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Context-Dependent Modulation by D_1 Receptors: Differential Effects in Hippocampus and Striatum

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Place-specific firing by hippocampal and striatal neurons was recorded simultaneously following injection of a D_1 receptor antagonist (SCH23390) and during spatial working memory task performance. SCH23390-induced changes in unit responses were observed during light and dark test conditions. Although hippocampal place field locations were altered by the contextual change, the reliability and specificity of place fields was disrupted only by combining D_1 antagonism and a change in context. Striatal place field locations were reorganized after either contextual change or D_1 antagonism, without altering place field reliability and specificity. Disrupted velocity encoding by place cells in both regions was induced by darkness, whereas greater stability in acceleration encoding followed removal of D_1 receptor activity. Dopamine may differentially regulate hippocampal context learning and striatum-based predictive codes.

Keywords: place cells, spatial memory, rat, dopamine, spatial context

Imaging studies have shown that hippocampal activation is associated with use of spatial cues or the evaluation of contextual information related to spatial memory (Maguire et al., 1998; Rosenbaum, Gao, Richards, Black, & Moscovitch, 2005). Without an intact hippocampus (HPC), humans demonstrate impaired performance during tasks requiring the use of spatial information (Parslow et al., 2005). In rodents, hippocampal pyramidal neurons fire selectively when animals occupy specific locations (*place fields*) within a given environment (O'Keefe & Dostrovsky, 1979). Current research has indicated that these "place cells" may encode the situational relevance of locations in space, or spatial context, and reinforce a role for HPC in spatial processing (Jeffery, Anderson, Hayman, & Chakraborty, 2004; Mizumori, Cooper, Leutgeb, & Pratt, 2000; Mizumori, Ragozzino, Cooper, & Leutgeb, 1999; Nadel & Hardt, 2004).

It is likely that other brain regions contribute to spatial learning. In rodents, lesions of the dorsal striatum (STR) result in spatial learning deficits (Devan, McDonald, & White, 1999; Sakamoto & Okaichi, 2001). In addition, striatal place fields have been identified (Mizumori et al., 1999, Mizumori, Cooper, et al., 2000), and these, like hippocampal place fields, change locations, or reorganize, after alterations in spatial context (Yeshenko, Guazzelli, & Mizumori, 2004). Similar to hippocampal place fields, striatal place fields dynamically respond to context changes regardless of the task at hand.

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It appears that HPC and STR continually process context information regardless of whether the evaluation of context is essential for task performance. Seemingly inconsistent with the unit results, hippocampal and striatal damage results in distinct deficits in spatial and response learning, respectively (McDonald & White, 1993; Packard & McGaugh, 1996). That is, HPC-lesioned rats show spatial learning deficits but intact nonspatial learning, whereas STR-lesioned rats demonstrate the opposite pattern of learning impairments. As mentioned previously, HPC is necessary in humans for the active use of currently available spatial or contextual cues as part of its role in episodic memory formation (Holdstock et al., 2002; Rosenbaum, Winocur, & Moscovitch, 2001). In contrast, damage to STR selectively interferes with procedural learning while leaving the spatial memory process relatively intact (Packard & Knowlton, 2002). To account for the finding of parallel neural representation in HPC and STR, and differing effects of hippocampal and striatal lesions on learning, it had been proposed (Mizumori, Yeshenko, Gill, & Davis, 2004) that task-relevant firing by hippocampal or striatal neurons may come to control behavioral expression systems during learning as the relative strength of hippocampal or striatal output changes during learning. Output strength can be determined according to task demands. In this way, hippocampal or striatal modes of processing can have greater or lesser influence on behavioral output in a task-relevant manner. It has been suggested that neuromodulators (e.g., dopamine) contribute to the determination of the relative strengths of the efferent signals (Mizumori et al., 2004). The present study provides a first test of this hypothesis by assessing whether dopamine has different effects on neural representation by hippocampal and striatal neurons.

Behavioral evidence has indicated that dopamine can act locally within HPC and STR to differentially impact processing relevant to different kinds of learning. Selective lesions of striatal and hippocampal dopamine afferent systems impair response or spatial learning, respectively (Da Cunha, et al., 2003; Gasbarri, Sulli,

Innocenzi, Pacitti, & Brioni, 1996; Miyoshi et al., 2002). Similarly, posttraining infusion of selective dopamine agonists in STR can enhance win–stay or stimulus–response learning on the radial maze, whereas win–shift performance is enhanced by similar infusions in HPC (Packard & White, 1991). The physiological mechanism underlying the dissociation between hippocampal and striatal function is not known. Anatomically, the pattern of dopamine innervation of HPC and STR is distinct. Although dopamine terminals within the STR have multiple synaptic targets, those arriving in HPC typically exhibit single synaptic connections (Fallon, 1981). HPC receives dopamine input from the ventral tegmental area, whereas the substantia nigra provides the same input to the STR (Beckstead, Domesick, & Nauta, 1979; Gerfen, Staines, Arbuthnott, & Fibiger, 1982). Despite different patterns of connectivity, dopamine appears to exert significant influences on both striatal and hippocampal neuroplasticity. For example, dopamine D_1 receptor activity has been shown to be important for either the induction or maintenance of long-term potentiation in both HPC and STR (Calabresi, Centonze, Gubellini, Marfia, & Bernardi, 1999; Centonze, Gubellini, Pisani, Bernardi, & Calabresi, 2003; Frey, Matthies, Reymann, & Matthies, 1991; Kerr & Wickens, 2001) and of the stabilization of hippocampal place fields (Kentros, Agnihotri, Streater, Hawkins, & Kandel, 2004).

In this study, we sought to determine whether dopamine plays a significant role in determining the relative strengths of hippocampal or striatal neural firing patterns or output signals. Presumably, more reliable and specific neural signaling has a greater likelihood of impacting efferent structures. Consequently, the reliability and specificity of neural representations could be taken to reflect the strength of the output signal. The specific hypothesis then is that manipulation of the dopaminergic system differentially affects the reliability or specificity of the neural codes within HPC and STR. Because place cells are common to both the STR and HPC (O'Keefe, 1979; Mizumori et al., 1999; Mizumori, Cooper, et al., 2000), we compared the responses of simultaneously recorded striatal and hippocampal cells with the selective D_1-receptor antagonist, SCH23390 (Sigma Chemical, St. Louis, MO). Rats were trained on a spatial working memory task in which accurate performance requires an intact HPC (Becker, Walker, & Olton, 1980). Our previous work showed that imposed darkness causes reliable behavioral impairments and neural responses during performance of the spatial working memory task (Ragozzino, Leutgeb, & Mizumori, 2001). Therefore, this study tested the effects of D_1 antagonism on behavioral and neural responses to dark testing to maximize our ability to explore the extent to which D_1 receptors gate context-dependent neural plasticity. By selecting a spatial task, we hoped to bias the signaling strength of hippocampal neurons such that hippocampal place fields would appear more selective and/or reliable than would striatal place fields. If the dopaminergic system contributes to the biased signal strength, then disruption of dopamine function should have a preferentially greater effect on the specificity and reliability of hippocampal place fields than striatal place fields.

Method

Subjects

Male Long-Evans rats ($N = 12$) obtained from Charles River Laboratories (Raleigh, NC) were used in the following experiment. Rats were housed individually in a temperature- and humidity-controlled environment with a 12-hr light cycle (lights on at 7 a.m.). Rats were given 1 week on arrival to acclimate to the laboratory environment prior to any experimental procedures. During this time, rats had ad libitum access to food and water while being handled and weighed daily. Once behavioral training commenced, rats were maintained at approximately 80% of their free-feeding weight.

Apparatus

All behavior in this study was conducted on a semiautomated modified eight-arm radial maze, consisting of eight black Plexiglas runways (58 × 5.5 cm) that extended from a central platform (19.5 cm in diameter) and were 79 cm tall. Each runway was hinged in the center and could be raised and lowered via remote control. Rats were able to reach the reward at the ends of maze arms only after the arms were raised to be flush with the center platform. The maze was enclosed within a circular black curtain (10′ in diameter) hung from an overhead track. Visual cues were hung on the curtain in constant locations.

Behavioral Training

During pretraining, rats were made accustomed to the chocolate milk reward to be used during training by receiving it in their home cage. On Day 1 of the maze exposure all eight arms were available and baited. Once rats consistently retrieved rewards from all arms, they were then trained daily to perform a spatial working memory task on the eight-arm radial maze. Each trial consisted of an initial training phase of the random presentation of a four-arm forced-choice sequence. When rats consumed the reward on the fourth forced-choice arm, the test phase commenced and all arms were made available. Errors were recorded when a rat placed all four paws on an arm previously visited in either the training phase of the test phase. Time to complete each trial was measured by the rat's initial entry into the first forced-choice arm in the training phase until the return to the center platform following reward consumption on the final arm. Prior to surgery, rats were trained to perform 10 trials until an accuracy rate of 80% of trials completed without errors was attained.

After allowing 1 week of recovery following surgery, rats were retrained to asymptotic levels prior to any experimental manipulations to ensure stable performance and to allow acclimation to the headstage assembly. Subsequently, unit recording began along with counterbalanced presentation of both pharmacological and environmental manipulations. During each day of testing, rats performed five baseline trials to provide both control unit and behavioral data (Block 1). Rats were then removed from the maze and were administered a subcutaneous injection of either saline or the D_1 antagonist, SCH23390 (5 μg/kg) before being returned to the center platform for a 5-min postinjection interval. Rats then performed five additional trials with either normal room lighting or all lights extinguished. Therefore, there were four treatment conditions: saline–light, saline–dark, SCH23390–light, and SCH23390–dark.

Electrode Construction and Surgical Procedures

Stereotrode and microdrive construction was based on techniques provided by McNaughton, Barnes, and O'Keefe (1983a). Two Teflon-coated platinum wires were twisted together and coated in Epoxylite prior to being loaded into a 30-gauge cannula, leaving 1–2 mm of wire exposed at the bottom. Each drive assembly consisted of two to three loaded cannulas spaced 0.4 mm apart. Two microdrives were placed above each hemisphere, one above STR and the other above HPC. Prior to surgery, the stereotrode tips were cut at a 45° angle and gold plated to an impedance of 100–200 Kohm (tested at 1 kHz). Rats were anesthetized with sodium Pentobarbital (40 mg/kg initial dose and 0.05 cc supplements as needed) and fixed in a stereotaxic apparatus (David Kopf Instruments, Tujunga,

CA). To minimize respiratory distress, atropine sulfate was administered as well (0.2 mg/kg). Burr holes were drilled through the skull and electrode drive assemblies were then bilaterally placed above the STR (0.2–1.2 mm anterior to bregma, 1.7 mm lateral, 1.8 mm ventral to the brain surface) and HPC (−4.5–5.5 mm posterior to bregma, 2.5 mm lateral, 1.8 mm ventral). A reference electrode (114 μm Teflon-coated stainless steel wire) was inserted into the corpus callosum, and a ground screw was attached to the skull. To prevent infection, all rats were administered Baytril (5 mg/kg, im), and Ketofen (5 mg/kg, im) was given as a postsurgical analgesic. Rats were allowed 1 week of recovery, during which time they were allowed free access to food. Food restriction was reinstituted prior to advancement of drives as was monitoring of unit activity on each stereotrode in preparation for behavioral testing.

Drug Preparation and Administration

SCH23390 was mixed fresh daily in 0.9% saline and administered by subcutaneous injection. Pilot studies have shown 5 μg/kg to be an effective subcutaneous dose that elicits changes in striatal and hippocampal unit activity without causing an inability to complete the task. Other studies that have used similar doses have illustrated reductions in reaction times and anticipatory responses that are indicative of impaired voluntary movement (Bushnell & Levin, 1993; Courtiere, Hardouin, Goujon, Vidal, & Hasbroucq, 2003).

Behavioral Monitoring

The movement of each rat was monitored via a pair of front and back infrared light-emitting diode arrays. An automatic tracking system sampled the position of the front diode array (20 Hz) and determined the rat's position in the maze (resolution = 2.5 cm/pixel). Both diode arrays were used to determine the directional heading of the rat. Time stamps for both positional and unit data were recorded by Cheetah data acquisition software (Neuralynx, Tucson, AZ).

Unit Identification

Four stereotrodes were used to record cellular activity in each of the STR and HPC. The preamplification headstage (NB Labs, Denison, TX) consisted of 48 high-input field-effect transistors. Using the Cheetah data acquisition system (Neuralynx, Tucson, AZ), each waveform was amplified 1,000 to 10,000 times, and filtered at 600 Hz and 6 kHz. Prior to behavioral testing, stereotrodes were observed for the presence of spontaneous cellular activity. If no clear units were present, stereotrodes were lowered in 22-μm increments or up to 200 μm per day. Only signals exhibiting activity that was at least 3 times greater than background levels and exceeded a user-defined threshold were recorded. Units were clustered offline by using MCLust software (by A. Redish, University of Minnesota, Minneapolis). Additional template matching analysis routines were provided by Chris Higginson. Mean spike amplitude, spike width, and average firing rate were calculated for each cell. Place cells were defined in part by their low firing rates (<3 Hz) and broad spike widths (>300 ms; latency difference between the maximum and minimum voltage points of the analog signal).

Data Analysis

Several analysis routines were used to compare unit characteristics with behavioral events (custom software provided by Chris Higginson, University of Washington, Seattle). Positional data for each recording session was viewed offline. Event flags were assigned to the beginning of each trial (when the rat entered the first forced-choice arm) and to the end of each trial (when the rat returned to the center platform after consuming the reward on the last remaining arm). In addition, flags were inserted to divide the record into Block 1 (initial five baseline trials) and Block 2 (five trials performed after pharmacological and environmental manipulations). The average firing rates during Block 1, Block 2, and the entire session were determined for each cell. The behavior of each rat was assessed in terms of the average number of errors performed in each block as well as latency to complete each trial.

Classification and Analysis of Location Specific Neurons

To determine the spatial distribution of cell firing, the maze area was divided into pixels of equal size (2.8 × 2.8 cm), and an average firing rate was calculated for each pixel. For illustration purposes, the spatial firing pattern was revealed by highlighting those pixels in which the firing rate exceeded 20% of the maximum firing rate for the session. Place fields were characterized by several criteria: (a) The area of highest firing encompassed at least four adjacent highlighted pixels, (b) the firing rate that occurred inside the field area was at least twice as large as the rate that occurred at locations outside of the field, and (c) the cell that fired during at least 50% of the passes through the location of the principle (i.e., largest) field was considered to have a reliability of at least 50%. The same criteria for establishing spatially selective neurons were used in STR and HPC.

Once a neuron was recognized to possess spatial properties during either the baseline or manipulation phases, it was subject to further analysis. Reliability (defined previously) and specificity measures for the primary field of each cell were calculated. Place-field specificity scores reflected the probability that the rat was in a given location when the cell fired. Because both positive and negative changes in these measures were observed, the absolute value of the change in field reliability and specificity across blocks was calculated, and an analysis of variance (ANOVA) was used to determine the effects of treatment condition. In addition, linear regression was used to compare baseline and treatment condition place field reliability and specificity. A spatial correlation score was also obtained by calculating a pixel by pixel Pearson correlation of cell firing across commonly visited pixels in Block 1 and Block 2. The spatial correlation scores were used as a measure of place field reorganization. ANOVA of the average spatial correlation values for each treatment condition was used to identify differences between striatal and hippocampal neural responses to D_1 antagonism or contextual changes.

Analysis of Velocity and Acceleration Encoding by Location Specific Neurons

Past studies have reported the encoding of egocentric movement by place cells in HPC (Czurko, Hirase, Csicsvari, & Buzsaki, 1999; McNaughton, et al., 1983b). Consequently, all place cells recorded in the HPC and STR were analyzed for potential correlations between firing rates and movement velocity or acceleration. Significant (linear) relationships between neural firing rates and velocity (2.24 cm/s bin size) or acceleration (2.24 cm/s^2) were identified on the basis of a 95% confidence interval (α = .05). The number of cells gaining or losing significant correlations with velocity or acceleration during the manipulation phase of testing was determined. For cells that remained significantly correlated with velocity or acceleration across both phases of testing, a Wilcoxon's analysis ($\alpha < .05$) was performed to determine whether the distribution of firing across different velocity or acceleration bins was altered as a function of experimental manipulation. The proportion of cells that showed a significant change from baseline in terms of velocity or acceleration correlates was determined by adding the number of cells that exhibited significantly different linear relationships after a manipulation to the number of cells gaining or losing significant correlations with velocity or acceleration. For both HPC and STR, chi-square analysis was used to determine whether the proportions of cells changing after manipulations were different from those observed in the saline–light condition.

Histological Procedures for Electrode Placement Verification

Once electrodes had been lowered past the region of interest (5.0 mm ventral to the brain surface for STR and 4.0 mm for HPC), rats were deeply anesthetized with sodium pentobarbital and perfused transcardially with a 0.9% buffered NaCl solution followed by 10% formalin. Brains were sliced in 40 μm sections on a vibratome and stained with cresyl violet. Electrode track verification was accomplished by comparing depth measurements at the time of recording with electrode track reconstructions from serial sections from each hemisphere.

Results

Behavioral Effects of Dopamine Antagonism

Behavioral data were pooled from eight rats that received all possible treatment combinations (e.g., saline–light, saline–dark, SCH23390–light, SCH23390–dark) and four rats tested only during the two dark condition procedures (saline–dark and SCH23390–dark). For each day of testing, the average number of errors committed and the amount of time spent per arm entry were calculated for both the baseline and manipulation phases. Difference scores for both measures were obtained by subtracting the manipulation phase average values from those recorded during the baseline phase. In cases when an individual rat received multiple exposures to a given treatment condition, average difference scores for each condition were used in the statistical analysis. Analysis of the difference scores revealed treatment effects in terms of an increase in errors during the manipulation phase (see Figure 1A), $F(3, 36) = 18.30$, $p < .001$. Tukey's post hoc comparisons of the number of errors between saline–light ($M \pm SEM = 0.23 \pm 0.50$) and each of the dark conditions (saline–dark and SCH23390–dark) revealed an increase in the average number of errors (5.9 ± 0.90 errors, $p < .001$), and (6.67 ± 0.91 errors, $p < .001$), respectively. This effect on behavior could not be attributed to D_1 antagonism per se, because performance during the SCH23390–light condition (0.11 ± 0.68 errors, *ns*) was not significantly different from the saline control and because saline–dark showed the same effect as SCH23390–dark.

The differences in choice latency between baseline and manipulation phases were used as a measure of experimental-induced alterations in motor function. Overall, there was a significant difference across the treatment conditions in terms of the amount of time required for each arm entry (see Figure 1B), $F(3, 36) = 5.20$, $p < .01$. In both SCH23390–light and SCH23390–dark conditions, the average arm entry time was significantly longer than during the baseline phase (4.60 ± 2.01 s, $p < .05$, and 5.41 ± 0.74 s, $p < .001$, respectively). This pattern indicates that SCH23390 had the effect of slowing performance regardless of lighting condition. To determine whether this slowed performance was related to choice accuracy, we tested whether latency was correlated with the number of errors. For only one condition (SCH23390–dark) did we find a significant negative correlation between arm entry time and the error difference scores ($r = .62$, $p < .05$). In this case, contrary to a motor impairment-induced increase in errors, rats committed fewer errors when the arm-entry time increased (see Figure 2).

Overall, altering the visual environment had more devastating effects than did D_1 antagonism on the ability of the rats to perform the working memory task accurately. D_1-antagonism may have behavioral effects as well, yet given the substantial nature of the dark-induced impairment, we may not have been able to detect further decline in performance accuracy from the SCH23390 injection. However, SCH23390 was ineffective in increasing errors when administered without a simultaneous contextual change but did have an effect in disrupting response latency. Thus, D_1 antagonism per se did not impact choice accuracy despite having effects on response latency.

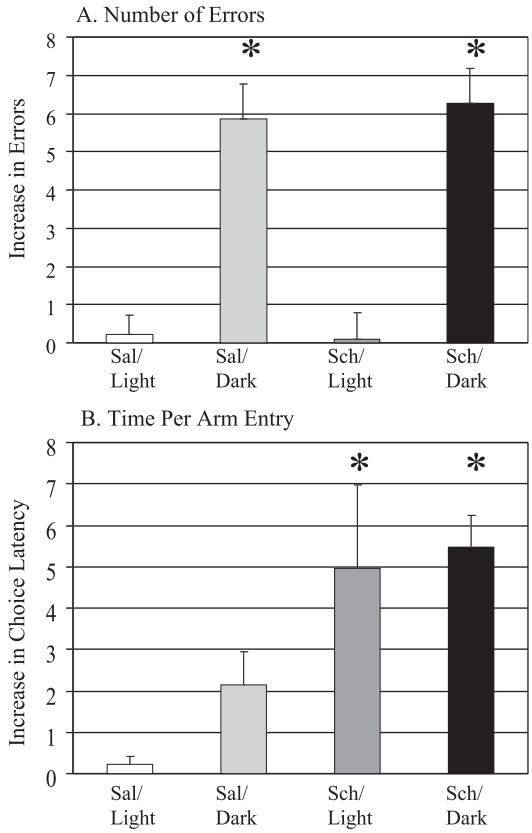

Figure 1. Summary of the behavioral responses to D_1 antagonism and imposed darkness. A: Relative to the baseline period, an increase in errors was detected by calculating a difference score (average errors per baseline phase – average errors per manipulation phase). Rats committed significantly more errors during dark trials. There was no SCH23390 induced increase in errors. B: Relative to the baseline phase, the change in time (seconds) required to make a choice was determined (difference in the average amount of time per arm choice across phases of testing). It was found that animals took significantly longer for each arm choice during the two drug treatment conditions. An asterisk denotes significant differences, $p < .05$. Sal/Light = saline–light condition; Sal/Dark = saline–dark condition; Sch/Light = SCH23390–light condition; Sch/Dark = SCH23390–dark condition.

Neural Responses to Dopamine (DA) Antagonism

We conducted analysis of spatial firing properties on a total of 78 hippocampal ($n = 6$ rats) and 76 striatal ($n = 9$ rats) place cells.

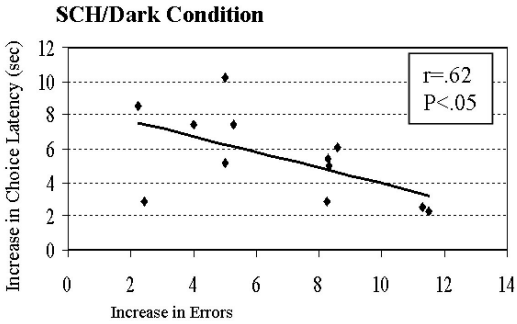

Figure 2. A significant relationship between the increase in choice latency and increase in errors was observed only for the SCH23390–dark condition. In this case, when animals spent more time for each arm choice in the manipulation phase, they committed fewer errors.

Figures 3A and 3B illustrate the location of recording electrodes in HPC and STR where place cells were observed. All hippocampal and striatal place cells discharged at relatively low rates (1.15 ± 0.13 Hz and 1.54 ± 0.18 Hz, respectively). The average spike width for hippocampal place cells (321.29 ± 9.71 μs) was significantly greater than that observed for striatal place cells (235.91 ± 2.89 μs), $F(1, 152) = 27.91$, $p < .01$. The average amplitude for hippocampal (91.29 μV ± 2.89) and striatal (87.79 μV ± 3.07) place cells did not differ, $F(1, 152) = 0.69$, *ns*. There were no statistical differences in the responses of neurons recorded from the dentate and CA1. As a consequence, reliability, specificity, and spatial correlation values from both regions were combined to examine manipulation effects.

Place-Field Reliability

Baseline (i.e., pretreatment) reliability scores were calculated for each treatment condition. Baseline reliability measures of hippocampal neurons did not differ across the four treatment conditions, $F(3, 74) = 0.77$, *ns*. Likewise in STR, baseline reliability measures were consistent across treatment groups, $F(3, 73) = 1.70$, *ns*. Because baseline reliability did not vary across the treatment conditions, all reliability values were pooled for each structure to establish whether the baseline reliability of hippocampal and striatal place fields differed. The baseline reliability measures for hippocampal and striatal fields were not different, $F(1, 152) = 0.00$, *ns*.

Both dopamine and environment manipulations acted to increase or decrease reliability of hippocampal and striatal cell firing within the place field. This increase in variability might have obscured an effect of D_1 antagonism or contextual manipulation on place field reliability. Consequently, analysis of variance of the absolute value of the change in place field reliability was used to compare treatment effects. The effect on hippocampal place field reliability difference scores varied significantly across the four treatment conditions, $F(3, 75) = 7.37$, $p < .01$. Tukey's post hoc comparisons revealed that similar to the modest change in reliability that typically occurred during the saline–light condition for hippocampal place cells (difference score = .14 ± .02; see Figure 4A, left panel: HPC), neither darkness nor D_1 antagonism alone significantly altered field reliability (.20 ± .04, $p > .05$, and .13 ± .03, $p > .05$, respectively). A significant change in reliability was observed only following the combination of SCH23390–dark manipulations (.26 ± .05, $p < .05$). It is interesting to note that the difference scores obtained during the SCH23390–dark manipulation were greater than the other three treatment groups, which suggests that this combination of D_1 antagonism and darkness had the most profound effects on place field reliability.

Unlike hippocampal place fields, striatal place fields did not exhibit manipulation–induced instability in reliability difference scores, $F(3, 73) = 2.56$, *ns*. Relative to the saline–light condition (.14 ± .04), average STR reliability difference scores did not distinguish the three treatment conditions: saline–dark (.24 ± .06), SCH23390–light (.22 ± .04), and SCH23390–dark (.19 ± .06; see Figure 4A, right panel: striatum).

To further demonstrate the changes in reliability after experimental manipulation, we next determined whether the initial reliability measures during the baseline condition were predictive of the reliability measures during the treatment condition. We conducted linear regression analyses on the raw reliability scores to compare the baseline (Block 1) and treatment (Block 2) conditions. The reliability of hippocampal and striatal place fields during Block 1 was significantly correlated with place field reliability during Block 2 for the saline–light condition, $F(1, 17) = 8.21$, $p < .05$, and $F(1, 12) = 8.56$, $p < .05$, respectively (see Figure 5A). These results indicate a consistency in place field reliability when environmental variables remain constant. SCH23390 and darkness had differential effects in altering hippocampal and striatal place field reliability across the testing phases. In HPC, the SCH23390–light condition resulted in a nearly identical positive linear relationship as observed in the saline–light condition. Although hippocampal place field reliability during Block 1 of the saline–dark condition also predicted reliability during Block 2, the absolute value of the reliability score was consistently lower in Block 2 than in Block 1. The combined SCH23390–dark treatment, in contrast, completely eliminated the linear relationship between hippocampal place field reliability for Blocks 1 and 2, $F(1, 22) = .47$, $p > .05$. This reinforces the conclusion that the combination of darkness and D_1 receptor blockade causes the greatest alterations in the reliability of hippocampal place fields.

In contrast to the manipulation-specific effects on hippocampal place field reliability, the predictability of striatal place field reliability during Block 2, on the basis of Block 1 reliability scores, was disrupted for all treatment conditions: saline–dark, $F(1, 25) = 0.51$, *ns*; SCH23390–light, $F(1, 17) = 0.17$, *ns*; SCH23390–dark, $F(1, 14) = 2.49$, *ns* (see Figure 5B).

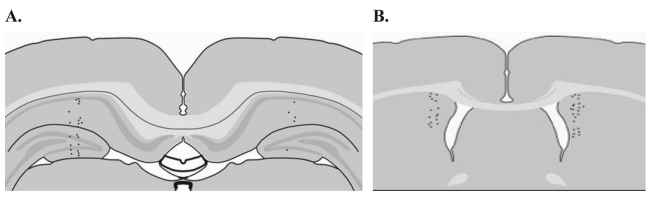

Figure 3. Schematic of coronal sections illustrating recording sites in hippocampus (A) and dorsal striatum (B; modified from Swanson, 2003). Some dots represent multiple cells recorded at a single depth. Reprinted from *Brain Maps: Structure of the Rat Brain* (3rd ed.), Larry Swanson, Levels 35 and 39, Copyright 2003, with permission from Elsevier.

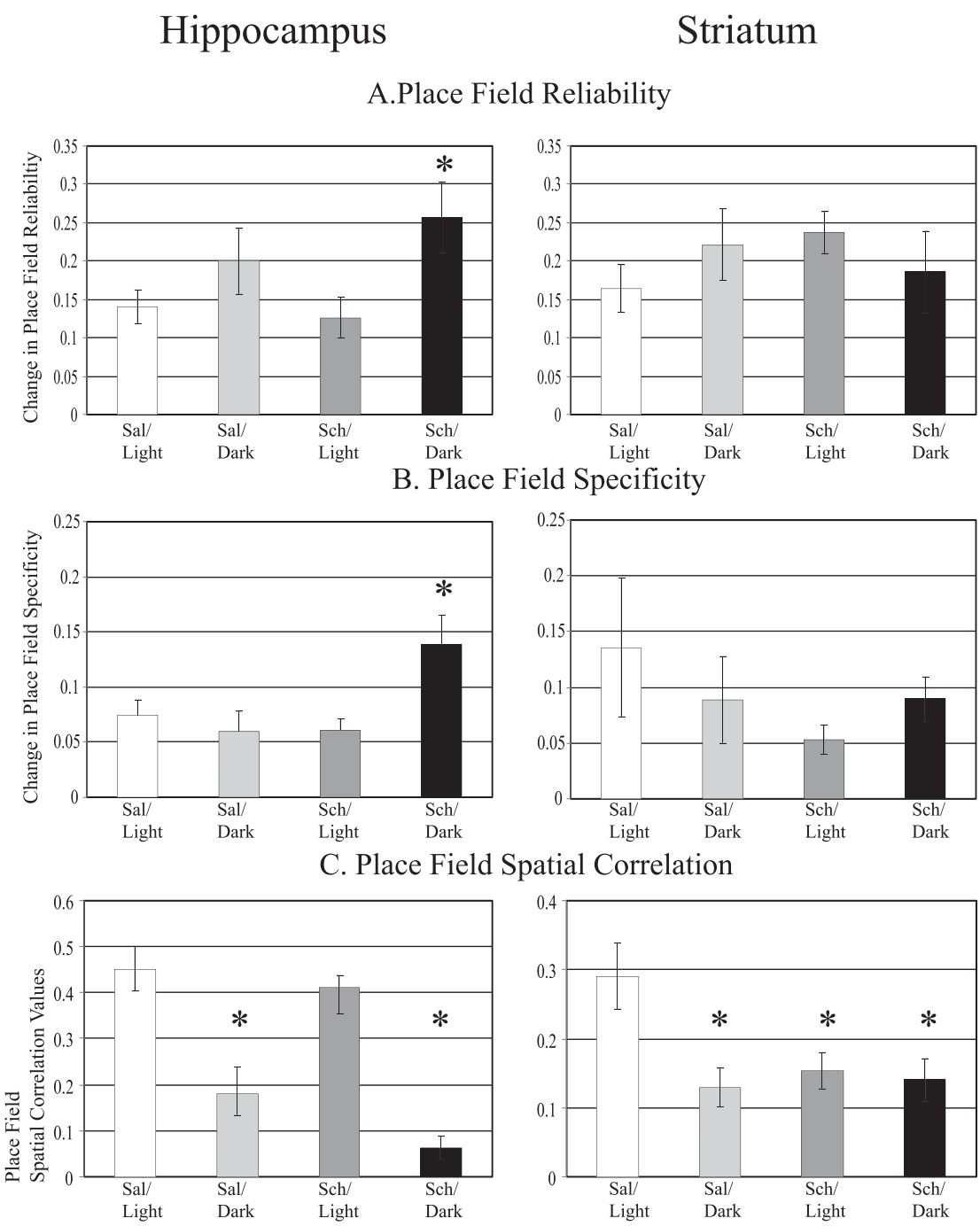

Figure 4. Summary of changes in hippocampal and striatal place field reliability, specificity, and spatial correlation resulting from D_1 antagonism and/or changes in the visual environment. Difference scores for reliability and specificity were calculated using the absolute value of the change in place field reliability or specificity across baseline and manipulation phases of testing (see text). A: The combination of SCH23390 and darkness produced the greatest disruption in hippocampal place field reliability. Striatal place field reliability was unaffected by darkness, injections of SCH23390, or the combination. B: Summary of changes in hippocampal and striatal place field specificity in response to a D_1 antagonist and/or changes in the visual environment. Darkness, as well as injections of SCH23390, did not cause significant changes in hippocampal place field specificity. Similar to the affect observed on hippocampal place field reliability, the combination of SCH23390 and darkness produced the greatest disruption in hippocampal place field specificity. Striatal place field specificity was unaltered by darkness, SCH23390, or the combination. C: Summary of spatial reorganization of hippocampal and striatal place fields resulting from a contextual change and/or a D_1 antagonist. Spatial

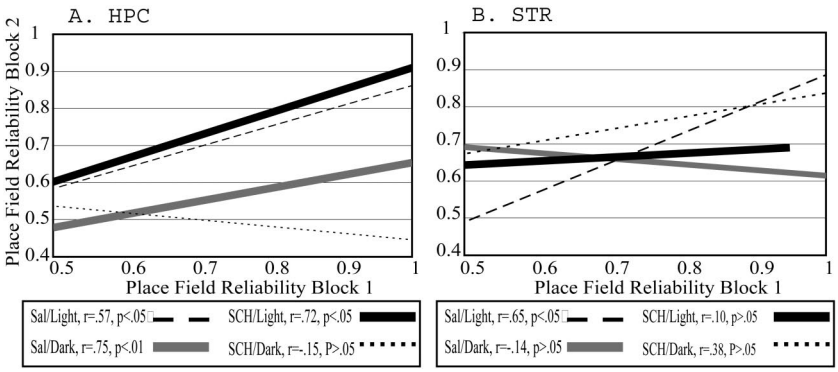

Figure 5. Linear regression analysis of hippocampal and striatal place field reliability observed across testing phases (Blocks 1 and 2). Hippocampal and striatal place fields exhibited a significant linear relationship between baseline and testing phase reliability. A: In hippocampus (HPC), the combination of darkness and D_1 antagonism eliminated this relationship, consistent with the changes that were observed in the reliability difference scores. B: In striatum (STR), all treatment combinations eliminated the significant linear relationship in place field reliability across testing blocks that was observed in the saline–light condition. Sal/Light = saline–light condition; Sal/Dark = saline–dark condition; SCH/Light = SCH23390–light condition; SCH/Dark = SCH23390–dark condition.

According to both difference scores and linear regression analyses, removal of D_1 receptor input influences hippocampal place field reliability in a context-dependent way. In contrast, although context or dopamine manipulations did not affect the magnitude of change in striatal place field reliability, all treatments eliminated the predictability of place field reliability during Block 2 (on the basis of Block 1 scores). These data are consistent with the hypothesis that dopamine differentially effects hippocampal and striatal neural codes during learning.

Place-Field Specificity

Baseline place field specificity values did not distinguish treatment conditions for hippocampal place cells, $F(3, 74) = .67$, *ns*. There were also no group differences in baseline specificity values for place cells recorded in STR, $F(3, 73) = 1.40$, *ns*. Therefore, for each structure, the baseline specificity measures for each treatment condition were pooled. It is interesting to note that the two structures differed significantly in terms of the specificity of their place fields, $F(1, 152) = 5.12$, $p < .05$. During the baseline phase, hippocampal place fields (.14 ± .01) were more specific than striatal place fields (.11 ± .01) even though both populations satisfied standard criteria for place fields. A similar result of structural disparity in baseline specificity values has been described previously (Mizumori, Ragozzino, & Cooper, 2000; Yeshenko et al., 2004). Similar to changes in reliability, both increases and decreases in place field specificity were observed following environment and dopamine manipulations. As a consequence, analysis of variance of the absolute values of these changes were used to identify treatment effects in both regions. In HPC, significant alterations in specificity were similar to those that occurred for reliability, $F(3, 74) = 3.65$, $p < .05$ (see Figure 4B, left panel: HPC). Tukey's post hoc comparisons revealed that the average change in specificity that occurred during the saline–light condition (difference score = .08 ± .01) was significantly less than that observed during the SCH23390–dark condition (.14 ± .03, $p < .05$). This effect appeared to result from the combination of darkness and D_1 antagonism, because the average values recorded for saline–dark (.06 ± .02) and SCH23390–light (.06 ± .01) failed to differ from the saline–light control (see Figure 4B, left panel: HPC). Overall the pattern of results on hippocampal place field reliability and specificity indicates that the combination of compromised dopamine processing along with the challenge of navigating in darkness causes the greatest disruption of normal place cell activity. In contrast, and consistent with the lack of treatment effect on the magnitude of difference scores for striatal place field reliability, the average striatal specificity difference scores did not distinguish the four treatment conditions, $F(3, 73) = 1.62$, $p > .05$ (saline–light: .14 ± .06, saline–dark: .09 ± .04,

Figure 4 (opposite). correlation scores are based on a pixel-by-pixel correlation analysis across training blocks. In hippocampus, darkness caused reorganization (i.e., low correlation) of place fields. Although SCH23390 injections alone did not induce the reorganization of hippocampal place fields, the combination of darkness and SCH23390 caused significant reorganization. Striatal, but not hippocampal, place fields underwent reorganization following SCH23390 injections. As in hippocampus, darkness, as well as the combination of D_1 antagonism and darkness, caused significant reorganization of striatal place fields. An asterisk denotes significance, $p < .05$. Sal/Light = saline–light condition; Sal/Dark = saline–dark condition; Sch/Light = SCH23390–light condition; Sch/Dark = SCH23390–dark condition.

SCH23390–light: .05 ± .01, SCH23390–dark: .09 ± .02; see Figure 4B, right panel: striatum).

We also conducted linear regression analysis of the baseline and treatment condition specificity scores to test the predictability of specificity scores during Block 1 for specificity scores during Block 2. During the saline–light condition, hippocampal, but not striatal, place fields displayed a significant linear relationship in place field specificity across phases, $F(1, 17) = 21.33$, $p < .01$, and $F(1, 12) = 0.07$, *ns*, respectively. There was no across block relationship in HPC specificity following context manipulations in the saline–dark and SCH23390–dark conditions, $F(1, 15) = 1.46$, *ns*, and $F(1, 22) = 0.09$, *ns,* respectively. This loss of predictability appeared to be context-induced, because the positive relationship in hippocampal place field specificity across blocks that was observed during the saline–light condition was also seen in the SCH23390–light condition, $F(1, 16) = 9.02$, $p < .01$. Within STR, only the dark conditions produced a significant positive linear relationship between baseline and treatment phase place field specificity that was not present in the saline–light condition: saline–dark, $F(1, 25) = 6.15$, $p < .05$, and SCH23390–dark, $F(1, 14) = 58.76$, $p < .01$, respectively.

Consistent with the effects on hippocampal place field reliability, specificity measures showed a context-dependent effect of D_1-receptor antagonism. The predictability of specificity scores during Block 1 for Block 2 was diminished following context but not following dopamine manipulation. This indicates that hippocampal field specificity is determined by nondopaminergic input. Consistent with the lack of effects observed for striatal place field reliability, field specificity difference scores did not change after context or dopamine manipulation. Unlike HPC, during baseline conditions, there was no significant relationship between the specificity of striatal place fields during Block 1 and Block 2. A significant correlation emerged following a context shift.

Spatial Correlation Analysis

Spatial reorganization of place field locations was evidenced by significant reductions in the spatial correlation values, which compared the spatial distribution of activity in the baseline phase to that observed during the manipulation phase. For both hippocampal and striatal neurons, the degree of place field reorganization varied significantly across the treatment conditions, $F(3, 74) = 11.62$, $p < .001$, and $F(3, 73) = 5.47$, $p < .01$, respectively (see Figure 4C). For hippocampal place fields, Tukey's post hoc comparisons showed that compared with average saline–light correlation values (.39 ± .05; see Figure 4C, left panel: HPC), there was significant reorganization during only the saline–dark and SCH23390–dark manipulations (.12 ± .05, $p < .0001$, and .05 ± .03, $p < .0001$, respectively). In addition, as shown in Figure 4C, striatal place field spatial correlation values varied across the four treatment groups. Relative to correlation values obtained during the saline–light condition (.28 ± .05), average striatal spatial correlation values differed significantly for all three treatment groups: saline–dark (.13 ± .03), SCH23390–light (.15 ± .03), and SCH23390–dark (.14 ± .03), ps $< .01$ (see Figure 4C, right panel: striatum). The latter three conditions did not differ from each other.

Although both hippocampal and striatal place fields reorganized following a change in context, only striatal neurons exhibited independent responses to D_1 antagonist treatment and darkness. The stability of hippocampal place field locations, however, appeared to be selectively sensitive to the changes in context, because the effects were observed for only the saline–dark and SCH23390–dark conditions. It appears that D_1 receptor activity and context information impacts the reliability, specificity, and location of hippocampal and striatal place fields. It is important to note, however, that the details of the effects vary for the two structures (see summary in Table 1). In general, hippocampal place fields were most sensitive to the context manipulations. Dopamine manipulations were observed only when they co-occurred with the context change. Striatal place fields, in contrast, tended to be roughly equally and perhaps independently sensitive to context or dopamine manipulations. Figure 6 provides examples from individual hippocampal and striatal place cells that illustrate the typical patterns of neural changes associated with either darkness or SCH23390.

Velocity and Acceleration Encoding

Both HPC and STR contained place cells whose firing was clearly related to movement velocity or acceleration in addition to spatial selectivity. It was anticipated that interfering with dopamine processing would differentially disrupt the natural encoding of egocentric movement in these two structures. To address this prediction, the number of cells either gaining or losing a significant relationship between firing rate and movement was first summed.

Table 1
Effect of D_1 Receptor Activity and Context Information on Hippocampal (HPC) and Striatal (STR) Place Fields

	Reliability				Specificity				Change in spatial correlation value	
	Change in absolute value		Change in predictability		Change in absolute value		Change in predictability			
Condition	HPC	STR	HPC	STR	HPC	STR	HPC	STR	HPC	STR
Saline–dark	∅	∅	∅	↓	∅	∅	↓	↑	↓	↓
SCH–light	∅	∅	∅	↓	∅	∅	∅	∅	∅	↓
SCH–dark	↓	∅	↓	↓	↓	∅	↓	↑	↓	↓

Note. SCH = SCH23390; ∅ = no change; ↓ = decrease; ↑ = increase.

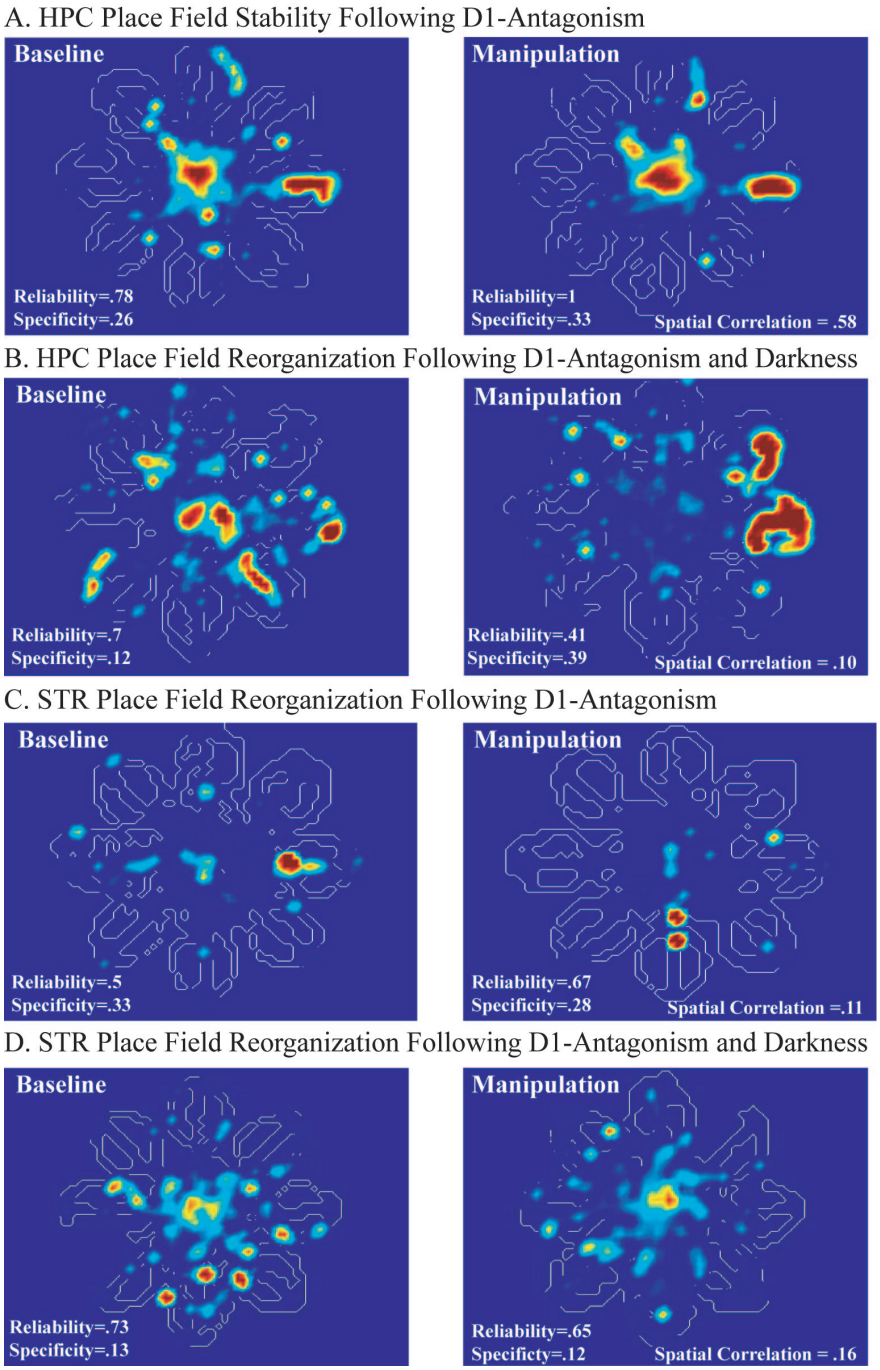

Figure 6. Color spatial density plots illustrating the effects of D_1 antagonism alone or in combination with darkness on hippocampal and striatal place fields recorded while animals performed the spatial working memory task. For each cell, colors represent areas associated with the maximum firing (shown in red), as well as proportions of the maximum firing in 25% increments (from blue to red). hippocampal place fields appeared resistant to reorganization (A) unless alterations in dopaminergic function were accompanied by a change in context (B). In contrast, striatal place fields reorganized during all treatment conditions (C and D). (Cell A max firing rate = 12.71 Hz, Cell B max firing rate = 10.31 Hz, Cell C max firing rate = 10.47 Hz, Cell D max firing rate = 9.58 Hz).

In addition, Wilcoxon's analyses of cells that retained significant correlations with velocity or acceleration across baseline and manipulation blocks of trials was performed to ascertain whether the degree of correlation changed across blocks. Thus, the total number of cells that changed movement correlates was equal to the number that lost, gained, or changed velocity–acceleration-correlated firing. Subsequently, the proportion of cells in HPC that changed during the saline–light condition (n = 6/19 cells) was

used for chi-square comparisons with the other treatment condition values. An identical analysis was used to analyze striatal movement data.

In HPC, the percentage of cells unable to maintain their initial relationship with velocity differed across treatment conditions (see Table 2), $\chi^2(3, N = 78) = 30.45$, $p < .001$. A greater percentage of cells exhibited alterations from the baseline correlation with velocity during the saline–dark ($n = 8/17$ cells) and SCH23390–dark ($n = 14/24$ cells) conditions, $\chi^2(1, N = 36) = 5.02$, $p < .05$, and $\chi^2(1, N = 43) = 27.01$, $p < .001$, respectively. It is interesting to note that when the same analysis was performed for acceleration encoding by hippocampal place cells, a different pattern of results occurred. Once again, there was a significant difference across the treatment conditions in terms of changes in acceleration-related firing (see Table 2), $\chi^2(3, N = 78) = 24.50$, $p < .01$. However, the SCH23390–dark ($n = 6/24$ cells) and SCH23390–light ($n = 6/18$ cells) conditions varied significantly from the saline–light ($n = 10/19$ cells) condition with a reduction in proportion of cells losing their baseline correlation with acceleration, $\chi^2(1, N = 43) = 16.07$, $p < .001$, and $\chi^2(1, N = 37) = 7.60$, $p < .001$. Acceleration encoding did not exhibit context-induced alterations in the saline–dark ($n = 9/17$ cells) condition. It appears that velocity correlates of hippocampal neurons are regulated by context, whereas the acceleration correlate of the same neurons is regulated more by dopamine. Figures 7A and 8A provide individual examples of different types of changes in velocity and acceleration correlate of hippocampal neurons.

Given the alleged role of STR in mediating egocentric behaviors, it was anticipated that altering dopamine signaling would also cause disruptions in velocity and acceleration encoding. In STR, there was a significant difference between the treatment groups in the proportion of cells exhibiting altered velocity encoding (see Table 2), $\chi^2(3, N = 76) = 20.20$, $p < .001$. Specifically, only the combination of darkness and SCH23390 destabilized velocity correlation (see Figures 7B and 8B; $n = 12/16$ cells), $\chi^2(1, N = 30) = 7.11$, $p < .01$. This effect was not seen in the saline–dark ($n = 13/27$ cells) or SCH23390–light ($n = 9/19$ cells) conditions, $\chi^2(1, N = 41) = 1.62$, $p > .05$, and $\chi^2(1, N = 33) = 1.92$, $p > .05$, respectively. Thus, whereas hippocampal velocity correlations seemed context-sensitive (with or without a dopamine challenge), striatal velocity correlations were sensitive to only the combination of context and dopamine manipulation.

There was also treatment-induced variation in the relationship between behavioral acceleration and the firing rates of striatal place cells (see Table 2), $\chi^2(3, N = 76) = 8.93$, $p < .001$. This was the case despite the fact that striatal place cells did not show stable acceleration codes during the saline–light condition: More than 50% failed to maintain their baseline relationship with acceleration after saline injection. The instability during baseline saline–light conditions suggests that acceleration encoding by striatal place cells may be regulated by other internally regulated variables. Only the SCH23390–light condition exhibited a reduction in the percentage of cells that changed baseline acceleration encoding, that is, the correlation with acceleration became more consistent (see Figure 8B, $n = 7/19$ cells), $\chi^2(1, N = 33) = 8.27$, $p < .001$. This effect was eliminated in the SCH23390–dark condition ($n = 8/16$ cells), $\chi^2(1, N = 30) = 7.11$, $p > .05$. It seems that the addition of darkness interfered with any stability conferred by D_1 antagonism.

To summarize, dopamine appears to exert different types of effects on similar kinds of neural (i.e., movement) representation in HPC and STR. For striatal neurons, both context manipulation and SCH23390 impacted the stability in the velocity and acceleration encoding by place cells. In contrast, a context change induced instability of velocity encoding for hippocampal neurons, whereas SCH23390 stabilized acceleration-correlated tuning by hippocampal neurons.

Relationship Between Behavioral and Unit Effects

In terms of establishing a link between dopamine effects on spatial processing in HPC and STR and effective spatial navigation, attempts were made to correlate the number of errors made during the manipulation phase and the various unit changes described earlier. There was no consistent relationship between the behavioral accuracy of the rat and the changes in spatial correlation, reliability, or specificity of the spatial processing in the HPC and STR (all ps $>.05$).

Because there was a SCH23390-induced increase in arm-choice latencies, it was necessary to determine whether these latency changes were also correlated with changes in the unit responses. The average arm-entry latency differences between baseline and manipulation blocks were not correlated with spatial correlation values obtained during any treatment condition for either HPC or

Table 2
Percentages and Chi-Square Values for Hippocampal (HPC) and Striatal (STR) Place Cells Exhibiting Changes From Baseline Velocity and Acceleration

	Velocity				Acceleration			
	HPC		STR		HPC		STR	
Condition	%	χ^2	%	χ^2	%	χ^2	%	χ^2
Saline–light	31.58		57.14		52.63		57.14	
Saline–dark	47.06*	5.02	48.15	1.62	52.94	.002	51.85	0.56
SCH–light	38.89	1.17	47.36	1.92	33.33*	7.60	36.84*	8.27
SCH–dark	68.33*	27.01	75.00*	7.11	25.00*	16.07	50.00	1.02

Note. SCH = SCH23390.
* $p < .05$.

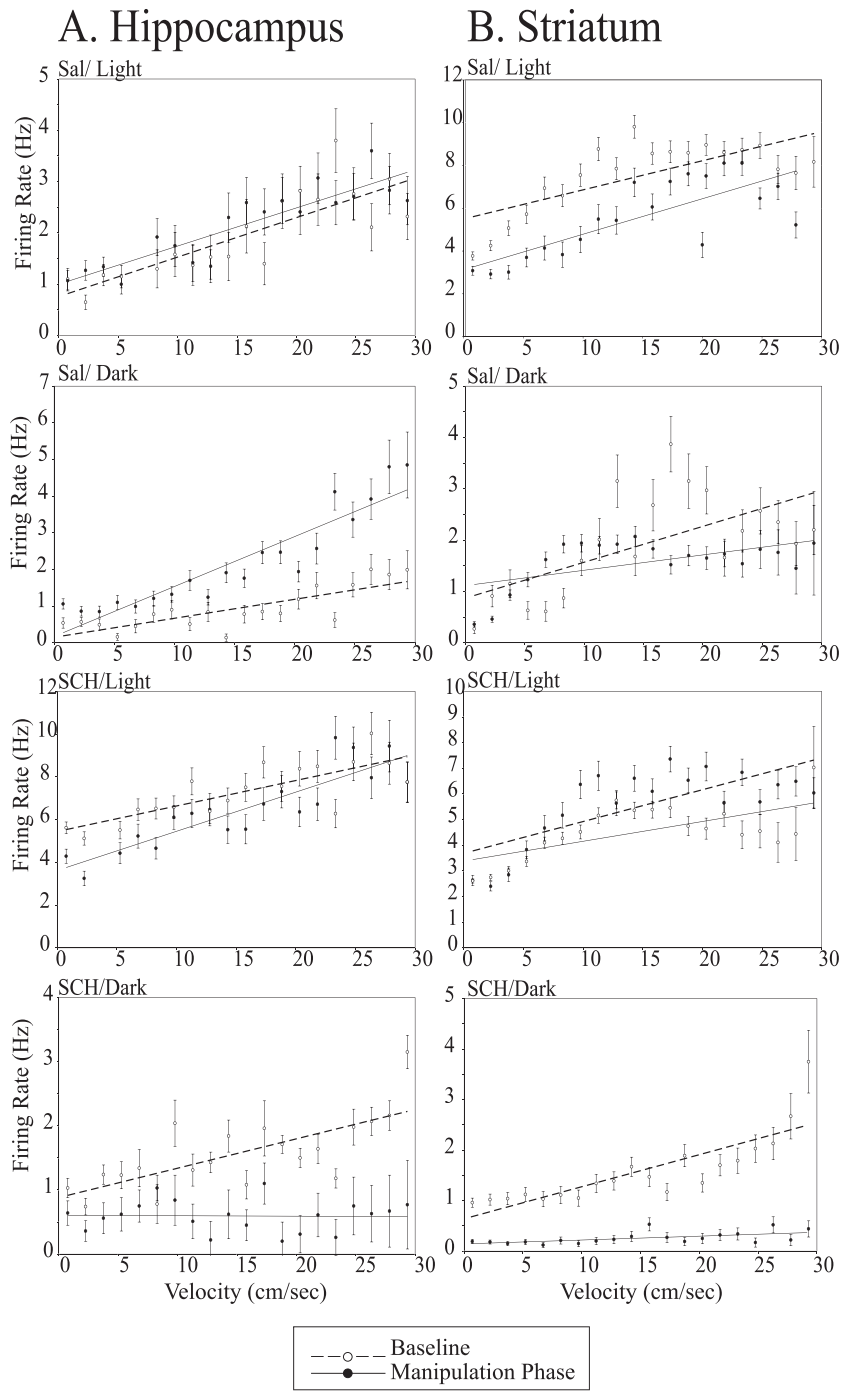

Figure 7. Individual examples of velocity encoding by hippocampal and striatal place cells during baseline and manipulation phases. Each line represents the linear regression between firing rate (Hz) and velocity (cm/sec). A: In hippocampus, greater disparity between the baseline and manipulation regression lines occurred in saline–dark conditions. B: In striatum, a greater difference between the baseline and manipulation regression lines occurred in the SCH23390–dark condition. Sal/Light = saline–light condition; Sal/Dark = saline–dark condition; SCH/Light = SCH23390–light condition; SCH/Dark = SCH23390–dark condition.

STR. This indicates that the place field reorganization observed was not related to slowed movement of the rat. The change in hippocampal place field reliability was also not correlated with the increase in arm-entry latencies observed in the SCH23390–dark condition. Consistent with the effect on reliability, the increased disruption of place field specificity during the combined D_1 antagonism and dark condition was not associated with the increase in arm-entry latencies. Although striatal place fields did not exhibit

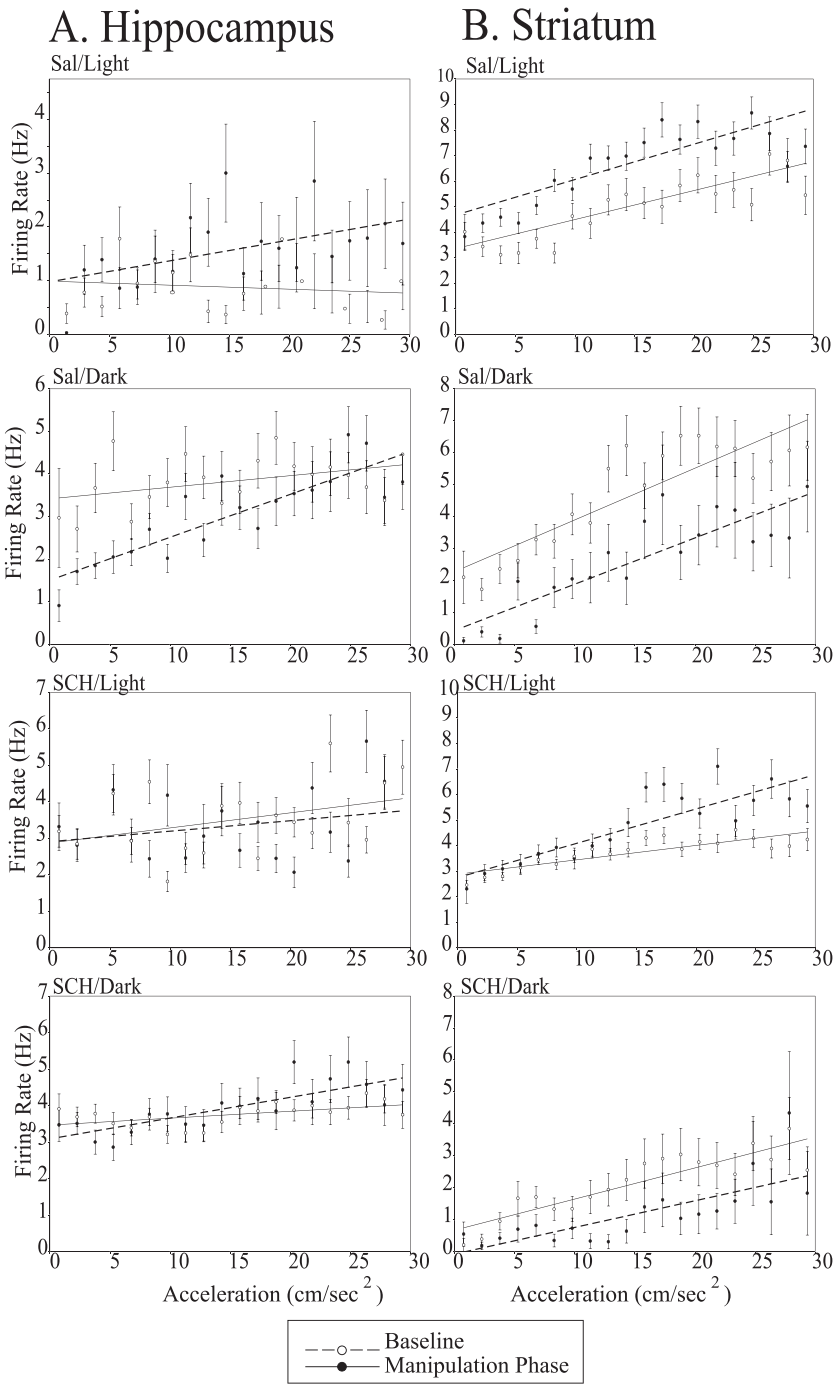

Figure 8. Individual examples of acceleration encoding by hippocampal and striatal place cells during baseline and manipulation phases. Each line represents the linear regression between firing rate (Hz) and acceleration (cm/sec^2). A: In hippocampus, greater disparity between the baseline and manipulation regression lines occurred in saline–light and saline–dark conditions; SCH23390 appeared to reduce this effect. B: When compared with the saline–light condition, striatal place cells showed a smaller difference between the baseline and manipulation regression lines in the SCH23390–light condition. Sal/Light = saline–light condition; Sal/Dark = saline–dark condition; SCH/Light = SCH23390–light condition; SCH/Dark = SCH23390–dark condition.

context- or SCH23390-induced alterations in reliability or specificity, it was still possible for changes in either measure to be correlated with changes in egocentric movement. However, the significant increase in arm choice latency was not correlated with changes in reliability or specificity during any treatment condition. In sum, the effect of D_1 antagonism on increasing arm-entry latencies was not associated with changes in place field specificity, reliability, or organization during the two drug conditions.

Discussion

To test the hypothesis that dopamine differentially regulates the output signals from HPC and STR, this study examined the responses of place cells recorded from these structures to D_1 receptor antagonism and to a change in the environmental context. We hypothesized that hippocampal and striatal place fields would exhibit disparate responses to context alterations (i.e., imposed darkness) and to D_1 receptor antagonism (SCH23390 injection). To the extent that dopamine and context effects are interdependent, it was expected that place fields would display an increased sensitivity to the combination of darkness and SCH23390.

Hippocampal and striatal place fields exhibited unique alterations following the loss of D_1 receptor input. The reliability and specificity of hippocampal fields was affected by the dopamine manipulation but only after a context change. The location of place fields, however, was changed after the context change regardless of the presence of SCH23390. In contrast, the reliability and specificity scores of striatal place fields did not respond to either context or dopamine manipulation. Rather, a context change or dopamine treatment altered the extent to which baseline (Block 1) reliability and specificity scores predicted Block 2 reliability and specificity measures. The location of striatal place fields shifted in response to either dopamine or context manipulation. This pattern of effects has general implications. First, there are likely multiple factors that determine the specificity, reliability, and location of place fields for both HPC and STR. Second, these data suggest that dopamine plays an important role in defining striatal place field locations during the performance of a spatial task independent of context. In HPC, however, dopamine appears to contribute to determining the reliability and specificity of the spatial code only when there is a change in context.

The movement component of hippocampal and striatal place cell codes was also differentially sensitive to context and dopamine manipulations. The velocity correlate of hippocampal neurons was more sensitive to darkness than to SCH23390, whereas the acceleration correlate of the same neurons was more sensitive to SCH23390 than to darkness. Striatal place cells, however, exhibited velocity and acceleration correlates that were sensitive to either darkness or SCH23390. Thus, the response or movement components of hippocampal representations appear to be more precisely tuned (or affected) by specific types of context change (e.g., visual context or reinforcement state; Mizumori, Cooper, et al., 2000). In contrast, the response component of striatal place fields appears to be more generally sensitive to perhaps multiple forms of context change.

In general then, hippocampal neural representations seem most consistently responsive to the context manipulation. Dopamine may help to signify a shift in context, because dopamine antagonism reduced darkness-induced changes in reliability and specificity of HPC place fields. Dopamine signaling may also guide movement coding in HPC, because selective effects of SCH23390 were observed on the velocity and acceleration correlates of place cells. In contrast to what was observed for hippocampal place cells, the most striking response of striatal place fields to either darkness or dopamine antagonism was a change in the predictability of reliability and specificity. When combined, these data are consistent with the view that during spatial learning, dopamine serves different roles in HPC and STR.

Behavioral Effects of D_1 Antagonism and Context Change

Although darkness caused a significant increase in the number of errors, SCH23390 did not impair choice accuracy despite increasing the amount of time for each arm visit. In contrast with our results, other studies have shown an effect of D_1 receptor manipulation on spatial choice accuracy. Genetic deletion of D_1 receptors produced impairments in tasks requiring the use of spatial cues (El-Ghundi 'et al., 1999; Smith et al., 1998). However, pharmacological manipulation of D_1 receptor function shows more varied results. Systemic injection of low doses of SCH23390 results in movement slowing without necessarily causing memory impairments in asymptotic performance of a delayed nonmatching-to-position task (Bushnell & Levin, 1993). In contrast, place- or response-learning enhancements are found following local infusion of D_1-receptor agonists into HPC or STR, respectively (Packard & White, 1991), and spatial learning impairments in aged animals can be reversed by D_1-agonist treatment (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994; Bach, et al., 1999).

Given the evidence that suggests a link between D_1-receptor activity and spatial learning, it was unexpected that SCH23390 did not impair learning in this study. A behavioral effect may not have been observed, because asymptotic performance that is measured or a contextual change that is presented during asymptotic performance is not sufficient to produce a vulnerability to D_1 receptor blockade. Indeed, although phasic activity of dopamine neurons is crucial during the early learning of appropriate stimulus–response associations (Packard & Knowlton, 2002; Schultz, Tremblay, & Hollerman, 2003), a role for dopamine during asymptotic performance is less clear. Theoretically, it has been proposed that dopamine may coordinate striatal responses with descending cortical input to produce a system by which ongoing behavior can be matched against expected outcomes during acquisition and asymptotic performance. This general function may rely on more than just the D_1-receptor system (Mizumori, Cooper, et al., 2000; Mizumori et al., 2004).

In addition, darkness was used as an environmental context manipulation in an effort to induce reliable behavioral impairments that could be compared with corresponding unit changes. Such a global interference with multiple sensory systems could likely be the cause of the robust increase in working memory errors. It is possible then that an interaction effect between darkness and D_1 antagonism was obscured by a floor effect on behavioral performance.

Hippocampal and Striatal Unit Responses to D_1 Antagonism and Context Change

Despite the fact that SCH23390 did not affect choice accuracy in our task, it clearly had profound neurophysiological effects. The combination of SCH23390 with a spatial context change caused a greater alteration of spatial encoding of place cells in HPC than either treatment alone. D_1 dopamine receptors have previously been shown to contribute to hippocampal plasticity in response to spatial novelty. For example, CA1 long-term potentation that is induced by exposing animals to novel environments can be

blocked by the application of SCH23390 (Li, Cullen, Anwyl, & Rowan, 2003). In addition, place learning has been associated with elevated CREB in HPC, which may rely on dopamine-mediated signaling (Colombo, Brightwell, & Countryman, 2003). Therefore, changes in the visual environment may account for the increased sensitivity of hippocampal neurons to D_1 receptor blockade. This pattern suggests that dopamine may play a special role in context discrimination by HPC.

The dissociation of effects of D_1 antagonism on striatal place field reorganization, reliability, and specificity could reflect selective responses of medium spiny neurons to D_1 receptor activation. Presumably, removing D_1 receptor influence disrupted the natural gating of multiple cortical, glutamatergic synapses converging on a single cell (for a review, see Nicola, Surmeier, & Malenka, 2000). Perhaps this low dose of SCH23390 selectively enhanced a subset of cortical input that allowed these connections to have greater influence. This could translate into an alteration in the spatial location of place fields without affecting the reliability of the spatial signal. Similarly, dysregulation of cortical input to STR could result in changes in the precise coordination of movement velocity and acceleration with cell firing rates. It is not known whether the altered movement codes are causes or consequences of the longer latencies observed after SCH23390 treatment.

One of the most striking and consistent effects of either darkness or D_1 antagonism on striatal (but not hippocampal) place fields was the change in the predictive nature of baseline measures of reliability and specificity (see Table 1). This suggests that the postulated striatal function of predicting future reinforcement conditions (Mizumori, Pratt, & Ragozzino, 1999; Schultz et al., 2003) is modulated not only by the dopamine system, but also by the external environmental context.

Relationship Between Behavioral and Unit Responses

The present study revealed a mismatch between the various unit responses to the SCH23390 manipulation and any increase in errors. Other studies have shown similar disparity between alterations in hippocampal place fields and lack of corresponding changes in behavior (Cooper & Mizumori, 2001; Jeffery et al., 2003). As discussed previously, asymptotic performance may represent a situation in which stable place field responses are no longer a sufficient predictor of behavior. That is, studies of earlier stages of learning may yield better concordance between place field stability and effective navigation. Performance of a well-learned task, such as the one used in the present study, may reflect coordinated activity across multiple neural systems (Mizumori, Cooper, et al., 2000). Such coordination could allow animals to compensate behaviorally (i.e., switch cognitive strategies) when a single physiological process (e.g., D_1-receptor system) malfunctions.

The saline–dark and SCH23390–dark conditions, which resulted in the greatest change in working memory, were also the conditions that generated the greatest reorganization of hippocampal place fields. There was no such correspondence between striatal place field reorganization and behavioral impairments. This could reflect the greater importance of HPC, rather than STR, during performance of this task. Failure to retrieve the same neural pattern (*N*-methyl-D-aspartate –mediated) could result in behavioral impairments (Kentros et al., 1998). In this study, the maintenance of hippocampal place fields was likely important for selection of the appropriate behavioral strategy in a given spatial context. Therefore, in the two dark treatment conditions, unsuitable hippocampal reorganization may have interfered with spatial navigation. Similar declines in spatial performance that occur with age are also associated with alterations in connectivity and activation patterns in CA1 and dentate (Barnes, Rao, & Shen, 1997).

Implications for Multiple Memory Systems Function

The present study provides clear evidence that the dopamine system differentially regulates similar types of neural representations (i.e., place fields) in HPC and STR during spatial performance on a maze. In this way, dopamine may bias the efferent messages of these structures such that during spatial memory performance, HPC comes to exert stronger (i.e., more reliable or specific) control over other neural systems that determine behavioral output (Morris, Arkadir, Nevet, Vaadia, & Bergman, 2004). Such a mechanism is entirely consistent with the finding of parallel neural representations in HPC and STR during spatial and response tasks (Yeshenko et al., 2004) and the finding that hippocampal and striatal lesions result in differential effects on spatial and response learning (McDonald & White, 1993; Packard & McGaugh, 1996).

It is likely that other neurotransmitters, such as acetylcholine (ACh), could also contribute to the selection of behaviors or behavioral strategies. Peak ACh levels in HPC and STR are associated with place and response strategy on the plus maze, respectively (Chang & Gold., 2003; McIntyre, Marriott, & Gold, 2003). In addition, effective performance during a spatial working memory task may involve interactions between the cholinergic and dopaminergic systems. Working memory deficits on the radial arm maze caused by interfering with cholinergic transmission, either via nicotinic receptor antagonists or lesions of the medial cholinergic pathway, are exacerbated by a mixed D_1–D_2 antagonist or alleviated by D_1 or D_2 agonist treatment (Levin & Rose, 1995; McGurk, Levin, & Butcher, 1992).

In both HPC and STR, the interactions between the dopaminergic and cholinergic systems may account for the contributions of these two neurotransmitter systems to behavior. In STR, ACh and dopamine have opposing effects on the regulation of long-term potentiation in medium spiny neurons (Centonze et al., 2003). Similar effects occur in the HPC, where cholinergic-induced field potential oscillatory activity can be suppressed by D_1 receptors (Weiss, Veh, & Heinnemann, 2003). Thus, in future experiments, it would be of interest to determine whether ACh can reverse the effects reported in this study following the compromise of dopamine function. Furthermore, potential dopamine and ACh contributions to the modulation of spatial processing in STR during a nonspatial (response) task warrants exploration.

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