Behavioral/Systems/Cognitive

Dopamine D_1 Receptor Modulates Hippocampal Representation Plasticity to Spatial Novelty

Anh Hai Tran,[1,4] Teruko Uwano,[2,4] Tatsuo Kimura,[1,4] Etsuro Hori,[1,4] Motoya Katsuki,[3] Hisao Nishijo,[1,4] and Taketoshi Ono[1,4,5]

[1]System Emotional Science and [2]Department of Integrative Neuroscience, University of Toyama, Toyama 930-0194, Japan, [3]National Institute for Basic Biology, National Institutes of Natural Sciences, Okazaki 444-8585, Aichi, Japan, [4]Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, Saitama 332-0012, Japan, and [5]Department of Emotional Neuroscience, Showa University School of Medicine, Tokyo 142-8555, Japan

The human hippocampus is critical for learning and memory. In rodents, hippocampal pyramidal neurons fire in a location-specific manner, forming relational representations of environmental cues. The importance of glutamatergic systems in learning and in hippocampal neural synaptic plasticity has been shown. However, the role of dopaminergic systems in the response of hippocampal neural plasticity to novel and familiar spatial stimuli remains unclear. To clarify this important issue, we recorded hippocampal neurons from dopamine D_1 receptor knock-out (D1R-KO) mice and their wild-type (WT) littermates under the manipulation of distinct spatial cues in a familiar and a novel environment. Here we report that in WT mice, the majority of place cells quickly responded to the manipulations of distal and proximal cues in both familiar and novel environments. In contrast, the influence of distal cues on spatial firing in D1R-KO mice was abolished. In the D1R-KO mice, the influence of proximal cues was facilitated in a familiar environment, and in a novel environment most of the place cells were less likely to respond to changes of spatial cues. Our results demonstrate that hippocampal neurons in mice can rapidly and flexibly encode information about space from both distal and proximal cues to cipher a novel environment. This ability is necessary for many types of learning, and lacking D1R can radically alter this learning-related neural activity. We propose that D1R is crucially implicated in encoding spatial information in novel environments, and influences the plasticity of hippocampal representations, which is important in spatial learning and memory.

Key words: dopamine receptor; hippocampus; place cells; brain stimulation reward; neural plasticity; spatial novelty

Introduction

Hippocampal formation (HF) in human and other primates is critical for episodic memory (Maguire et al., 1998; Eichenbaum et al., 1999; Rolls, 2005; Rolls and Xiang, 2005). Lesions or manipulations of the HF in rodents cause spatial learning deficits (Gasbarri et al., 1996; Whishaw et al., 1997; Wilkerson and Levin, 1999), and recordings of hippocampal neurons in rodents have revealed that they fire in a location-specific manner (O'Keefe and Dostrovsky, 1971; Wilson and McNaughton, 1993; O'Keefe and Burgess, 1996) in association with external and internal cues (Muller and Kubie, 1987; Wiener et al., 1989; Gothard et al., 1996; Hetherington and Shapiro, 1997; Shapiro et al., 1997; Knierim et al., 1998; Zinyuk et al., 2000; Lever et al., 2002; Leutgeb et al., 2005a,b) or contextual information (Gill and Mizumori, 2006), indicating a role in spatial memory (Wilson and McNaughton, 1993; Leutgeb et al., 2005). In addition, the HF appears to provide a neural representation of physical space, although broader functions have also been suggested (Maguire et al., 1998; Eichenbaum et al., 1999). The place-cell representation of space is thought to underlie certain forms of spatial learning (McHugh et al., 1996, 2007; Cho et al., 1998; Kentros et al., 1998; Eichenbaum et al., 1999; Rotenberg et al., 2000; Dragoi et al., 2003). It was found that dopamine D_1 receptor knock-out (D1R-KO) mice had impaired spatial learning and altered spatial activity in the nucleus accumbens (El-Ghundi et al., 1999, Tran et al., 2005). Since dopamine modulates hippocampal synaptic plasticity (Otmakhova and Lisman, 1996; Matthies et al., 1997; Swanson-Park et al., 1999; Li et al., 2003), it is hypothesized that the acquisition of spatial representations in the hippocampus is impaired in D1R-KO mice. The present study tested this hypothesis by comparing place-cell activity in D1R-KO and wild-type (WT) mice in response to spatial cue manipulations in familiar and novel environments.

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Correspondence should be addressed to Taketoshi Ono, System Emotional Science, University of Toyama, Sugitani 2630, Toyama 930-0194, Japan. E-mail: onotake@med.u-toyama.ac.jp.

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Materials and Methods

Animals. Ten male WT mice (26–33 g) and 7 male D1R-KO mice (24–29 g) were used in the present neuronal recording experiment. Mice were reproduced at a collaborative laboratory (National Institute for Basic Biology, National Institutes of Natural Sciences).

Generation of D1R-KO mice. The mouse dopamine D_1 receptor gene was isolated from a 129/Sv mouse genomic DNA library (Stratagene) by hybridization with an 884 bp PCR product, the primer pairs of which are 5′-TCC AAG GTG ACC AAC TTC TTT GT-3′ and 5′-CTA TAG CAT

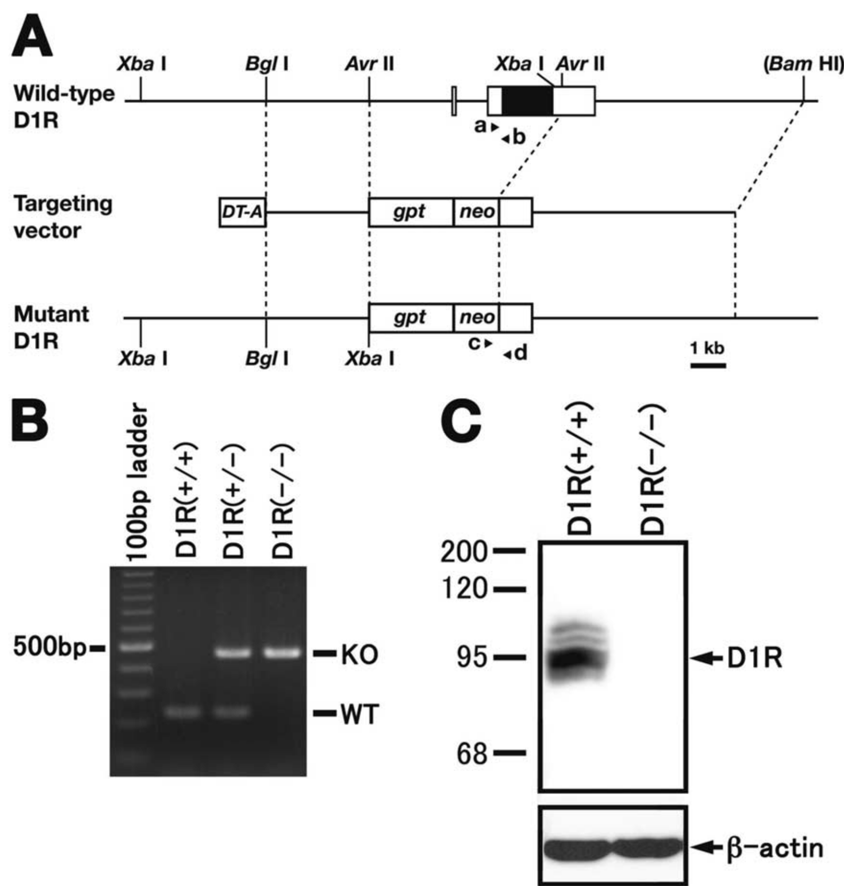


Figure 1. Generation of the D1R-KO mice and expression of the D1R protein in the brains of WT and D1R-KO mice. ***A***, Schematic representation of the WT allele, the targeting vector, and the mutant allele of the mouse D1R gene. The coding and untranslated regions are shown as closed and open boxes, respectively. Primers for PCR genotyping (primers a, b, c, and d) are shown as small arrowheads indicated by a, b, c, and d, respectively. A *Bam*HI site is indicated with parentheses when relevant. The diphtheria toxin A subunit (DT-A), *E. coli* xanthine-guanine phosphoribosyl transferase (gpt) and neomycin resistant (neo) genes are shown as open boxes. ***B***, PCR genotyping of wild-type (D1R+/+), heterozygous (D1R+/−), and homozygous (D1R−/−) mutant mice. PCR products from the WT allele and the mutant (KO) are 234 bp and 460 bp, respectively. ***C***, Western blot using a D1R-specific antibody revealed that D1R protein was completely absent from D1R−/− mice.

CCT AAG AGG GT CGA-3′. The targeting vector was constructed so as to delete the whole coding sequence using the following DNA fragments: a 1.2 kb MC1 promoter-diphtheria toxin-A fragment gene (DT-A) for negative selection, a 2.8 kb *Bgl*I-*Avr*II fragment containing the upstream region of the mouse D1R gene, a 2.3 kb PGK promoter-*Escherichia coli* xanthine-guanine phosphoribosyl transferase gene (gpt), a 1.1 kb MC1 promoter-neomycin gene (neo), a 6.5 kb *Avr*II-*Bam*HI fragment containing the 3′-untranslated region and the flanking region, and the plasmid pBluescript (Fig. 1*A*). Cultured E14TG2a IV ES cells (2.5×10^7 cells) were transfected with 50 μg of the linearized targeting vector by electroporation 500 μF capacitance, 270 V/1.8 mm (ECM600, BTX Electro Cell Manipulator), followed by selection with G418 treatment (250 μg/ml) after the transfection. Altogether, 120 drug-resistant colonies were picked up, and the genomic DNA was subjected to Southern blot analysis for confirmation of homologous recombination. The D1R-KO mice were generated using the homologous recombinant ES cells essentially as described previously (Yamaguchi et al., 1996; Koera et al., 1997). The D1R-KO mice were backcrossed to a C57BL/6J (B6/J) strain for 10 generations and maintained in a B6/J genetic background. Tail DNA of offspring was analyzed by PCR using four primers: (primer a) D1TET-1, 5′ CAG AAG ACA GGT GGA AAG CA 3′, (primer b) mD1Rexon2.seq, 5′ TCC ATG GTA GAA GTG TTA GGA GCC 3′, (primer c) neo10, 5′ ATC AGA GCA GCC GAT TGT CTG TTG 3′, and (primer d) D1R3′60R, 5′ GTT GGA GAA GTT CTG TAA CTG TCC 3′. The PCR condition was as follows: denaturation at 94°C for 4 min, followed by 30 cycles of 1 min at 94°C, 1 min at 60°C, 1 min at 72°C, a final extension at 72°C for 5 min, and storage at 4°C. The wild-type and mutant alleles corresponded to PCR products of 234 and 460 bp (Fig. 1*B*), respectively. All the experiments were conducted in accordance with guidelines of the University of Toyama and the National Institute for Basic Biology.

Western blot analysis. The brain was homogenized in a buffer containing 100 mM Tris-HCl, pH 6.7, 1% SDS, 143 mM 2-mercaptoethanol, and 1% protease inhibitor mixture for mammalian cells (Nacalai Tesque). Total lysates (200 μg of protein each) were electrophoresed on a 10% SDS-polyacrylamide gel and transferred to an Immobilon-P membrane (Millipore). The membrane was blocked in PBS containing 10% skim milk (BD Biosciences) at room temperature for 30 min and sequentially incubated with rat monoclonal antibody against D1R (Sigma, 1:1000 dilution), followed by incubation with horseradish peroxidase-conjugated goat antibody against rat IgG (Sigma, 1:1000 dilution), or with rabbit antibody against actin (Sigma, 1:1000 dilution), followed by incubation with horseradish peroxidase-conjugated goat antibody against rabbit IgG (Sigma, 1:1000 dilution). Immunoreactive protein bands were detected according to the protocol of the ECL detection kit (GE Healthcare).

Electrode implantation. Mice were housed individually with a 12 h light cycle (lights on at 8:00 A.M.) and had *ad libitum* access to food and water. Mice were given at least 1 week upon arrival to acclimate to the laboratory environment before experimental procedures. On the surgery day, mice were anesthetized (pentobarbital, 40 mg/kg, i.p.) and implanted bilaterally with monopolar stimulating electrodes (100 μm diameter, stainless steel) for intracranial self-stimulation in the medial forebrain bundle at the level of the posterior lateral hypothalamic area (Franklin and Paxinos, 1997) (anterior, −2.3 mm; mediolateral, ±0.70–0.75 mm; and dorsoventral, −5.3–5.4 mm). A movable recording assembly consisting of 2 tetrodes of twisted 17 μm nichrome wire (California Fine Wire Company), or a bundle of 8 wires was implanted into the dorsal part of the hippocampal CA1 region (Franklin and Paxinos, 1997) (1.8 mm posterior to bregma, 1.8 mm lateral to bregma, and 1.4 mm below the skull surface) during the same surgery. A jeweler's screw fixed to the skull served as a ground electrode in all mice. The microdrive was secured to the skull using jeweler's screws and dental cement. Electrode tips were gold-plated before surgery to reduce impedances to 100–300 kΩ at 1 kHz.

Experimental apparatus and spatial task training. The apparatus for spatial task training was a circular open field (80 cm diameter, 25 cm high wall); it was elevated 80 cm above the floor on a cart with casters that allowed rotating and moving the open field manually (Fig. 2*A*). The open field was painted black inside and enclosed by a black curtain (180 cm diameter and 200 cm height). The ceiling of the enclosure contained four small speakers mounted near the circumference, spaced 90° apart, 4 incandescent light bulbs individually mounted near the inner edge of each speaker, and a video camera at the center. Usually a light bulb was lit at the three o'clock position, and a speaker continuously emitted white noise at the nine o'clock position. The lit light bulb and emitting speaker served as distal cues. A small 6 V light bulb was mounted on the head of the mouse. The video camera (CinePlex, Plexon) converted a real video image signal to a binary signal, and tracked the horizontal motion of the small bulb. A laboratory computer (Dell, Precision 380) received the *x*

and *y* coordinates of the position of the mouse head at 33 frames/s. Mice were trained in a random foraging task in the open field (Fig. 2*B*). For the foraging task, a program delimited circular areas (reward sites) with their centers chosen at random within a square circumscribed around the open field, and it triggered the delivery of brain stimulation rewards (BSR) when the mouse entered the reward site. After a 5 s interval, the reward place was moved to a different location and reactivated

Unit isolation and recording. The recording electrode assembly was advanced in the HF at ∼20 μm/d. Neural activities were recorded using a conventional recording procedure when mice performed foraging. Complex-spike cells were determined with criteria described in previous studies (Ranck, 1973; Foster and Wilson, 2006). Data collection started when the signal-to-noise ratio exceeded ∼4 times on one of the electrodes. Signal amplification, filtering, and digitizing of spike waveforms using a principle component analysis platform were accomplished using a Plexon system. Recorded signals were amplified 10,000 times, filtered between 0.6 and 3 kHz, digitized at a 40 kHz sampling rate, and stored on a computer hard disk for off-line spike sorting. The digitized neuronal activities were isolated into single units by their waveform components using an off-line sorter program (OfflineSorter, Plexon). Superimposed wave forms of the isolated units were drawn to check the invariability throughout the recording sessions. Each cluster was then checked manually to ensure that the cluster boundaries were well separated and that waveform shapes were consistent with action potentials. For each isolated cluster, an interspike interval histogram was constructed and an absolute refractory period of at least 1.0 ms was used to exclude suspected multiple units. An example of a tetrode recording is shown in Figure 3.

Manipulations in the circular open field (familiar environment). Place-cell activity was monitored in a circular cylindrical chamber over several 10 min sessions, during which mice randomly sought out BSR. Neurons were recorded in sequential sessions to determine the stability of place fields between sessions and the amount of extramaze (distal) and intramaze (proximal) control. Figure 2*C* shows the diagram of testing sequential sessions. In the standard session (prerotation, baseline 1), neuronal activity was monitored while mice foraged in the circular open field with a speaker continuously emitting white noise at a 9 o'clock position and an incandescent electric bulb was turned on at a 3 o'clock position. Neurons were then recorded in distal cue rotation and proximal cue rotation sessions. In the distal cue rotation session, the position of the distal cues was rotated 180°, while the chamber was kept constant. In the proximal cue rotation, the chamber was rotated 180° while the distal cues remained unchanged. After each manipulation of the distal or proximal sessions, an additional session was recorded with the distal and proximal cues being returned to the standard conditions. Since multiple sessions were recorded sequentially, the mouse was usually not disconnected from the recording cable between sessions. We did not carry out any manipulation to interfere with the spatial orientation of the animal. Before and after each recording session, the mouse rested on a box placed on a pedestal outside of the recording chamber for 5 min.

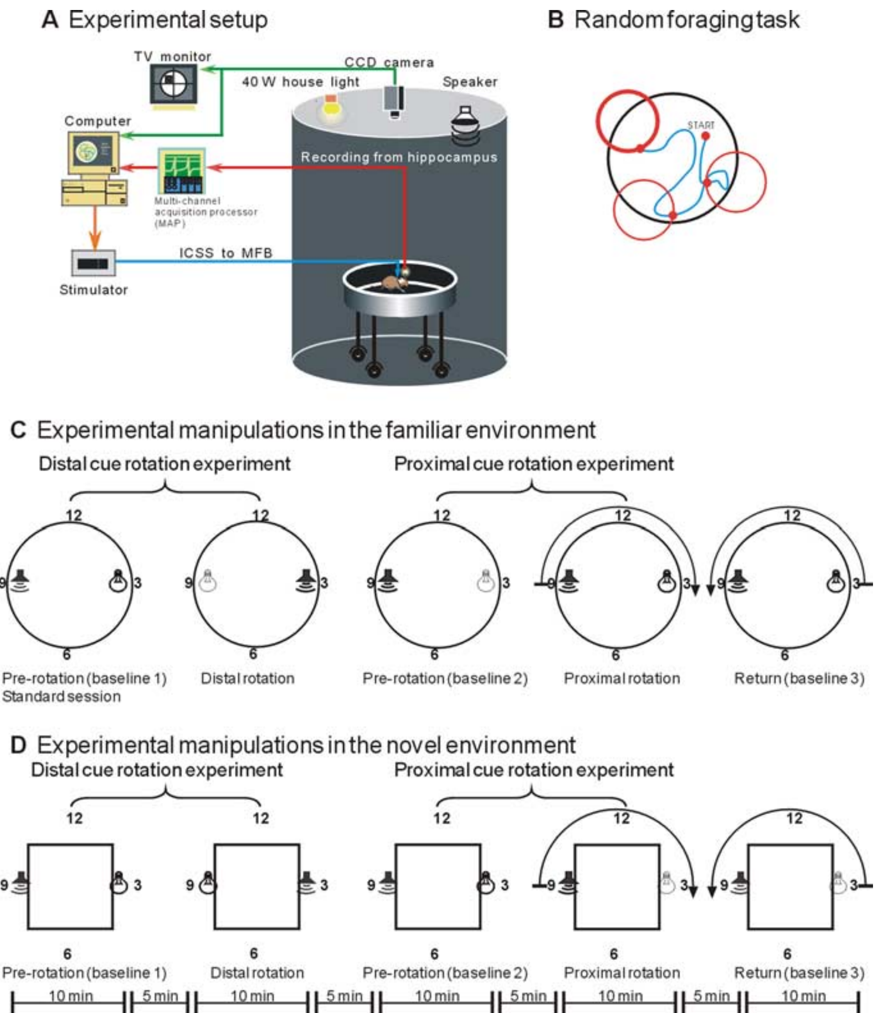


Figure 2. Experimental setup, spatial tasks, and experimental manipulations. ***A***, Experimental setup. An open field containing a mouse was viewed from the top center by a CCD camera that signaled the mouse's position. As distal cues, the incandescent electric light bulbs and speakers for white noise emissions were mounted on the four peripheral positions of the ceiling. A computer plotted the trail of the mouse and controlled reward delivery from a stimulator. ***B***, Random foraging task: a computer program randomly delineated a circular reward place (small thick red circle). The mouse was rewarded when it entered the reward place, which was then made inactive (small thin red circle). START, Location of the mouse at start of session. Red dots, locations of reward delivery. ***C***, Manipulations in the familiar open field. In the standard session (baseline 1), a light bulb was turned on at the 3 o'clock position, and a speaker continuously emitted white noise at the 9 o'clock position. In the distal rotation session, the position of the distal cues was rotated 180° with the chamber constant. In the proximal rotation session, the open field chamber was rotated 180°, while the distal cues remained unchanged. ***D***, Manipulations in the novel open field. A square chamber replaced the circular open field. All manipulation tests were similar to those used in the familiar open field. A time scale shows the duration for recording sessions and intersession intervals.

Manipulations in the square open field (novel environment). Place cells were then recorded in a new open field that the mouse was exposed to for the first time. The new open field was a square chamber (sized 55 × 55 cm, 25 cm height) that replaced the familiar open field. Two identical square chambers were used alternatively. The sequences of manipulations in the new environment were similar to those used in the familiar environment (Fig. 2*D*). Before each session in either the familiar or new environment, the floor was cleaned with a 0.5% Hibitan solution (Sumitomo Company).

Place field delineation. Dividing the total number of spikes by the cumulative dwell time in each pixel for the entire session yielded a firing rate map. The distribution map of the pixel firing rate was represented by a color scale with a pixel size of 2.4 × 2.4 cm. Pixels that the mouse had not visited in the open field are shown in gray, and those where the mouse visited but the cell never fired are by white pixels. A firing rate greater than zero was rated on an ascending scale, with the color scales being cyan, blue, green, yellow, and red. Pixels with firing rates greater than

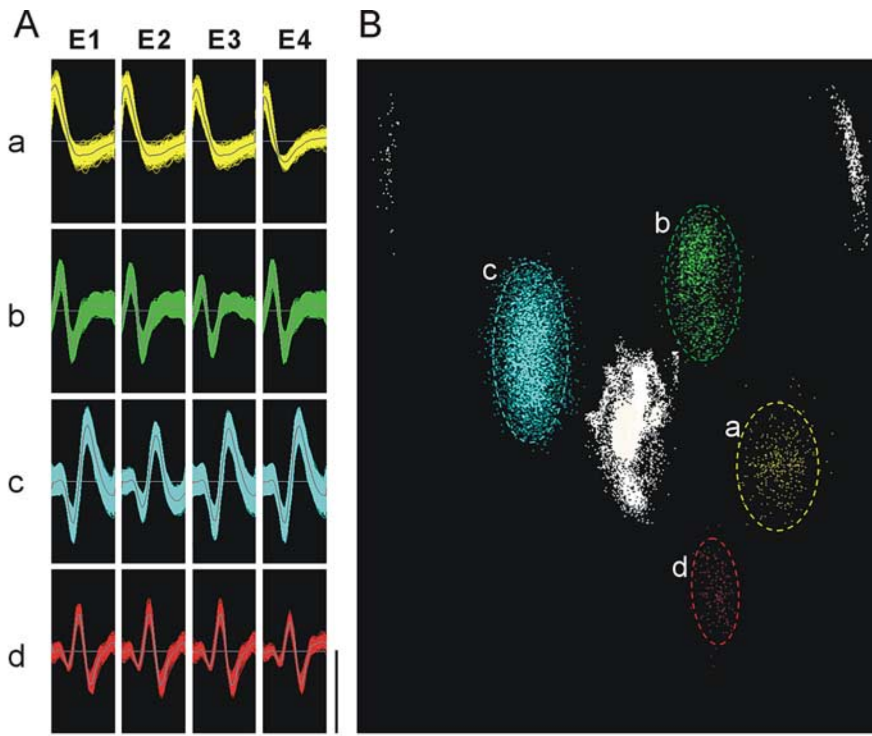


Figure 3. An example of multiple-unit recording with a tetrode isolated by an off-line sorter. ***A***, Superimposed waveforms of 4 neurons (a, b, c, d) recorded by each electrode (E1-E4) from a tetrode corresponding to cluster analysis in ***B***. ***B***, Cluster analysis. The *x*- and *y*-axes represent peak values of signals in electrode 2 and 1 of the four tetrode electrodes, respectively. Each dot represents one neuronal spike that exceeded the defined threshold. Four encircled clusters (a, b, c, d) were identified. White clusters dispersed in the center and at left and right corners represent baseline noise and stimulation signals, respectively. Calibration: 0.8 ms, 0.5 mV.

twice the mean are shown as red pixels. Place fields were delineated as clusters of pixels with firing rates exceeding twice the average of the sessions firing rates. A place field could be continued through any edge shared by two pixels meeting the criterion, but not through corners. If one or more neighboring pixels satisfied the criterion, the field was expanded to include the pixels. Each added pixel was then tested for the presence of a neighboring pixel that met the criterion. When no neighboring pixels satisfied the criterion, the limit of the field was identified. The minimum field size of a place-related cell was set at 9 pixels. Noncontiguous patches of adjacent pixels containing significantly increased firing rate were defined as "subfields" if they satisfied the above criterion of place fields.

Standard session analysis. For each place-related neuron, the firing rate plot during the standard session was used to determine (1) the place field size; (2) the mean overall firing rate; (3) the mean infield firing rate; (4) the mean outfield firing rate; (5) the maximum infield firing rate; (6) sparsity; (7) spatial tuning; (8) spatial coherence; and (9) the spatial information content (bits/spike). These analyses were performed using previously described methods (Wiener et al., 1989; Skaggs et al., 1993; Jung et al., 1994; Hetherington and Shapiro, 1997; Shapiro et al., 1997). The values of these parameters were compared between the two groups of mice using a Student's *t* test. Briefly, the size of the place field was estimated as the percentage of the place field over the visited arena. The mean overall firing rate was calculated as the total number of spikes fired within a session divided by the session time. The mean infield and mean outfield firing rates were determined as the averaged firing rate of the cell within and outside the place field. The maximum infield firing rate was the highest firing rate of all the pixels with the place field. Spatial tuning of the cell was determined as the ratio of the mean firing rate of the place field to the mean outfield firing rate (Wiener et al., 1989). The spatial coherence was calculated by performing z-transform to the correlation between the rate in a pixel and the mean rate in the adjacent pixels. The spatial information (Inf) signaled by each unit (Skaggs et al., 1993) was calculated by the following equation:

$$\mathrm{Inf} = \sum_i P_i \times r_i / R \log_2(r_i/R),$$

where R is the session average firing rate, r_i is the rate in pixel i, and P_i is the probability that the mouse was detected in pixel i.

Distal rotation, proximal rotation, and remapping analyses. To quantify the rotation of place fields between different sessions with environmental manipulation (a rotation of the distal or proximal cues), a rotation correlation score was measured for each place cell. The bins were smoothed by recalculating the firing rate of each bin as the average of itself and adjacent bins. For each cell, (1) the Pearson product-moment correlation between the firing rate array in the original session and that in the second session with environmental manipulation was measured, and then (2) the amount of angular rotation of the firing rate maps was quantified between the pair of sessions. This latter value was determined by rotating the firing rate map of the second session in 5° rotational increments to determine the position at which the rotated firing map was maximally correlated with the firing rate map of the original session. The rotation angle that produced the highest correlation was taken as the amount that the place field had rotated between the two sessions, and a cell was justified as following the cues if its place fields shifted >50% of the angle rotated for the given cue rotation session compared with the preceding baseline session. The measures for the divergence of firing fields (remapping) in the two chambers were also computed. A cell was considered to remap if it met one of the following conditions: (1) the cell stopped firing after being exposed to the novel chamber, (2) the cell became more robustly active in the novel chamber than in the familiar chamber, or (3) the field moved to a location not overlapping in position and direction with the previous location in the familiar chamber.

Visual acuity testing. A modified visual cliff test (Fox, 1965; Crawley, 2000) was used to test the visual acuity of our mice. A wooden box (46 cm × 46 cm) with a horizontal plane connected to a vertical drop (48 cm), which in turn connected to a lower horizontal plane at the nadir of the vertical drop. A black and white checkerboard-patterned paper covered the surface of the horizontal planes and the vertical drop. A sheet of transparent Plexiglas covered the cliff. A ridge of aluminum (2.54 cm wide and 3.8 cm thick) was placed at the edge of the cliff. Both sides of the apparatus were highly illuminated. The whiskers were removed before the visual cliff test to eliminate tactile information. Two groups with each of 10 adult males from the D1R-KO and WT mice were used. The mouse was placed on the center ridge at the start of each of 10 consecutive trials (after 5 trials the apparatus was turned 180° and 5 more trials were conducted). When the mouse chose to step down onto the horizontal checkered surface, it was regarded as a "positive" response, while the mouse stepping down onto the cliff drop side was regarded as a "negative" response. The time taken for the mouse to step down from the center ridge was recorded as a latency of response.

Histology. After the recording electrodes were estimated to be advanced below the pyramidal cell layer of the hippocampal CA1, the locations of the recording electrodes were verified histologically. Mice were deeply anesthetized with pentobarbital sodium (40 mg/kg i.p.). An electrolytic lesion (30 μA negative current for 15 s) was applied through the recording electrodes. The mouse was perfused with 0.9% saline followed by 10% buffered formal-saline. The brain was removed and fixed in 30%

formal-saline for a week. The brains were sectioned coronally (50 μm) on a freezing microtome and stained with cresyl violet.

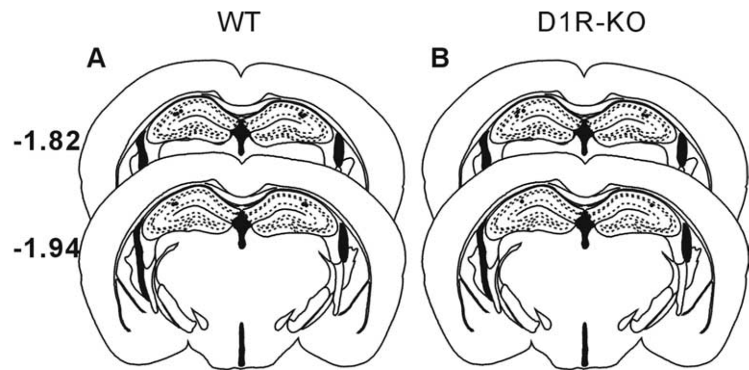


Figure 4. Verification of electrode placements. Location of recording electrode tips (black filled circles) for WT mice (***A***) and D1R-KO mice (***B***) used for the unit recording experiment. Plates were modified to resemble those from Franklin and Paxinos (1997). Numbers beside each section correspond to millimeters from bregma.

Results

Generation and characterization of D1R-KO mice

To disrupt the D1R gene in mouse ES cells by homologous recombination, we constructed a targeting vector so as to delete the whole coding sequence (Fig. 1*A*). Four clones with the disrupted D1R gene out of 120 G418-resistant colonies were obtained by transfection of E14TG2a IV ES cells with the targeting vector by Southern blot analysis (data not shown), and chimeras derived from the clones transmitted the mutation through the germline. Heterozygous progenies were intercrossed to generate homozygous mutant mice. Figure 1*B* shows the PCR analysis for the genotypes of progenies from heterozygous matings. Total lysates of adult mouse brain were examined by Western blot analysis. The expression of D1R was completely absent in the D1R-KO mice when compared with that in the WT mice (Fig. 1*C*). In contrast, β-actin was normally expressed in the striatum of both D1R-KO and WT mice (Fig. 1*C*).

Histology

The positions of the recording electrodes were verified microscopically and mapped onto the appropriate tissue sections, and the sections were compared with the mouse brain atlas of Franklin and Paxinos (1997). All the recording sites were located in the CA1 region for both types of mice (Fig. 4).

Hippocampal cells in D1R-KO and WT mice in a familiar environment

We recorded neuronal activity from the CA1 region in D1R-KO and their WT littermates. One hundred eighty-three cells were recorded from WT mice and 82 cells from D1R-KO mice. Of those cells, 99 from WT mice displayed place-related activity (by tetrodes, 77/99, 77.8%; by single electrodes, 22/99, 22.2%), and 52 from D1R-KO mice displayed place-related activity (by tetrodes, 42/52, 80.8%; by single electrode, 10/52, 19.2%). There was no difference in the number of recorded cells displaying place-related activity between the two groups of mice (WT, 99/183, 54.1% vs KO, 52/82, 63.4%, $p = 0.156$, χ^2 test). Thus, knockout of the D1R does not diminish the number of place cells. For place cells, we characterized the basic firing properties in the standard session in the familiar environment (Table 1). There were no significant differences in any spatial firing parameters between the two groups of mice (in all comparisons, $p > 0.05$), suggesting that lack of the D1R does not compromise the basic firing properties of place cells in a stable and well explored environment.

D1R-KO reduces place cells responding to distal cues in a familiar environment

We consequently examined the neural plasticity of hippocampal place cells under rotation manipulations of distal and proximal cues in the familiar circular recording chamber. The responses of place cells to the manipulations of environmental cues were categorized as being controlled by distal cues, proximal cues, both cue types, and neither cue type (Table 2). In WT mice, the effects of the distal cues predominated over the proximal cues (Table 2), in that the majority of place cells (52/91, 57.1%) followed the rotation of the distal cues (Fig. 5*A*, 1–5), fewer place cells (15/91, 16.5%) followed the rotation of the proximal cues (Fig. 5*B*, 1–5), and a fifth (18/91, 19.8%) followed the rotation of both distal and proximal cues (Fig. 5*C*, 1–5). Strikingly, in D1R-KO mice (Table 2), no place cells (0/50, 0%) followed the rotation of the distal cues, but most of the recorded place cells (40/50, 80%) followed the rotation of the proximal cues (Fig. 6*A*,*B*, 1–5). The number of neurons that were affected by cue rotation (following the distal + proximal + both cues) in D1R-KO mice was fewer than that in WT mice (KO, 40/50, 80% vs WT, 85/91, 93.4%, $p < 0.05$). These results show that though the number of neurons that changed their activity in response to proximal cues increased in D1R-KO mice, this increase still did not compensate for all responses, as was observed in WT mice.

Altered responses of place cells in D1R-KO mice in the novel environment

We performed further experiments to elucidate the flexibility of hippocampal place cells in processing environmental stimuli in novel environments, and to determine whether the D1R system is involved in this process. When initially exposed to the novel square chamber, of 86 place cells tested in WT mice, 38 cells showed remapping, with 7 cells turned off their firing and 31 cells changing their firing fields. Of the 26 cells tested in D1R-KO mice, 8 cells were remapped, with 3 cells turned off their firing, and 5 cells changed their firing fields. There were no marked differences in the number of cells remapped in the novel environment between the two groups of mice (WT, 37/86, 44.2% vs KO, 8/26, 30.8%, $p = 0.223$), though more cells changed their firing fields in WT mice (WT, 31/86, 36.1% vs KO, 5/26, 19.2%, $p = 0.107$). These results suggest that exposure to a novel environment has influences on a number of cells in both WT and D1R-KO mice. To test the neuronal responses of place cells in both familiar and novel chambers, animals were required to perform over 10 sequential sessions. In D1R-KO mice, for several cells, the performance of mice during recording deteriorated after 4–5 sessions, as they began to stop frequently and to run less randomly, as in circles (Tran et al., 2005), and their trajectories covered only a small area of the recording arena, which was insufficient for analyzing place fields. To maintain the reliability of the data regarding neuronal representations in both familiar and environments, in the present study we included only cells recorded over 10 sessions with sufficient behavioral performance,

Table 1. Comparisons of hippocampal place-cell firing properties in WT and D1R-KO mice in a familiar environment

Basic firing properties	WT (n = 99)	D1R-KO (n = 52)	p value
Place-field size (% of total visited area)	14.5 ± 0.77	13.7 ± 0.91	0.52
Place-field number	1.65 ± 0.08	1.73 ± 0.12	0.58
Mean overall firing rate (spikes/s)	1.75 ± 0.22	1.72 ± 0.21	0.92
Mean infield firing rate (spikes/s)	5.2 ± 0.64	4.9 ± 0.49	0.65
Mean outfield firing rate (spikes/s)	1.15 ± 0.22	1.14 ± 0.19	0.97
Maximum infield firing rate (spikes/s)	29.5 ± 1.85	28.8 ± 1.97	0.81
Sparsity	0.46 ± 0.02	0.44 ± 0.02	0.37
Spatial tuning	7.26 ± 0.81	7.11 ± 0.90	0.91
Spatial coherence	0.58 ± 0.02	0.56 ± 0.03	0.53
Spatial information content (bits/spike)	1.89 ± 0.08	2.0 ± 0.09	0.23

Values are mean ± SEM. Comparisons between the two groups of mice were made using a Student's t test.

Table 2. Numbers of hippocampal place cells in WT and D1R-KO mice tested for their responses to changes in distal and proximal cues in both familiar and novel environments

Mice	Chamber	No. (%)	Distal, no. (%)	Proximal, no. (%)	Both, no. (%)	Neither, no. (%)
WT	Familiar	91 (100)	52 (57.1)	15 (16.5)	18 (19.8)	6 (6.6)
	Novel	74 (100)	51 (68.9)	5 (6.8)	7 (9.5)	11 (14.8)
D1R-KO	Familiar	50 (100)	0 (0.0)**	40 (80.0)**	0 (0.0)**	10 (20.0)
	Novel	18 (100)	0 (0.0)**	4 (22.2)*##	0 (0.0)	14 (77.8)**##

In WT mice the majority of place cells had their place fields followed changes of the distal and proximal cues, with the effect of the distal cues being predominant in both familiar and novel environments. There was no difference in the number of total responding place cells (following distal + proximal + both cues) in between the familiar and novel environments (novel, 63/74, 85% vs familiar, 83/91, 91.2%, $p = 0.22$). In D1R-KO mice, no neurons were influenced by the distal cues in the novel environment. The total number of place cells with their place fields changed by cues in the novel environment was far less than that in the familiar environment (novel, 4/18, 22.2% vs familiar, 40/50, 80%, $p < 0.001$). The number of place cells responding to neither cue increased notably in D1R-KO mice compared with those in the familiar environment, suggesting that spatial novelty detection is lacking in D1R-KO mice. *$p < 0.05$; **$p < 0.01$ versus WT group (χ^2 test). #$p < 0.05$; ##$p < 0.001$ versus familiar (χ^2 test).

meaning that a limited number of cells in D1R-KO mice were tested in the novel environment.

In WT mice, the tendency for place cells to preferentially use the distal cues to locate their place fields (Fig. 5*A*, 6–10) over the proximal cues (Fig. 5*B*, 6–10) was more pronounced in the novel environment (Fig. 7*E*,*G*; Table 2). Interestingly, a small fraction of neurons had previously responded to both distal and proximal cues in the familiar environment (Fig. 5*C*, 1–5); in the novel environment, however, their location-specific firing was anchored to distal but not proximal cues (Fig. 5*C*, 6–10). In addition, the total number of place cells that responded to environmental cues did not differ between the familiar and novel environments (Table 2). These results suggest that hippocampal place cells in WT mice can use environmental information to represent their location in the environment. The fact that encoding of information from the distal cues was predominant over the proximal cues in both familiar and novel conditions in WT mice suggests that using this information is effective in enabling the animal to deal with a constantly changing environment. Furthermore, some of the place cells tested first followed distal cues in the new environment and then became tuned to the proximal information in the familiar environment, or vice versa. This result is consistent with a known idea that there are different cue reference systems for hippocampal neurons, and that they can be flexibly interchangeable or partly overlap under certain conditions (Gothard et al., 1996; Knierim et al., 1998; Zinyuk et al., 2000).

In D1R-KO mice, there were no place cells influenced by the distal cues in the novel environment (Fig. 6*A*,*B*, 6–10; Fig. 7*E*; Table 2). This result may have been due to some changes in cognitive functions in relation to the external environment caused by a lack of D1R (Kentros et al., 2004). Interestingly, in D1R-KO mice, a smaller fraction of place cells followed the rotation of the proximal cues in the novel environment, although most of the place cells followed the rotation of the proximal cues in the familiar environment. It is notable that the number of place cells responding to neither cue in the novel environment increased (Table 2). These results suggest that place cells in the D1R-KO mice seem less likely respond to the manipulations of distal cues, and that sufficient encoding of proximal cues might require a longer exposure to the environment to tailor this information to hippocampal activity.

The existence of dopamine receptors in the retina has previously been reported (Djamgoz et al., 1997; Nguyen-Legros et al., 1999; Courtière et al., 2003). Their presence raises a concern regarding the visual acuity of D1R-KO mice. We therefore performed a visual acuity test for mice (Fox, 1965; Crawley, 2000). No differences were found in the numbers of positive responses and latencies in response between the two types of mice (Table 3) (positive response: WT, 90/100 vs KO, 87/100, $p = 0.51$; latency: WT, 170.1 ± 12.8 vs KO, 181.8 ± 11.8 s, $p = 0.49$), showing that visual perceptibility in the D1R-KO mice was not markedly deficient compared with that in WT mice.

Discussion

To test the hypothesis that D1R modulates spatial representations in the hippocampus in response to environmental changes, we recorded hippocampal place cells in D1R-KO and WT mice with manipulations of environmental cues. The D1R-KO mice can have a number of hippocampal place cells with intact basic firing properties in a standard session comparable with that of WT mice. We have previously found a reduction in the average place field size of place-related activity in the nucleus accumbens (NAc) in D1R-KO mice (Tran et al., 2005). Thus, though the HF and NAc are interconnected and both are innovated by dopaminergic systems, the effects of D1R modulation on spatial representations in these two structures may be processed distinctively. Pharmacological manipulations of the D1R system (Gill and Mizumori, 2006) have demonstrated that the reliability and specificity of rat hippocampal place cells are disrupted only by combining a D_1 antagonist with a change in context. In the standard session in our experiment, there was a deletion of D1R, but the context was stable, with the result being that the basic firing prop-

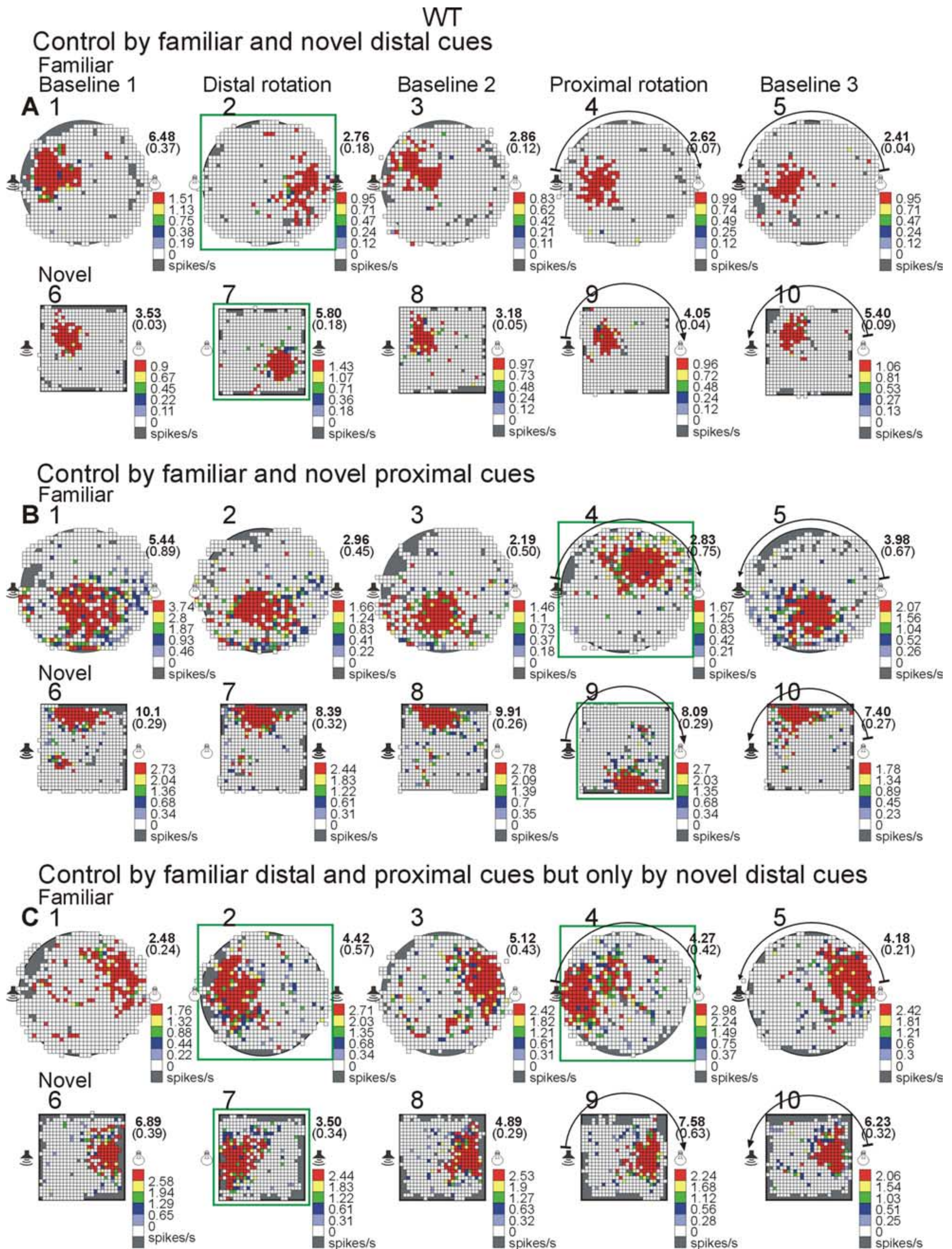
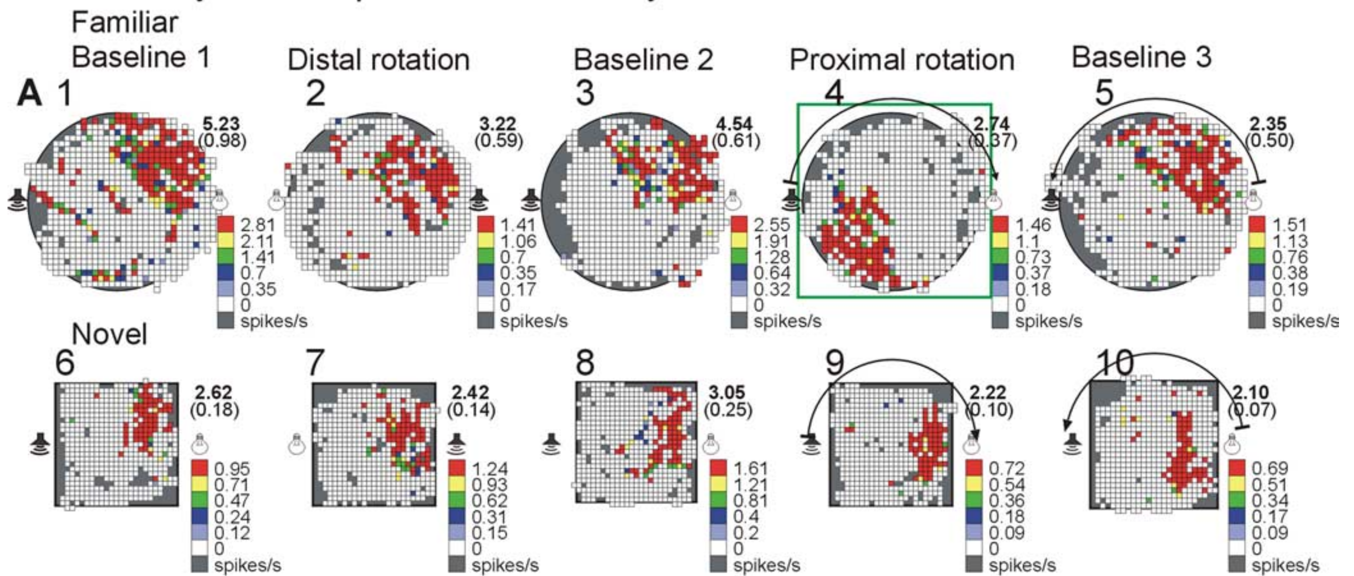


Figure 5. The effects of changes in the spatial relations between the distal and proximal cues on the hippocampal place-related activity in WT mice in the familiar (1–5) and novel environments (6–10). ***A***, In the familiar environment, a place cell had a place firing field at around the 9 o'clock position (1) in the standard session, and its place field shifted to the 3 o'clock position (2) in the distal rotation session, returned to the same position (3) as in the standard session in the baseline 2 session, no shift (4) in the proximal rotation session, and no change (5) in the return session in which the recording chamber was returned to the normal position. In the novel environment, the location-specific firing of this cell also followed the distal cues (6–7), but not the proximal cues (8–9). ***B***, A place cell had a place field that did not follow the rotation of the distal cues (1–2) but followed the proximal cues (3–4) in the familiar environment. The place field of this cell was remapped in the novel environment when its place field appeared opposite to that in the familiar environment, but still followed the rotation of the proximal cues (8–9). (*Figure legend continues*.)



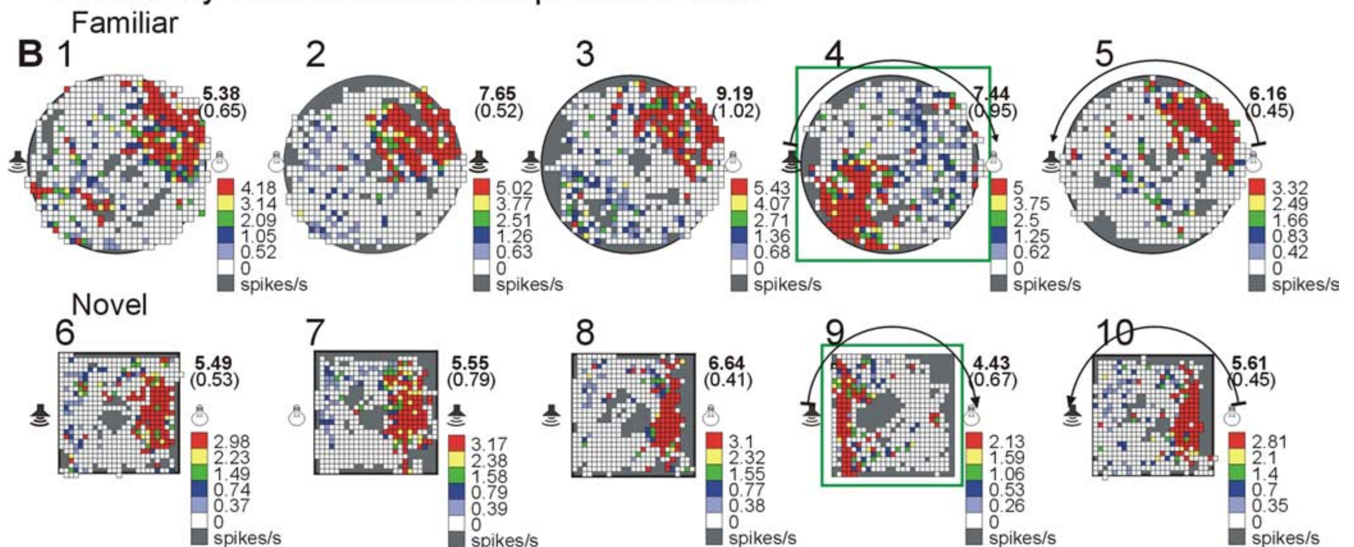


Figure 6. The effects of changes in the spatial relations between distal and proximal cues on the hippocampal place-related activity in D1R-KO mice in the familiar (1–5) and novel environments (6–10). ***A***, A typical place cell had a place field that did not follow the rotation of the distal cues (1–2), but followed the rotation of the proximal cues (3–4) in the familiar environment. In the novel environment, the place field of this cell was not changed by either the distal or the proximal cue manipulations. ***B***, Another example of a place cell whose place-related activity did not follow the rotation of the distal cues (1–2) but did follow the rotation of the proximal cues (3–4) in the familiar environment, and this cell responded similarly in the novel environment (6–10). Note that no place cells in D1R-KO mice followed the change in the distal cues. Other descriptions are as those for Figure 2.

←

(*Figure legend continued*.) ***C***, A place cell had a place field that followed the change of both the distal cues (1–2) and proximal cues (3–4) in the familiar environment. Interestingly, in the novel environment, the place field of this cell followed only the distal cues (5–6), not the proximal cues. Pictures of light bulbs and speakers beside the firing maps indicate their arrangements under the manipulation conditions of the distal and proximal cues. The rotation arrows indicate the rotation of the recording chamber in the proximal cue rotation session. Color scale tables to the right of the firing maps indicate the calibration for the firing rate. The numbers in bold and in parentheses to the right of the firing rate maps indicate the infield and outfield firing rates, respectively. The green open squares enclose the firing rate maps to emphasize the sessions in which the place field of the cell had rotated.

erties of HF neurons in D1R-KO mice were unchanged, which is consistent with that finding in rats. In the familiar environment, mice had substantial prior experience, which stabilized the reliability of place cells, and this may be more important for spatial navigation than the size of the place fields per se. However, when the environmental cues were manipulated, we found intriguing alterations in context-dependent plasticity in D1R-KO mice, as described.

The hippocampal representation can be altered by modification of long-term potentiation (LTP) (Rotenberg et al., 2000; Dragoi et al., 2003), and this synaptic plasticity can be modulated by dopamine (Otmakhova and Lisman, 1996; Matthies et al.,

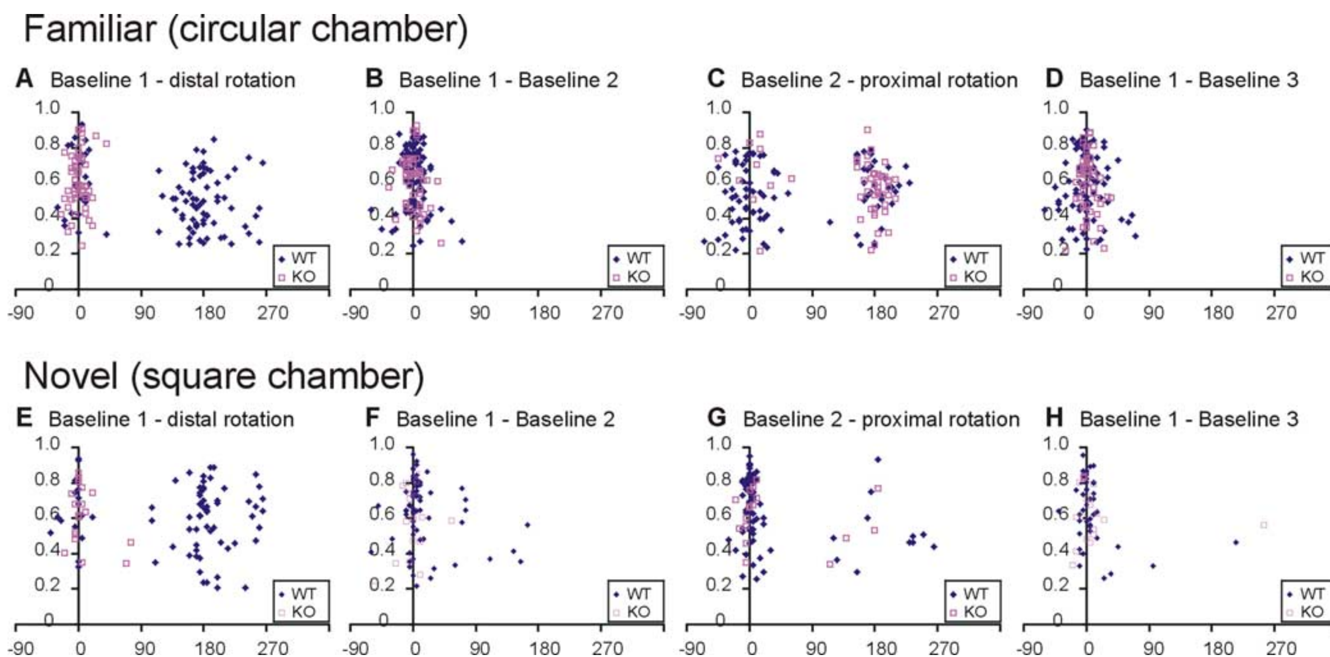


Figure 7. Scatterplots of spatial correlation values versus rotation angles that produced maximal correlation values between pairs of sessions for hippocampal place cells in WT and D1R-KO mice. Rotation angles are represented on the abscissa, and spatial correlation values between pairs of sessions are represented on the ordinate; blue filled diamonds are for WT mice, and red open squares for D1R-KO mice. ***A–D***, In the familiar environment, there were two subpopulations of place cells in WT mice in which the place fields were influenced by distal cues (distributed around 180°, standard session vs distal rotation session) (***A***) and proximal cues (distributed around 180°, baseline session 2 vs proximal rotation session) (***C***), with the influence of the distal cues predominant over the proximal cues. For D1R-KO mice, no place cells shifted their place fields by rotation of the distal cues (all around 0°) (***A***), and most cells shifted their place fields by rotation of the proximal cues (***C***). ***E–H***, In the novel environment, the predominant effect of the distal cues (***E***) over proximal cues (***G***) was still seen and was more pronounced in WT mice. In D1R-KO mice, only a few cells responded to the rotation of the distal cues (***E***) and proximal cues (***G***), and many cells did not follow distal or proximal cue changes in the novel environment.

Table 3. Results of the visual cliff test in WT and D1R-KO mice

	WT	D1R-KO	*p* values
Positive	90	87	0.49
Negative	10	13	
Latency (s)	170.1 ± 12.8	181.8 ± 11.8	0.51

The numbers of positive and negative responses between the two groups of mice were compared using a χ^2 test, and comparison of latencies in those responses used a Student's *t* test. Values of latencies in response are mean ± SEM.

1997; Swanson-Park et al., 1999; Li et al., 2003) and spatial novelty (Li et al., 2003). The comprehensive encoding of spatial cues may be crucial for place cells to rapidly recognize the layout of the environment, which in turn may contribute to the integration with idiothetic information. This ability may be important for spatial learning, especially in novel environments. The absence of D1R hindered the integration of spatial cue information flow, resulting in a decrease in the number of place cells responding to changes in spatial cues in the novel environment. The representation of the environment by hippocampal place cells, however, can still be stabilized by other information flows derived from other sources, such as idiothetic cues (Gothard et al., 1996; Whishaw et al., 1997; Knierim et al., 1998; Zinyuk et al., 2000; Stuchlik et al., 2001) used in path integration (Gothard et al., 1996; Whishaw et al., 1997; McNaughton et al., 2006), with the involvement of other neurotransmitter systems such as glutamatergic systems (McHugh et al., 1996; Cho et al., 1998; Kentros et al., 1998; McHugh et al., 2007). This neural plasticity may require a longer exposure to the environment. With a lack of D_1 modulation, this neural plasticity in D1R-KO mice could be preferentially tied to idiothetic cues (e.g., the path integrator) compared with distal cues from the environment. Hippocampal place cells are a part of a broader circuit for dynamic representation of self-location (Moser et al., 2008), and are now known to interact with grid cells in the entorhinal cortex (Brun et al., 2002; Hafting et al., 2005; Sargolini et al., 2006; Fyhn et al., 2007). The grid cells may provide the elements of a path integration-based neural map (McNaughton et al., 2006; Moser et al., 2008). Perhaps without D1R the cells turn back on a default "map" based primarily on path integration, causing the number of place cells following proximal cues to predominate in the familiar environment.

Spatial novelty encoding of hippocampal neurons, a phenomenon that conforms with what many other authors call 'remapping' (Leutgeb et al., 2005b) and that is thought to be a D1R-dependent ability (Li et al., 2003), may influence synaptic-dependent plasticity (Li et al., 2003) not only by the direct effect of D1R depletion but also by the effect of this on other neuromodulatory systems (Levine et al., 1996; Mele et al., 1996; Swanson-Park et al., 1999). Such changes compromise the representation of hippocampal neurons, resulting in an alteration in spatial cognition (Kentros et al., 2004; Stuchlik and Vales, 2006) or impairments in spatial learning requiring the use of spatial cues and the memory of places (El-Ghundi et al., 1999; Tran et al., 2005). Moreover, Kentros et al. (2004) also found that the application of D_1/D_5 receptor agonists and antagonists in wild-type mice increased or decreased place field stability. Together with the results of Gill and Mizumori (2006) and those of the present study, these data implicate the role of dopaminergic neuromodulation in the formation of hippocampal representation. Some other studies have shown less impairment in spatial learning in D1R-manipulated rats (Wilkerson and Levin, 1999), and manipulations of other neuromodulatory systems such as NMDA receptors can cause impairments in spatial tasks and the instability of place cells (McHugh et al., 1996, 2007; Cho et al., 1998; Kentros et al., 1998; Rotenberg et al., 2000) in an unchanged environ-

ment, further suggesting that hippocampal functions may rely on more than just the D1R system in a familiar environment. The results of equal positive responses and latencies in a visual acuity test suggested that alterations in spatial representation in the present study could arise from cognitive functions rather than deficits in visual perception.

Our results support the notion that the integration of information from spatial landmarks and idiothetic cues in place cells may involve the mutual interaction of dopaminergic and other neuromodulatory systems, including glutamatergic systems (McHugh et al., 1996, 2007; Mele et al., 1996; Kentros et al., 1998) in the hippocampus and among information processing systems (Sawaguchi and Goldman-Rakic, 1991; Wilkerson and Levin, 1999; Durstewitz et al., 2000; Tran et al., 2005), as dopamine can modulate the NMDA current (Mele et al., 1996; Durstewitz et al., 2000) and hippocampal plasticity, and this modulation is related to the stability of working memory (Sawaguchi and Goldman-Rakic, 1991; Durstewitz et al., 2000). In this context, we concluded that D1R plays an important role in detecting spatial novelty encoded by spatial representations of hippocampal place cells, a prerequisite for spatial learning. The present work together with other recent studies (Gasbarri et al., 1996; Matthies et al., 1997; Otmakhova and Lisman, 1996; El-Ghundi et al., 1999; Swanson-Park et al., 1999; Wilkerson and Levin, 1999; Tran et al., 2002, 2005; Li et al., 2003; Kentros et al., 2004; Gill and Mizumori, 2006; Stuchlik and Vales, 2006) should help significantly in revealing the mechanisms underlying the involvement of dopamine in learning and memory, from the molecular, to the neuronal, to the behavioral level.

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