associations. Signals corresponding to match detection

from either hippocampus or striatum could strengthen (or maintain) currently active networks of memory representations.

9. Implications for multiple memory systems theory

As noted above, several distinguishing features of hippocampal and striatal neural representations were identified that could contribute to their differential influence on learning. These include slight variation in the types of neural representation and/or the differential sensitivity of similar types of representations to changes in spatial context. Perhaps more surprising findings, however, were findings that (a) there were significant numbers of hippocampal and striatal neurons that represented similar kinds of information (e.g., place and egocentric movement) and (b) these representations responded in similar ways to changes in spatial context regardless of the current cognitive strategy. It would appear, then, that there is significantly more parallel processing across anatomically defined memory systems than previously thought. Moreover, this processing appears to be continuously, or automatically, engaged regardless of the specific task at hand.

Several patterns of neural responsiveness emerged, each one of which suggests new insight into the fundamental nature of the processing within and between neural systems. For example, one common observation across different categories of correlated neurons from both hippocampus and striatum was that changes in context produced only partial reorganization 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., expect spatial contexts, learned responses, or expected reinforcement outcomes), and if we assume that context-dependent neural codes reflect ongoing features of a current situation, then a fundamental principle that applies to diverse neural systems could be to engage 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 it provides a mechanism by which past experience can impact the processing of different forms in incoming information.

To determine whether parallel processing is the rule rather than the exception, it is worth noting the types of representations that have been reported for amygdala and prefrontal cortex, brain structures that allegedly mediate cue-affect association and working memory, respectively. Using comparable navigation-based tasks, Pratt and Mizumori (1998) reported that there is a combination of egocentric movement, reward, and spatial correlates of neurons within rat basolateral amygdala. Rat prefrontal cortex appears to contain mostly reward and egocentric movement correlates, with modest evidence of spatial codes (Jung, Qin, McNaughton, & Barnes, 1998; Poucet, 1997; Pratt & Mizumori, 2001). Thus, significant parallel processing may commonly occur during many forms of learning. There may be, however, region-specific variation to these processing functions.

During active navigation, representation of egocentric movement was the most common correlate type found across the neural systems that are thought to mediate different forms of learning. We also found that 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. [In this case, the term 'behavior' refers not only to the broad category of behavior exhibited (e.g., turn correlate), but also to the details of the behavior such as 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 sensory context-sensitive movement codes suggests that the behavioral context in which learning occurs is a fundamental unit of information that is useful for multiple forms of learning. The broad presence of behavioral context information may provide one (of many?) functional architectures through which different neural processing systems can be orchestrated (see Fig. 13). 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 mediates the global functional domain of behavioral expression (a processing domain that is responsible for behavioral selection, planning of actions, and the memory of behavioral acts). Frontal and parietal cortices are likely to be centrally involved in the operations of this functional domain. The feedback indicating a change in behavioral context may cause the activity landscape of the domain to reconfigure, which in turn provides adap-

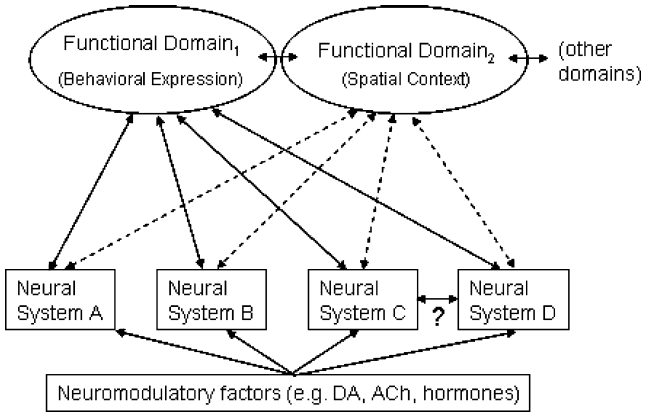


Fig. 13. A working hypothesis that describes how different neural systems interact to result in appropriate behavioral responses. *Neural systems* could refer to networks of structures, such as the basal ganglia or hippocampal system. Based on the data presented, it is postulated that each neural system operates continuously, and in parallel, regardless of the task at hand. In some cases, there may be direct interactions between neural systems (e.g., between hippocampus and amygdala). In other cases, there may not be direct communication (e.g., as in the case of hippocampus and striatum). However, the efficiency (and perhaps specificity) of processing within each neural system could differentially vary as a function of *neuromodulatory factors* such as dopamine, acetylcholine, or hormones such as estrogen. The output of each neural system is read by other neural networks (perhaps involving multiple areas of cortex) that are responsible for broad functions, termed *functional domains*. An example of a functional domain might be the expression of the appropriate behavior, or the understanding of the spatial context. Subprocesses with the behavioral expression domain might include behavioral selection, plans of action, or the memory of past behavioral acts. It is conceivable that each of the neural systems, as well as other functional domains, might inform each of the subprocesses within a given functional domain. The output of the behavioral expression domain, then, reflects the integration of the subprocesses to achieve the expression of the desired behavior. The appearance of different memory systems, then, could reflect the differential contributions of each neural system to the behavioral expression domain.

tive feedback that updates movement-sensitive representations in multiple neural systems.

Similar to the operation of the behavioral expression system, we postulate that there exists a distributed network that corresponds to spatial context memory (perhaps involving parietal and temporal cortices; Fig. 13). This network may function to coordinate spatial context codes within different neural systems, such as hippocampus and 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.

In addition to parallel processing of movement-related information, it appears that several structures contain place- and reward-related neural representations. This finding reveals that spatial and reward information may be integral for more than one type of neurocomputation. For example, place field information can be used to help identify changes in spatial context (in hippocampus) or to help define the overall learning context in which responses are made (in striatum). Reward-related information can be used to signal changes in the expected rewards (in striatum) or to identify the significance of locations in space (in hippocampus)

From the perspective of adaptation, it seems advantageous that discrete brain regions differentially process similar types of information in parallel. Such an organization creates a situation that allows for greater and more rapid behavioral flexibility in constantly changing environmental conditions (e.g., Mizumori, Ragozzino et al., 2000). Furthermore, more complex learning may be possible because there is greater potential for dynamic relationships between neural systems. These relationships may be dynamic in the sense that they can vary in type and degree depending upon a number of variables such as training conditions, hormone status, and task demands.

Similar to what is discussed in other articles within this issue, the specific relationship amongst neural systems can be *cooperative* in the sense that activation patterns in neural system A may be permissive for certain activation patterns in neural system B. When neural system B is activated in this way, there may be feedback to neural system A to affect future processing efficiency. The relationship amongst neural systems may also be *competitive*. In theory, such competition can take place in different ways. For example, activation of neural system A could directly preclude activation in a neural system B. This form of competition probably does not apply to hippocampus and striatum since both structures are clearly processing specific and task-related information in parallel. A different sort of competition is one that does not involve direct interactions between neural systems. Rather, the competition could take place within a Functional Domain. To apply this model to the relationship between hippocampus and striatum, one could argue that although they may continuously process information, it is the relative strengths of their output to the third neural system that determines their relative impact on ongoing behavior. The relative strengths of their output may be regulated by factors such as hormone status, task demands, and/or experience. Specific training protocols may differentially reinforce hippocampal or striatal processing styles, resulting in different strengths of output to behavioral control systems.

Our view of the distinctions between striatum and hippocampus can explain why only striatal lesions produce impairments in stimulus–response or egocentric learning. Both forms of response learning require an association between a well defined motor act, or current external stimulus, and the immediate consequence. Response learning can take advantage of the direct connections of lateral striatum with motor and somatosensory cortices. Hippocampus does not have such direct connections with motor or somatosensory cortex. Therefore we wouldn't expect hippocampus to be central for such response learning. We hypothesize that learning to navigate one's environment, on the other hand, can take place quickly because *both* striatal and hippocampal reference systems are engaged. To account for the finding that hippocampal lesions, but not striatal lesions, result in context learning deficits, we argue two points. First, in rodents, the lesions tend be found in either central or lateral dorsal striatum, leaving the medial striatum essentially intact. Selective medial striatal lesions produce spatial learning deficits (Devan & White, 1999), and medial striatum preferentially receives limbic input (Groenewegen, Vermeulen-Van de Zee, te Kortschot, & Witter, 1987). Also, medial and lateral striatum possess different NMDA systems, suggesting different mechanisms of neuroplasticity (Chapman, Keefe, & Wilcox, 2003). Second, there are two routes by which hippocampal information may impact behavior in an experience-dependent way (Mizumori, Pratt, Cooper, & Guazzelli, 2002) one initially involving striatal circuitry and another passing through cortical circuitry involving the retrosplenial cortex and medial precentral cortex (Mizumori, Ragozzino et al., 2000). Thus, even if the striatal route is rendered non-functional, spatial performance can improve. Since the spatial context comparator function of hippocampus is uniquely important for spatial or context learning, one usually finds deficits in such learning following lesions of only hippocampus. In sum, the extent to which one observes lesion-induced memory dissociations may reflect (at least in part) the unique patterns of extrinsic connections and the extent to which alternate systems are available to provide functional compensation.

10. Conclusion

Our search for the neural instantiation of the multiple memory systems theory has revealed that under natural (i.e., complex) learning situations such as adaptive navigation, several neural systems are actively engaged in task-relevant ways. Some differences were noted in terms of the types of neural representation found within each neural system, and these may importantly contribute to a selective role for these systems in learning. However, when considered on the whole, the most striking result is the high degree of similarity in terms of the types of neural representations found across diverse neural systems. Moreover, the dynamic responses of these representations were similar across structures. It is suggested that the important interactions between neural systems traditionally thought to subserve different forms of learning actually take place within a distributed network of neural activity that operate within functional domains, such as memory-guided behavioral expression or spatial context memory. Such a perspective leaves us with a view that different neural systems continuously engage in specific kinds of learning-related computations regardless of the task demands, and their relative influence on behavioral expression systems may vary depending upon a number of factors such as experience, hormone status, or motivation. Challenges facing the field is to identify the neural networks responsible for the selection of adaptive patterns of behavior, and how associative structures such as the hippocampus and striatum impact this process.

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References

Anderson, M. I., & Jeffery, K. J. (2003). Heterogeneous modulation of place cell firing by changes in context. *Journal of Neuroscience, 23*, 8827–8835.

Arnaud, E., Duffy, B., Pestre, M., & Vincent, J. D. (1981). Effects of estrogens on the responses of caudate neurons to microiontophoretically applied dopamine. *Neuroscience Letters, 21*, 325–331.

Becker, J. (1990a). Estrogen rapidly potentiates amphetamine-induced striatal dopamine release and rotational behavior during microdialysis. *Neuroscience Letters, 118*, 169–171.

Becker, J. (1990b). Direct effect of 17B-estradiol on striatum: Sex difference in dopamine release. *Synapse, 5*, 157–164.

Becker, J., Snyder, P. J., Miller, M. M., Westgate, S. A., & Jenuwine, M. J. (1987). The influence of estrous cycle and intrastriatal estradiol on sensorimotor performance in the female rat. *Pharmcology, Biochemistry and Behavior, 27*, 53–59.

Brito, G. N. O. (1992). Neurotransmitter systems in hippocampus and prelimbic cortex, dopamine-acetylcholine interactions in hippocampus, and memory in the rat. In E. D. Levin, M. W. Decker, & L. L. Butcher (Eds.), *Neurotransmitter interaction and cognitive function* (pp. 159–182). Boston: Birkhäuser.

Calabrese, P., Pisani, A., Mercuri, N. B., & Bernardi, G. (1996). The corticostriatal projection: From synaptic plasticity to dysfunctions of the basal ganglia. *Trends in Neuroscience, 19*, 19–24.

Chang, Q., & Gold, P. E. (2003). Switching memory systems during learning: Changes in patterns of brain acetylcholine release in the hippocampus and striatum in rats. *Journal of Neuroscience, 23*, 3001–3005.

Chapman, D. E., Keefe, K. A., & Wilcox, K. S. (2003). Evidence for functionally distinct synaptic NMDA receptors in ventromedial

versus dorsolateral striatum. *Journal of Neurophysiology, 89*, 69–80.

Colby, C. L., & Goldberg, M. E. (1999). Space and attention in parietal cortex. *Annual Review of Neuroscience, 22*, 319–349.

Cooper, B. G., & Mizumori, S. J. Y. (2001). Temporary inactivation of retrosplenial cortex causes a transient reorganization of spatial coding in hippocampus. *Journal of Neuroscience, 21*, 3986–4001.

Crutcher, M. D., & Alexander, G. E. (1990). Movement-related neuronal activity selectively coding either direction or muscle pattern in three motor areas of the monkey. *Journal of Neurophysiology, 64*, 151–163.

Crutcher, M. E., & DeLong, M. R. (1984). Single cell studies of the primate putamen. II. Relations to directions of movement and pattern of muscular activity. *Experimental Brain Research, 5*, 244–258.

Czurko, A., Hirase, H., Ssicsvari, J., & Buzsaki, G. (1999). Sustained activation of hippocampal pyramidal cells by 'space clamping' in a running wheel. *European Journal of Neuroscience, 11*, 344–352.

Devan, B. D., & White, N. M. (1999). Parallel information processing in the dorsal striatum: Relation to hippocampal formation. *Journal of Neuroscience, 19*, 2789–2798.

Dluzen, D. (2000). Neuroprotective effects of estrogen upon the nigrostriatal dopaminergic system. *Journal of Neurocytology, 29*, 387–399.

Eacott & Norman (2004). Integrated memory for object, place, and context in rats: A possible model of episodic-like memory? Journal of Neuroscience*, 24*, 1948–1953.

Eichenbaum, H., & Cohen, N. J. (2001). *From conditioning to conscious recollection: Memory systems of the brain*. New York: Oxford University Press.

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., & Tanila, H. (1999). The hippocampus, memory, and place cells: Is it spatial memory or a memory space? *Neuron, 23*, 209–226.

Ferbinteanu, J., & Shapiro, M. L. (2003). Prospective and retrospective memory coding in the hippocampus. *Neuron, 40*, 1227–1239.

Fernandez-Ruiz, J., Hernandez, M., de Miguel, R., & Ramos, J. (1991). Nigrostriatal and mesolimbic dopaminergic activities were modified throughout the ovarian cycle of female rats. *Journal of Neural Transmission: Genetics Section, 85*, 223–229.

Forster, G. L., & Blaha, C. D. (2000). Laterodorsal tegmental stimulation elicits dopamine efflux in the rat nucleus accumbens by activation of acetylcholine and glutamate receptors in the ventral tegmental area. *European Journal of Neuroscience, 12*.

Frank, L. M., Brown, E. N., & Wilson, M. A. (2001). A comparison of the firing properties of putative excitatory and inhibitory neurons from CA1 and the entorhinal cortex. *Journal of Neurophysiology, 86*, 2029–2040.

Gasbarri, A., Introini-Collison, I. B., Packard, M. G., Pacitti, C., & McGaugh, J. L. (1993). Interaction of cholinergic–dopaminergic systems in the regulation of memory storage in aversively motivated learning tasks. *Brain Research, 627*, 72–78.

Gasbarri, A., Packard, M. G., Campana, E., & Pacitti, C. (1994). Anterograde and retrograde tracing of projections from the ventral tegmental area to the hippocampal formation in the rat. *Brain Research Bulletin, 33*, 445–452.

Gill, K. M., & Mizumori, S. J. Y. (2002). Dopamine influences on neural representation in striatum during performance on a spatial task. *Society for Neuroscience Abstracts*.

Gold, P. E. (2003). Acetylcholine modulation of neural systems involved in learning and memory. *Neurobiology of Learning and Memory, 80*, 194–210.

Groenewegen, H. J., Vermeulen-Van de Zee, E., te Kortschot, A., & Witter, M. P. (1987). Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of *Phaseolus vulgaris* leucoagglutinin. *Neuroscience, 23*, 103–120.

Hayman, R. M., Chakraborty, S., Anderson, M. I., & Jeffery, K. J. (2003). Context-specific acquisition of location discrimination by hippocampal place cells. *Eur. J. Neurosci., 18*(10), 2825–2834.

Hikosaka, O., Sakamoto, M., & Usui, S. (1989). Functional properties of monkey caudate neurons. III. Activities related to expectation of target and reward. *Journal of Neurophysiology, 61*, 814–832.

Houk, J. C. (1995). Information processing in modular circuits linking basal ganglia and cerebral cortex. In J. C. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Models of information processing in the basal ganglia* (pp. 3–10). Cambridge: MIT Press.

Huxter, J., Burgess, N., & O'Keefe, J. (2003). Independent rate and temporal coding in hippocampal pyramidal cells. *Nature, 425*, 828–832.

Jog, M. S., Kubota, Y., Connolley, C. I., Hillegaart, V., & Graybiel, A. M. (1999). Building neural representations of habits. *Science, 286*, 1745–1749.

Jung, M. W., Qin, Y., McNaughton, B. L., & Barnes, C. A. (1998). Firing characteristics of deep layer neurons in prefrontal cortex in rats performing spatial working memory tasks. *Cerebral Cortex, 8*, 437–450.

Kennedy, P. J., & Shapiro, M. L. (2003). The hippocampal system and the expression of differentially motivated responses in a non-spatial task. Program No. 289.5. *2003 Abstract Viewer/Itinerary Planner*. DC: Society for Neuroscience, 2003. Online.

Kesner, R. P., Bolland, B. L., & Dakis, M. (1993). Memory for spatial locations, motor responses, and objects: Triple dissociation among the hippocampus, caudate nucleus, and extrastriate visual cortex. *Experimental Brain Research, 93*, 462–470.

Knierim, J. J. (2002). Dynamic interactions between local surface cues, distal landmarks, and intrinsic circuitry in hippocampal place cells. *Journal of Neuroscience, 15*, 6254–6264.

Knierim, J. J., Kudrimoti, H. S., & McNaughton, B. L. (1998). Interactions between idiothetic cues and external landmarks in the control of place cells and head direction cells. *Journal of Neuroscience, 80*, 425–446.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science, 273*, 1399–1402.

Korol, D. L., & Kolo, L. L. (2002). Estrogen-induced changes in place and response learning in young adult female rats. *Behavioral Neuroscience, 116*, 411–420.

Leutgeb, S., & Mizumori, S. J. Y. (1999). Excitotoxic septal lesions result in spatial memory deficits and altered flexibility of hippocampal single unit representations. *Journal of Neuroscience, 19*, 6661–6672.

Leutgeb, S., & Mizumori, S. J. Y. (2002). Context-specific spatial representations by lateral septal cells. *Neuroscience, 112*, 655–663.

Leutgeb, S., Ragozzino, K. E., & Mizumori, S. J. Y. (2000). Convergence of head direction and place information in the CA1 region of hippocampus. *Neuroscience, 100*, 11–19.

Matsuda, Y., Hirano, H., & Watanabe, Y. (2002). Effects of estrogen on acetylcholine release in frontal cortex of female rats: Involvement of serotonergic neuronal systems. *Brain Research, 937*, 58–65.

McDonald, R. J., & White, N. M. (1993). A triple dissociation of memory systems: Hippocampus, amygdala and dorsal striatum. *Behavioral Neuroscience, 107*, 3–22.

McEwen, B. S., & Alves, S. E. (1999). Estrogen actions in the central nervous system. *Endocrine Reviews, 20*, 279–307.

McNaughton, B. L., Barnes, C. A., & O'Keefe, J. (1983). The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Experimental Brain Research, 52*, 41–49.

Milner, B., Corkin, S., & Teuber, H. L. (1968). Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologia, 6*, 215–234.

Mizumori, S. J. Y., Cooper, B. G., Leutgeb, S., & Pratt, W. E. (2000). A neural systems analysis of adaptive navigation. *Molecular Neurobiology, 21*, 57–82.

Mizumori, S. J. Y., McNaughton, B. L., Barnes, C. A., & Fox, K. B. (1989). Preserved spatial coding in hippocampal CA1 pyramidal cells during reversible suppression of CA3 output: Evidence for pattern completion in hippocampus. *Journal of Neuroscience, 9*, 3915–3928.

Mizumori, S. J. Y., Pratt, W. E., Cooper, B. G., & Guazzelli, A. (2002). The behavioral implementation of hippocampal processing. In P. E. Sharp (Ed.), *The neural basis of navigation: Evidence from single cell recording* (pp. 197–216). Dordrecht: Kluwer.

Mizumori, S. J. Y., Ragozzino, K. E., & Cooper, B. G. (2000). Location and head direction representation in the dorsal striatum of rats. *Psychobiology, 28*, 441–462.

Mizumori, S. J. Y., Ragozzino, K. E., Cooper, B. G., & Leutgeb, S. (1999). Hippocampal representational organization and spatial context. *Hippocampus, 9*, 444–451.

Mizumori, S. J. Y., & Williams, J. D. (1993). Directionally-selective mnemonic properties of neurons in the lateral dorsal nucleus of the thalamus of rats. *Journal of Neuroscience, 13*, 4015–4028.

Morris, R. G. M. (2001). Episodic-like memory in animals: Psychological criteria, neural mechanisms and the value of episodic-like tasks to investigate animal models of neurodegenerative disease. *Philosophical Translations of the Royal Society of London, Series B: Biological Science, 356*, 1453–1465.

Muir, G. M., & Bilkey, D. K. (2003). Theta- and movement velocity-related firing of hippocampal neurons is disrupted by lesions centered on the perirhinal cortex. *Hippocampus, 13*, 93–108.

Muller, R. U., & Kubie, J. (1987). The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *Journal of Neuroscience, 7*, 1951–1968.

Nadel, L., & Wilner, J. (1980). Context and conditioning: A place for space. *Physiological Psychology, 8*, 218–228.

Nieoullon, A. (2002). Dopamine and the regulation of cognition and attention. *Progress in Neurobiology, 67*, 53–83.

O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely moving rat. *Brain Research, 34*, 171–175.

O'Keefe, J., & Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Clarendon.

O'Keefe, J., & Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus, 3*, 317–330.

O'Keefe, J., & Speakman, A. (1987). Single unit activity in the rat hippocampus during a spatial memory task. *Experimental Brain Research, 68*, 1–27.

Packard, M., & McGaugh, J. L. (1996). Inactivation of hippocampus and caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of Learning and Memory, 65*, 5–72.

Phillips, A. G., Ahn, S., & Howland, J. G. (2003). Amygdalar control of the mesocorticolimbic dopamine system: Parallel pathways to motivated behavior. *Neuroscience and Biobehavioral Reviews, 27*, 543–554.

Poucet, B. (1997). Searching for spatial unit firing in the prelimbic area of the rat medial prefrontal cortex. *Behavioural Brain Research, 84*, 151–159.

Pratt, W. E., & Mizumori, S. J. Y. (1998). Characteristics of basolateral amygdala neuronal firing on a spatial memory task involving differential reward. *Behavioral Neuroscience, 112*, 554–570.

Pratt, W. E., & Mizumori, S. J. Y. (2001). Neurons in rat medial prefrontal cortex show anticipatory rate changes to predictable differential rewards in a spatial memory task. *Behavioural Brain Research, 123*, 165–183.

Quirk, G. J., Muller, R. U., & Kubie, J. L. (1990). The firing of hippocampal place cells in the dark depends on the rat's recent experience. *Journal of Neuroscience, 10*, 2008–2017.

Ragozzino, K. E., Leutgeb, S., & Mizumori, S. J. Y. (2001). Conditional coupling of dorsal striatal head direction and hippocampal place representations during spatial navigation. *Experimental Brain Research, 139*, 372–376.

Ranck, J. B. Jr., (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. I. Behavioral correlates and firing repertoires. *Experimental Neurology, 41*, 461–531.

Rose, G. (1983). Physiological and behavioral characteristics of dentate granule cells. In W. Seifert (Ed.), *Neurobiology of the hippocampus* (pp. 449–472). New York: Academic Press.

Ruskin, D. N., Bergstrom, D. A., Kaneoke, Y., Patel, B. N., Twery, M. J., & Walters, J. R. (1999). Multisecond oscillations in firing rate in the basal ganglia: Robust modulation by dopamine receptors and anesthesia. *Journal of Neurophysiology, 81*, 2046–2055.

Schultz, W., & Dickinson, A. (2000). Neuronal coding of prediction errors. *Annual Review of Neuroscience, 23*, 473–500.

Schultz, W., Tremblay, L., & Hollerman, J. R. (2003). Changes in behavior-related neuronal activity in the striatum during learning. *Trends in Neuroscience*.

Seutin, V., Johnson, S. W., & North, R. A. (1993). Apamin increases NMDA-induced burst-firing of rat mesencephalic dopamine neurons. *Brain Research, 630*, 341–344.

Shapiro, M., Tanila, H., & Eichenbaum, H. (1997). Cues that hippocampal place cells encode: Dynamic and hierarchical representation of local and distal stimuli. *Hippocampus, 7*, 624–642.

Smialowski, A., & Bijak, M. (1987). Excitatory and inhibitory action of dopamine on hippocampal neurons in vitro. Involvement of D2 and D1 receptors. *Neuroscience, 23*, 95–101.

Taube, J. S. (1995). Head direction cells recorded in the anterior thalamic nuclei of freely moving rats. *Journal of Neuroscience, 15*, 70–86.

Taube, J. S., Muller, R. U., & Ranck, J. B. Jr., (1990). Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *Journal of Neuroscience, 10*, 420–435.

Thompson, T. L., Bridges, S. R., & Weirs, W. J. (2001). Alterations of dopamine transport in the striatum and nucleus accumbens of ovariectomized estrogen primed rats following N-(P-isothiocyanantophenethyl)spiperone (NIPS) treatment. *Society for Neuroscience Abstract*.

Vanderwolf, C. (1969). Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalography and Clinical Neurophysiology, 26*, 407–418.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science, 277*, 376–380.

Weiner, S. I. (1993). Spatial and behavioral correlates of striatal neurons in rats performing a self-initiated navigation task. *Journal of Neuroscience, 13*, 3802–3817.

Wood, E. R., Dudchenko, P. A., & Eichenbaum, H. (1999). The global record of memory in hippocampal neuronal activity. *Nature*, 613–616.

Yeshenko, O., Guazzelli, A., & Mizumori, S. J. Y. (2004). Context-dependent reorganization of spatial and movement representations by simultaneously recorded hippocampal and striatal neurons during performance of allocentric and egocentric tasks. *Behavioral Neuroscience, 118*, 751–769.