Behavioral Neuroscience
2008, Vol. 122, No. 1, 16–26

0735-7044/08/$12.00 DOI: 10.1037/0735-7044.122.1.16

The Interactions and Dissociations of the Dorsal Hippocampus Subregions: How the Dentate Gyrus, CA3, and CA1 Process Spatial Information

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Several studies have demonstrated the significance of a spatial cognitive map and its role for guided and accurate navigation through the environment. Learning and recalling spatial knowledge depends upon proper topological and metric spatial information processing. The present objectives are to better characterize the role of the hippocampus for processing topological and metric spatial information. Rats with dorsal hippocampal subregional lesions (dDG, dCA3, dCA1) were tested on a previously established metric task and topological task. The results of the present study suggest that dCA1, but not dDG or dCA3, mediates topological memory. Furthermore, dDG, dCA3, and dCA1 mediate metric memory. Dorsal DG is required for spatial information processing via pattern separation or orthogonalization of sensory inputs to generate metric representations. Dorsal CA3 and dCA1 then receive these metric representations transmitted from dDG along the trisynaptic loop. The present data add to a growing body of literature suggesting a diversity of function among the hippocampal subregions.

Keywords: metric, topological, dorsal CA1, dorsal CA3, dorsal DG

The hippocampus is distinctly responsible for encoding, storing, and replaying spatial knowledge in the form of a cognitive map (Marr, 1971; O'Keefe, 1990; O'Keefe and Nadel, 1978; Tolman, 1948) and for guided and accurate navigation through the environment (Long & Kesner, 1996; Muller, Poucet, & Fenton, 1999; Poucet, 1993). Previous studies suggest that there exist at least two essential spatial relationships, topological and metric relationships between stimuli (Gallistel, 1990; Goodrich-Hunsaker, Hunsaker, & Kesner, 2005; Herrmann & Poucet, 2001; Kuipers & Levitt, 1988; Poucet, 1993). Topological relationships are loose representations of space based upon connectivity or enclosure between stimuli; distances and angles have no effect on processing topological information (Gallistel, 1990; Goodrich-Hunsaker et al., 2005; Herrmann & Poucet, 2001; Kuipers & Levitt, 1988; Poucet, 1993). Topological relationships are a crude representation of space. On the other hand, metric relationships are based upon distances and angles and are therefore more mathematically refined than topological information (Gallistel, 1990; Goodrich-Hunsaker et al., 2005; Herrmann & Poucet, 2001; Kuipers & Levitt, 1988; Poucet, 1993). It is thought that processing metric information involves orthogonalization of the spatial cues via pattern separation processing (i.e., creating distinct spatial representations; Rolls & Kesner, 2006).

Topological and metric spatial information are processed in anatomically separate brain regions. In support of this hypothesis, parietal cortex (PC) lesions in rats impaired topological memory, whereas dorsal hippocampus (dHPC) lesions in rats impaired metric memory (Goodrich-Hunsaker et al., 2005). The functions of the hippocampal subregions, dorsal CA1 (dCA1), dorsal CA3 (dCA3), and dorsal dentate gyrus (dDG), have been dissociated using behavioral analyses. For a full review on dissociations among the hippocampal subregions see Kesner, Lee, and Gilbert (2004). The specific contribution of dDG, dCA3, and dCA1 for topological and metric information processing remains unknown.

In order to better characterize the diversity of functions associated with dDG, dCA3, and dCA1, we compared exploratory activity using the same testing apparatus, stimuli, and procedures used by Goodrich-Hunsaker et al. (2005) in control, dDG lesioned, dCA3 lesioned, and dCA1 lesioned rats. Rats achieve spatial knowledge through extensive exploration of the environment (Cassel, Galani, Kelche, & Weiss, 1998; Poucet, 1993; Thinus-Blanc, Poucet, & Save, 1998). Such exploration endows rats with knowledge of the environment (Poucet, 1993). Note that habituation is a process, whereby rats acquire information about an environment through exploration. When specific alterations occur within the environment after habituation, exploration increases (dishabituation) until familiarity is once again obtained (Buhot, Foreman, Poucet, & Save, 1992; Thinus-Blanc et al., 1998). For the present study, habituation and dishabituation behaviors were used to mea-

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This research was supported by NSF grant IBN-0135273 and NIH grant RO1 MH065314 awarded to R. P. Kesner.

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sure the extent of topological and metric spatial information processing of the environment.

We hypothesized that the hippocampus subregion lesioned rats (dDG, dCA3, dCA1) would not disrupt topological spatial information processing. Previous research suggests that the PC is responsible for topological spatial information, not dHPC (Goodrich-Hunsaker et al., 2005). We also predicted that the hippocampus subregion lesioned rats (dDG, dCA3, dCA1) would not respond similarly on the metric task. Previous research has shown that even though lesions of the full dHPC disrupted spatial pattern separation (e.g., the orthogonalization of two spatial cues) of the hippocampus subregions only dDG lesions resulted in impairments (Gilbert & Kesner, 2006; Gilbert, Kesner, & DeCoteau, 1998; Gilbert, Kesner, & Lee, 2001). Spatial pattern separation deficits were not observed with dCA3 or dCA1 lesions.

Method

Subjects

Forty-seven male Long Evans rats, approximately 2 months of age and weighing approximately 350 g at the start of the experiment, were used as subjects. Each rat was housed independently in standard plastic rodent cages in a colony room. The colony was maintained on a 12-hour light/dark cycle. All testing was conducted in the light proportion of the light/dark cycle. All rats were free fed and allowed access to water ad libitum. All animal care and experimental procedures conformed to the National Institutes of Health and Institution for Animal Care and Use Committee guidelines for proper care and use of experimental animals.

Surgery

All rats were handled fifteen minutes daily for a week prior to surgery. Each rat was randomly assigned to receive a dDG lesion ($n = 12$), a dCA3 lesion ($n = 14$), a dCA1 lesion ($n = 12$), or a control lesion ($n = 9$). Rats were anesthetized with isoflurane. Each rat was placed in a stereotaxic apparatus (David Kopf Instruments, Tunjana, CA) with an isothermal heating pad to maintain body temperature at 37°C. With its head level, the scalp was incised and retracted to expose bregma and lambda. Bregma and lambda were then positioned in the same horizontal plane to ensure a flat skull surface. Small holes were drilled into the skull for the following lesions: dDG lesion—(a) 2.7 mm posterior to bregma, 2.1 mm lateral to midline, and 3.4 mm ventral from dura, and (b) 3.7 mm posterior to bregma, 2.3 mm lateral to midline, and 3.0 mm ventral from dura; dCA3 lesion—(a) 2.5 mm posterior to bregma, 2.6 mm lateral to midline, and 3.2 mm ventral from dura, (b) 3.3 mm posterior to bregma, 3.3 mm lateral to midline, and 3.2 mm ventral from dura, and (c) 4.2 mm posterior to bregma, 4.2 mm lateral to midline, and 3.1 mm ventral from dura; dCA1 lesion—3.6 mm posterior to bregma, 1.0, 2.0, and 3.0 mm lateral to midline, and 1.9 mm ventral from dura. Previous research has established the delineation between dorsal and ventral hippocampus (Bannerman et al., 2002; Moser & Moser, 1998).

Axon-sparing, subregion-specific lesions of the dHPC were made with specific neurotoxins. Colchicine (2.5 mg/mL, 0.8 μL/site, 20.0 μL/hr) was used for the bilateral dDG lesions and was injected into the two demarcated sites per hemisphere. Ibotenic acid was used for both the bilateral dCA3 and bilateral dCA1 lesions. For dCA3 lesions, ibotenic acid (6 mg/mL, 0.1–0.2 μL/site, 6.0 μL/hr) was slowly injected into the three sites per hemisphere. For dCA1 lesions, ibotenic acid (6 mg/mL, 0.1–0.15 μL/site, 6.0 μL/hr) was slowly injected into the three sites per hemisphere. All injections were made with a 10- μL Hamilton (Reno, NV) syringe with a microinjection pump (Cole Parmer Instrument Company, Vernon Hill, IL) through a 26-gauge cannula needle. The cannula needle was left in the brain for 1-minute after drug injections. Control lesions were made into the three sub-regions (dDG, dCA3, and dCA1) with a vehicle solution (phosphate-buffered saline [PBS]), as well as three sham controls.

Following surgery, the incisions were sutured and the rats were allowed to recover for one week before experimentation. They also received Children's Tylenol in water as an analgesic.

Materials and Experimental Procedures

Apparatus

A round board served as the testing apparatus for the experiment. In addition, a white vinyl shower curtain completely covered the maze. The surface of the apparatus stood 65 cm above the floor, was 119 cm in diameter, and was 3.5 cm thick. The apparatus was kept in a well-lit room with no windows, one door, a chair, a small table, and posters on the walls served as distal spatial cues. A video camera was positioned directly above the maze. All testing was videotaped.

All rats were tested twice on each of the tasks (i.e., metric task and topological task) for four separate days of testing: the order of metric and topological tasks was counterbalanced between each of the four days and different objects were used for each test. This was done to avoid a confounding variable of task order. Objects used ranged from 7.5- to 20-cm high and 5- to 12.5-cm wide and included such items as yellow bathtub rubber duck, blue electrical outlet box, white inverted plastic cup, etc. The dependent variable on all the tasks was exploration time with the objects and activity levels measured via grid crossings. Exploration of the objects was determined by scoring active and direct contact with an object. Exploration included such behaviors as sniffing the objects, biting the objects, pawing at the objects, and even crawling all over the objects. Exploration as defined provided a clear measure of spatial information processing in the rat model (Poucet, 1993). In addition to object exploration, rat activity level was measured via grid crossings. The cheeseboard was divided into a 3 by 3 grid (i.e., 9-grid sections total). As the rat explored, the grids entered into were recorded. Object exploration and grid crossing were used to measure habituation and dishabituation behaviors.

Topological Spatial Information Task

The topological task used in the present experiment (Figure 1A) was a previously established spatial novelty detection paradigm (see Dix & Aggleton, 1999; Goodrich-Hunsaker et al., 2005). The topological task consisted of five 5 min sessions with a 3-min first and third intersession interval and a 10-min intersession interval for the second and fourth intersession interval. The longer 10-min delay was used in order provide adequate consolidation time for the task. The animals started from the same exact location for each

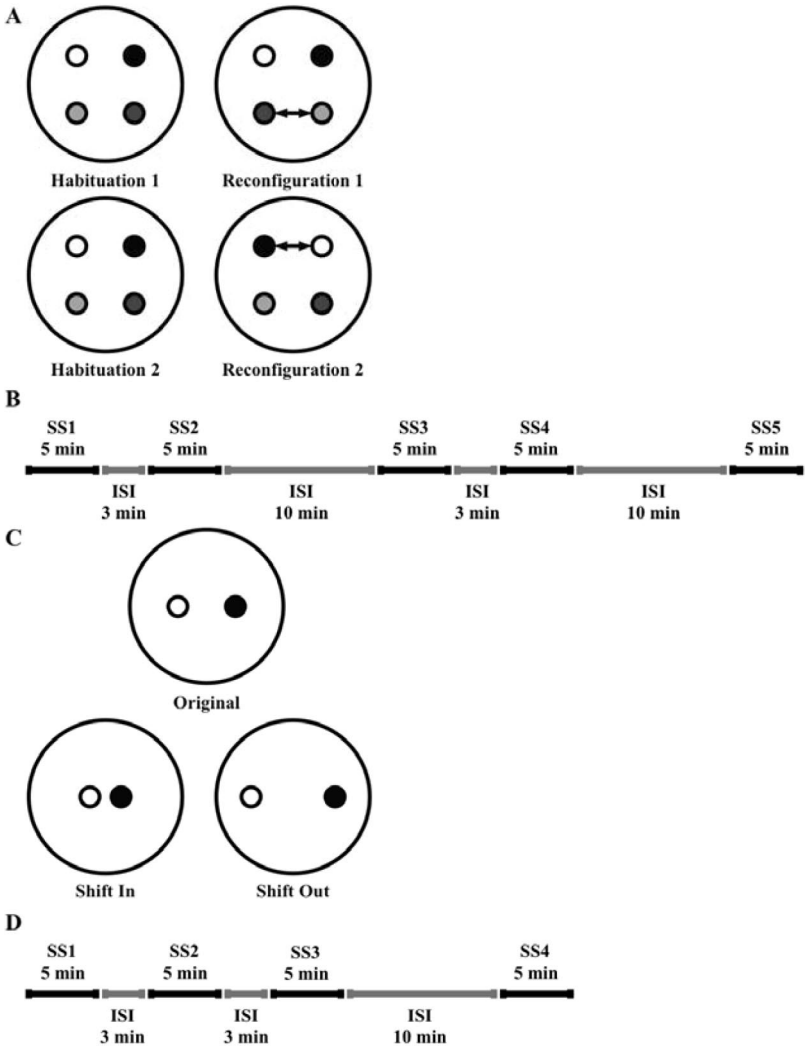

Figure 1. (A) Topological Task. Displayed are the general object geometric configurations on top of the round board. In the first panel, rats are habituated to the original geometric configuration. In the second panel, the front two objects are transposed creating a topological alteration. In the third panel, rats are habituated to the new configuration. In the last panel, the back two objects are transposed creating another topological alteration. (B) Topological Task. Displayed is a timeline for the topological task. The task consisted of five 5 min sessions (SS1, SS2, SS3, SS4, SS5) with a 3-min first and third intersession interval (ISI) and10 minutes for the second and fourth ISI. SS1 and SS2 allowed for familiarization and habituation. During SS3, after the first 10 min ISI, the front two objects were switched. SS3 and SS4 allowed for exploration and habituation to the new configuration. During SS5, after the second 10 min ISI, the back two objects were switched. (C) Metric Task. Displayed are the object positions on top of the round board. In the first panel, rats habituate to the original metric distance between the objects (i.e., 68 cm apart). In the second panel, the metric reconfiguration for the first task shortens the distance between the objects to 38 cm apart. In the last panel, the metric reconfiguration for the second task lengthens the distance between the objects to 98 cm apart. (D) Metric Task. Displayed is a timeline for the metric task. The task consisted of four 5-min session (SS1, SS2, SS3, SS4) with a 3-min first, second, and third intersession interval (ISI) and 10 minutes for the fourth ISI. SS1, SS2, and SS3 allowed for familiarization and habituation. During SS4, after the 10 min ISI, the objects either were shifted closer together or further apart.

session. For the topological test, four different objects were placed in a square arrangement each 68 cm apart on the round board. Sessions 1 and 2 allowed for familiarization and habituation. During Session 3, after the first 10-min intersession, the front two objects were switched. Sessions 3 and then Session 4 allowed for exploration and habituation to the new configuration. During Session 5, after the second 10-min intersession, the back two objects were switched. See Figure 1B for a timeline of the topological task. The second topological test used four entirely different objects on the same topological paradigm. As previously stated, the second topological task was administered on a different day than the first topological task. Although two topological shifts occurred

within one test, the topological task was repeated again for precise replication of the methods used by Goodrich-Hunsaker et al. (2005). The dependent variable was the time of object exploration in seconds. The time (in seconds) rats explored the displaced objects (front 2 objects during Session 3 and back 2 objects during Session 5) was compared to the time the animals explored the non-displaced objects (back 2 objects during Session 3 and front 2 objects during Session 5). After the topological shift, rats should explore the displaced, novel objects more that the non-displaced, familiar objects (Buhot et al., 1992; Goodrich-Hunsaker et al., 2005; Thinus-Blanc et al., 1998).

Metric Spatial Information Task

The metric task used in the present experiment (Figure 1C) was a novelty detection paradigm of four 5 min sessions with a 3 min first and second intersession interval and a 10 min intersession interval for the third intersession interval. The longer 10 min delay was used to provide adequate consolidation time for the task. Again, the animals began from the same exact location for each session (Figure 1C). On the first metric test, two different objects were placed 68 cm apart on the cheese board. Sessions 1, 2, and 3 allowed for familiarization and habituation. During Session 4, after the 10 min intersession interval, the two objects were moved so that the separation was 38 cm apart. The second metric test used two different objects, on the same metric paradigm. Sessions 1, 2, and 3 allowed for familiarization and habituation. During Session 4, the two objects were moved so that the separation was 98 cm apart. See Figure 1D for a timeline of the metric task. The second topological test used four entirely different objects on the same topological paradigm. The dependent variable was the time of object exploration in seconds. The time (in seconds) rats explored the displaced objects (Session 4) was compared to the time (in seconds) the rats explored the nondisplaced objects (Session 3). After the metric shift rats should explore the displaced, novel objects more than the non-displaced, familiar objects (Buhot et al., 1992; Goodrich-Hunsaker et al., 2005; Thinus-Blanc et al., 1998).

As previously stated, all tasks were counterbalanced (i.e., the metric tasks were not always before the topological tasks and visa versa) and each task was run on separate days. Rats were never tested more than once a day. In addition, no object was used more than once across tasks. Since there were two metric tasks each with two objects and two topological tasks each with four objects, 12 different objects were used in this experiment. Finally, all objects and the white, vinyl curtain covering the round board were wiped down with 70% alcohol between each session and after each task in order to eliminate any possible odor cues.

Histology

At the end of the experiments, each rat was given a lethal intra-peritoneal injection of sodium pentobarbital (70 mg/mL). The rat was perfused intracardially with PBS followed by 10% (wt/vol) formalin in 0.1 M PBS. The brain was then removed and stored in 30% (vol/vol) sucrose-formalin for 1 week. Transverse sections (24 μm) were cut with a cryostat through the lesioned area and stained with cresyl violet. A program, ImageJ 1.33 (National Institute of Health [NIH], 2005), was used to quantify the extent of the lesion.

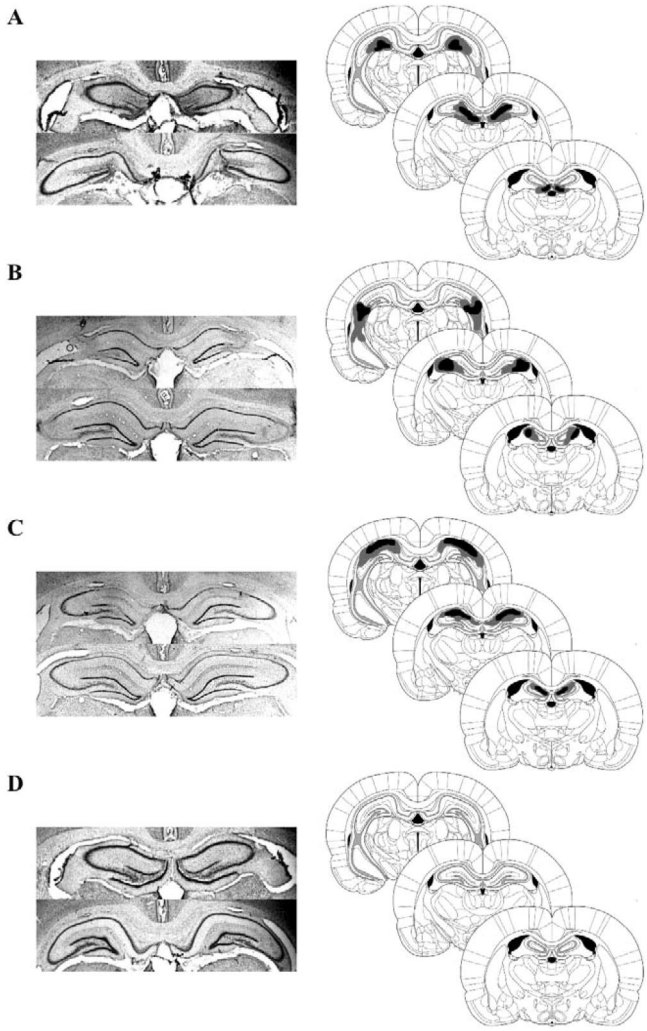

Figure 2. Serial sections were taken along the septotemporal axis from top to bottom. (A) Photomicrographs (12.5 ×) and schematic drawing of the largest (*gray*) and the smallest (*black*) of a dDG lesioned rat brain. Note the almost complete degeneration of the granule cells in dDG compared with the control brain sections. (B) Photomicrographs (12.5 ×) and schematic drawing of the largest (*gray*) and the smallest (*black*) of a dCA3 lesioned rat brain. Note the almost complete degeneration of the pyramidal cells in dCA3 compared with the control brain sections. (C) Photomicrographs (12.5 ×) and schematic drawing of the largest (*gray*) and the smallest (*black*) of a dCA1 lesioned rat brain. Note the almost complete degeneration of the pyramidal cells in dCA1 compared with the control brain sections. (D) Photomicrographs (12.5 ×) and schematic drawing of the largest (*gray*) and the smallest (*black*) of a control rat brain. Adapted from *The Rat Brain in Stereotaxic Coordinates* (4th ed.), G. Paxinos and C. Watson, 1998. Copyright 1998, with permission from Elsevier.

Results

Histology

Axon-sparing, subregion-specific lesions of the dHPC were made with specific neurotoxins. Lesions were quantified using the procedures of Gilbert et al. (2001) and Lee and Kesner (2003). Colchicine (2.5 mg/mL, 20.0 μL/hr) was used for the bilateral

dDG lesions and ibotenic acid (6.0 mg/mL, 6.0 μL/hr) was used for both the bilateral dorsal CA3 (dCA3) and bilateral dorsal CA1 (dCA1) lesions. A quantitative analysis revealed that lesions to dDG (Figure 2A) were > 95% complete with no visible damage to dCA3 and in one case under 5% damage to the overlying dCA1. Lesions to dCA3 (Figure 2B) were approximately 90% complete with sparing at the dCA2 aspect of dCA3 and no cortical damage. There were no instances of damage to dCA1 or to the dDG. Lesions to dCA1 (Figure 2C) were approximately 80% to 85% complete with sparing in the aspect closest to dCA2. No dCA3 damage was observed in dCA1 lesion animals and in one case, there was under 10% damage to the upper blade of the dDG. There was also minimal damage to the overlying cortex. In all lesions, there was some sparing mostly at the septal pole of the hippocampus, but the lesion could be verified from 3.0 to 4.3 mm posterior to bregma. There was no observed damage to the ventral half of the hippocampus. Figure 2D shows sections from a control rat brain. Eight animals had to be excluded from analysis due to the lesion extending to the entire dHPC ($n = 4$) or not enough damage to the pyramidal cell layers of dCA1 ($n = 2$) or dCA3 ($n = 2$). To the left of each lesion photomicrograph is a diagram displaying the maximal (gray) and minimal (black) damage for each lesion on plates modified from Paxinos and Watson (1997).

Behavioral Analysis

Topological Spatial Information Task

Activity levels. Table 1 reports the topological task grid-crossing means and standard errors for each lesion group within each habituation session. Figure 3A illustrates the time course of average grid crossings for each lesion group during the first habituation sessions (Session 1, Session 2). A repeated-measure two-way analysis of variance (ANOVA) with lesion group (dDG, dCA3, dCA1, control) as the between-group factor and average grid crossings for each habituation sessions (Session 1, Session 2) as the within-group factor revealed a significant main effect of lesion group, $F(3, 35) = 6.66$, $p < .001$, a significant effect of session, $F(1, 35) = 36.14$, $p < .0001$, and a significant lesion group × habituation session interaction, $F(3, 35) = 4.36$, $p < .0001$. A Fisher's LSD post hoc comparison test on lesion groups revealed that dCA1 lesioned rats had more grid-crossing activity compared to control ($p < .001$) and dDG lesioned ($p < .05$) rats. Dorsal CA3 lesioned rats also had heightened activity compared to control ($p < .001$) and dDG lesioned ($p < .05$) rats. A Fisher's LSD post hoc comparison on the lesion group × habituation session interaction revealed that Session 1 grid-crossing activity was significantly greater than Session 2 grid-crossing activity within controls ($p < .001$), dCA3 lesioned rats ($p < .001$), and dCA1 lesioned rats ($p < .05$). Even though activity levels for dDG lesioned rats did not reach significance, all lesion groups had decreased activity levels from Session 1 to Session 2.

Figure 3B illustrates the time course of average grid crossings for each lesion group during the second habituation sessions (Session 3, Session 4). A repeated-measure two-way ANOVA with lesion group (dDG, dCA3, dCA1, control) as the between-group factor and average grid crossings for each habituation session (Session 3, Session 4) as the within-group factor revealed a significant main effect of lesion group, $F(3, 35) = 4.10$, $p < .05$, a significant effect of session, $F(1, 35) = 28.18$, $p < .0001$, and a significant lesion group × habituation session interaction, $F(3, 35) = 3.23$, $p < .05$. A Fisher's LSD post hoc comparison on lesion group revealed that dCA1 lesioned ($p < .005$), dCA3 lesioned ($p < .01$), and dDG lesioned ($p < .05$) rats had more grid-crossing activity compared with controls. A Fisher's LSD post hoc comparison on lesion group × habituation session interaction revealed that Session 3 grid-crossing activity was significantly greater than Session 4 grid-crossing activity within dDG lesioned ($p < .05$), dCA3 lesion ($p < .001$), and dCA1 lesioned ($p < .005$) rats. Even though activity levels for control rats did not reach significance, all lesion groups had decreased activity levels from Session 3 to Session 4. Overall, each lesion group displayed decreased activity levels across topological spatial information task sessions (Session 1 to Session 2 and Session 3 to Session 4).

Object exploration. Table 2 reports the topological task object exploration means and standard errors for each lesion group within each habituation session. Figure 4A illustrates the average object exploration (in sec) for each lesion group during the first habituation sessions (Session 1, Session 2). A repeated-measure two-way ANOVA with lesion group (dDG, dCA3, dCA1, control) as the between-group factor and average object exploration for each

Table 1
Average Grid Crossings (± SE) for Each Group Across Sessions

Group	n =	Session 1	Session 2	Session 3	Session 4
			Topological task		
Control	9	51.67 ± 7.40	22.33 ± 3.18	21.54 ± 4.86	21.47 ± 5.23
dDG	8	51.00 ± 12.42	50.88 ± 12.08	60.88 ± 11.14	40.75 ± 10.08
dCA3	12	103.83 ± 15.60	75.75 ± 11.25	64.67 ± 10.70	42.25 ± 8.34
dCA1	10	100.30 ± 9.37	83.20 ± 8.05	68.60 ± 7.04	52.60 ± 9.42
			Metric task		
Control	9	43.89 ± 6.28	27.78 ± 6.12	18.56 ± 3.35	
dDG	8	55.50 ± 9.68	54.63 ± 6.66	44.88 ± 7.45	
dCA3	12	102.33 ± 11.34	76.08 ± 11.20	53.42 ± 11.08	
dCA1	10	91.40 ± 9.35	78.10 ± 7.51	58.60 ± 6.86	

Note. dDG = dorsal dentate gyrus; dCA3 = dorsal CA3; dCA1 = dorsal CA1.

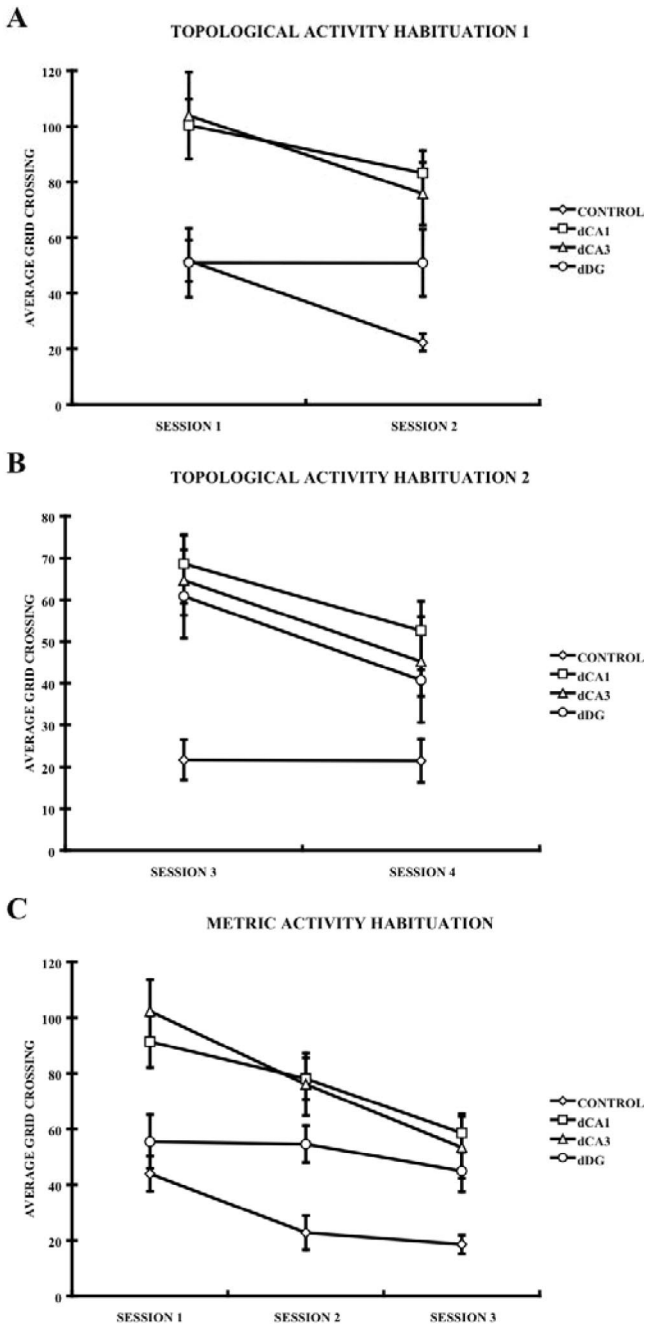

Figure 3. (A) Topological Task. Habituation 1. Graphed is the time course of average grid crossings ± *SE* for each lesion group for Session 1 and Session 2. (B) Topological Task. Habituation 2. Graphed is the time course of average grid crossings ± *SE* for each lesion group for Session 3 and Session 4. (C) Metric Task. Graphed is the time course of average grid crossings ± *SE* for each lesion group for Sessions 1, Session 2, and Session 3. Habituation was observed for all lesion groups for Figures 3A, B, and C.

habituation sessions (Session 1, Session 2) as the within-group factor revealed a significant main effect of lesion group, $F(3, 35) = 4.18$, $p < .01$, a significant effect of session, $F(1, 35) = 48.97$, $p < .0001$, and no significant lesion group × habituation session interaction, $F(3, 35) = .10$, $p > .05$. A Fisher's LSD post hoc comparison test on lesion groups revealed that dDG lesioned rats spent longer time exploring the objects compared to control ($p < .001$), dCA3 lesioned ($p < .02$), and dCA1 lesioned ($p < .05$) rats. A Fisher's LSD post hoc comparison test on sessions revealed that total object exploration (in sec) decreased from Session 1 to Session 2 ($p < .0001$).

Figure 4B illustrates the time course of average object exploration (in sec) for each lesion group during the second habituation sessions (Session 3, Session 4). A repeated-measure two-way ANOVA with lesion group (dDG, dCA3, dCA1, control) as the between-group factor and average grid crossings for each habituation session (Session 3, Session 4) as the within-group factor revealed no significant main effect of lesion group, $F(3, 35) = 2.33$, $p > .05$, a significant effect of session, $F(1, 35) = 46.62$, $p < .0001$, and no significant lesion group × habituation session interaction, $F(3, 35) = .84$, $p > .05$. A Fisher's LSD post hoc comparison on sessions revealed that total object exploration (in sec) decreased from Session 3 to Session 4 ($p < .0001$).

Overall, each lesion group displayed decreased object exploration and activity across topological spatial information task sessions (Session 1 to Session 2 and Session 3 to Session 4). These results suggest that rats habituated to their environment.

Because there was a discrepancy of habituation (i.e. total object exploration and grid crossing activity) for each lesion group, object exploration (in seconds) was standardized by the following ratio: the total time spent exploring the displaced objects (A) during the first reconfiguration session (Session 3) was divided by the sum of the total time spent exploring the displaced (A) and non-displaced (B) objects in Session 3, thereby creating the ratio A divided by the sum of A plus B. This exact formula was then used with the second reconfiguration session (Session 5). No preference was considered if an animal spent an equal amount of time exploring the displaced objects and the non-displaced objects. The ratio would be equal to .5. The ratios from Session 3 and Session 5 from the first and second topological task were averaged together for each rat. Figure 5A shows the ratio of object exploration during the topological task for each lesion group. Control rats ($M = .708$, std. error = .05) were significantly different from .5 (no preference; $t(8) = 4.44$, one-sided $p < .005$), suggesting that control animals spent more time exploring the displaced objects than the non-displaced objects.

Activity levels as measured by the total time spent exploration the objects during the last habituation sessions (Session 2, Session 4) and number of grid crossings during the reconfiguration sessions (Session 3, Session 5) may be hidden variables within the object re-exploration data analysis. These variables were used as covariates. A one-way analysis of covariance (ANCOVA) revealed a significant main effect of lesion group, $F(3, 31) = 3.44$, $p < .05$, no significant effect of Session 3 grid crossing activity, $F(1, 31) = .05$, $p > .05$, no significant effect of Session 5 grid crossing activity, $F(1, 31) = .55$, $p > .05$, no significant effect of Session 2 object exploration (in sec; $F(1, 31) = .01$, $p > .05$), and no significant effect of Session 4 object exploration, in sec; $F(1, 31) = 3.90$, $p > .05$). A Fisher's LSD post hoc comparison test for the lesion group revealed that dCA1 lesioned rats were impaired compared to control ($p < .005$), dCA3 lesioned ($p < .05$), and dDG lesioned ($p < .05$) rats. However, dCA1 lesioned rats were also significantly different from .5, no preference; $t(9) = 2.68$, $p <$

Table 2
Average Object Exploration (in sec; ± SE) for Each Group across Sessions

Group	*n* =	Session 1	Session 2	Session 3	Session 4
			Topological task		
Control	9	24.89 ± 3.76	5.67 ± 1.63	10.67 ± 2.14	3.22 ± 1.09
dDG	10	55.94 ± 5.91	36.69 ± 3.76	21.56 ± 4.78	8.63 ± 3.12
dCA3	12	34.75 ± 4.00	18.75 ± 2.26	15.04 ± 2.76	6.83 ± 1.33
dCA1	8	37.15 ± 3.19	19.95 ± 2.66	14.05 ± 2.10	6.35 ± 1.28
			Metric task		
Control	9	10.00 ± 1.53	1.89 ± 0.58	1.22 ± 0.43	
dDG	10	29.31 ± 7.55	22.44 ± 5.91	14.88 ± 6.68	
dCA3	12	21.38 ± 3.02	10.92 ± 1.90	4.63 ± 0.98	
dCA1	8	23.25 ± 4.03	14.90 ± 3.32	7.05 ± 1.41	

Note. dDG = dorsal dentate gyrus; dCA3 = dorsal CA3; dCA1 = dorsal CA1.

.05. These data suggest that dCA1 lesions impaired, but did not destroy topological spatial information processing.

Metric Spatial Information Task

Activity levels. Table 1 reports the metric task average grid crossing means and standard errors for each lesion group within each habituation session. Figure 3C illustrates the time course of average grid crossings for each lesion group during the habituation sessions (Session 1, 2, 3). A repeated-measure two-way ANOVA with lesion group (dDG, dCA3, dCA1, control) as the between-group factor and session (Session 1, Session 2, Session 3) as the within-group factor revealed a significant main effect of lesion group, $F(3, 35) = 5.64$, $p < .005$, a significant effect of session, $F(2, 70) = 50.90$, $p < .0001$, and a significant lesion group × habituation session interaction, $F(6, 70) = 4.12$, $p < .001$. A Fisher's HSD post hoc comparison on lesion group revealed that dCA1 lesioned rats had more grid-crossing activity compared to controls ($p < .001$). Dorsal CA3 lesioned rats also had more grid-crossing activity compared to control rats ($p < .0001$) and dDG lesioned rats ($p < .05$). A Fisher's LSD post hoc comparison on lesion group × habituation session interaction revealed that within controls, Session 1 grid-crossing activity was higher than Session 2 activity ($p < .01$) and Session 3 activity ($p < .001$). Session 2 grid-crossing activity was also significantly higher than Session 3 activity ($p < .05$). Within dDG lesioned rats, Session 1, Session 2, and Session 3 activity levels did not significantly differ. Within dCA3 lesioned rats, Session 1 grid-crossing activity was higher than Session 2 activity ($p < .001$) and Session 3 activity ($p < .0001$) and Session 2 activity was heightened compared to Session 3 activity ($p < .0001$). Within dCA1 lesioned rats, Session 1 grid-crossing activity was heightened compared to Session 2 activity ($p < .01$) and Session 3 activity ($p < .0001$) and Session 2 activity was heightened compared to Session 3 activity ($p < .0001$). Even though dDG activity levels did not reach significance, all lesion groups had decreased activity levels from Session 1 to Session 3. Overall, each lesion group displayed decreased activity levels across metric spatial information task sessions (Session 1 to Session 3).

Object exploration. Table 2 reports the metric task average object exploration means and standard errors for each lesion group within each habituation session. Figure 4C illustrates the average object exploration (in sec) for each lesion group during the habituation sessions (Session 1, 2, 3). A repeated-measure two-way ANOVA with lesion group (dDG, dCA3, dCA1, control) as the between-group factor and session (Session 1, Session 2, Session 3) as the within-group factor revealed a significant main effect of lesion group, $F(3, 35) = 5.27$, $p < .005$, a significant effect of session, $F(2, 70) = 56.51$, $p < .0001$, and no significant lesion group × habituation session interaction, $F(6, 70) = 1.00$, $p > .05$. A Fisher's HSD post hoc comparison on lesion group revealed that dDG lesioned rats spent more time exploring the objects compared to controls ($p < .0001$) and dCA3 ($p < .05$) lesioned rats. Dorsal CA1 lesioned rats also spent more time exploring the objects compared to control rats ($p < .05$). A Fisher's LSD post hoc comparison on session revealed that total object exploration decreased from Session 1 to Session 2 to Session 3.

Overall, each lesion group displayed decreased object exploration and activity across metric spatial information task sessions (Session 1 to Session 2 to Session 3).

Again since there was a discrepancy in habituation across lesion groups, a similar ratio to the topological ratio was formulated to standardize object exploration (in seconds): the total time spent exploring all objects (A) during the reconfiguration session (Session 4) was divided by the addition of the total time exploration all objects during the previous session (B) (Session 3) and itself (A) (Session 4); thereby creating a ratio of A divided by the sum of A plus B. As previously mentioned, if an animal spent an equal amount of time exploring the displaced objects and the nondisplaced objects, then the ratio would be equal to .5 (no preference). The ratios from the first and second metric task were averaged together for each rat. Figure 5B represents the ratio of object exploration during the metric task for each lesion group. Control rats ($M = .84$, std. error = .05) were significantly different from .5, no preference; $t(8) = 6.65$, one-sided $p < .001$, suggesting that the control group spent more time exploring the displaced objects than the nondisplaced objects.

Activity levels as measured by the total time spent exploration the objects during the last habituation sessions (Session 3) and number of grid crossings during the reconfiguration sessions (Session 4) may be hidden variables within the object re-exploration

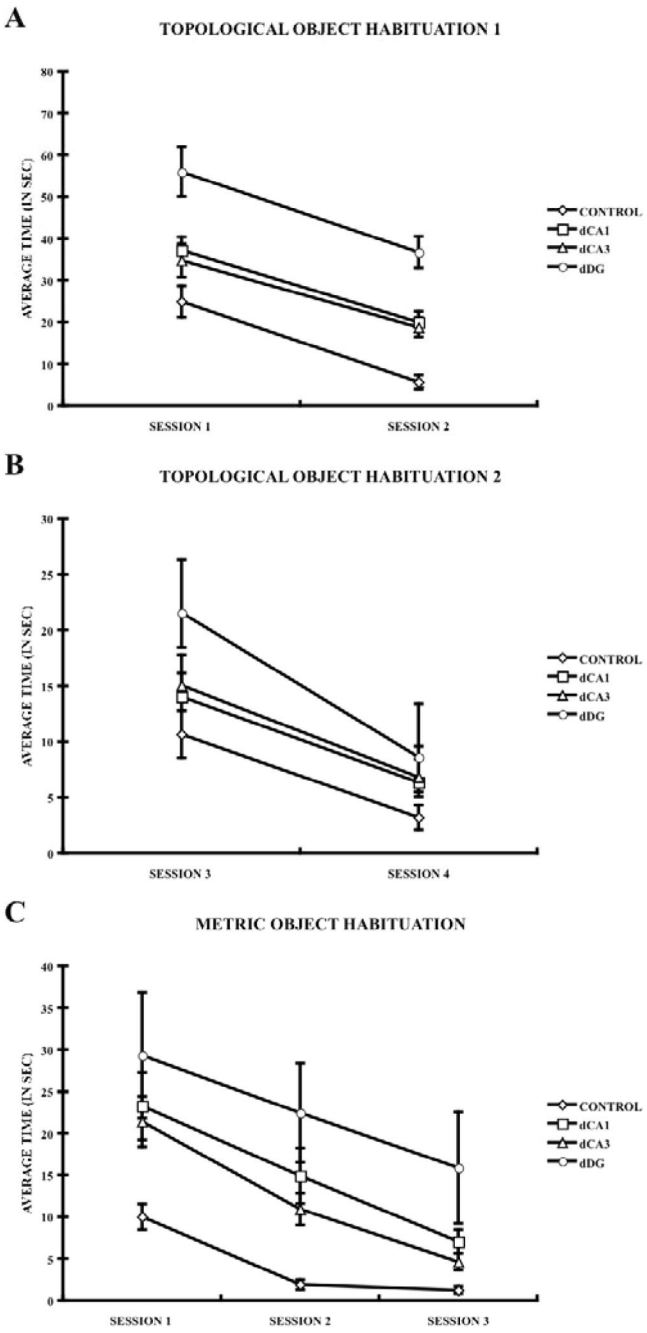

Figure 4. (A) Topological Task. Object Habituation 1. Graphed is the average object exploration ± *SE* (in sec) for each lesion group for Session 1 and Session 2. (B) Topological Task. Object Habituation 2. Graphed is the average object exploration ± *SE* (in sec) for each lesion group for Session 3 and Session 4. (C) Metric Task. Graphed is the average object exploration ± *SE* (in sec) for each lesion group for Sessions 1, Session 2, and Session 3. Habituation was observed for all lesion groups for Figures 4A, B, and C.

data analysis. These variables were used as covariates. A one-way ANCOVA revealed a significant main effect of lesion group, $F(3, 33) = 6.60$, $p < .001$, no significant effect of Session 4 grid crossing activity, $F(1, 33) = .07$, $p > .05$, and no significant effect of Session 3 object exploration, (in seconds), $F(1, 33) = .16$, $p > .5$. A Fisher's LSD post hoc comparison test for lesion group revealed that dDG lesioned ($p < .0001$), dCA3 lesioned ($p < .005$), and dCA1 lesioned ($p < .005$) rats were impaired compared to controls. Moreover, dDG lesioned rats were impaired compared to dCA3 lesioned ($p < .05$) and dCA1 lesioned ($p < .05$) rats. These data suggest that dDG, dCA3, and dCA1 are all necessary for metric information processing, but their roles for processing metric representations are different.

Discussion

The results of the present study better characterize the role of dDG, dCA3, and dCA1 of the hippocampus for topological and metric spatial information processing. For this study, we compared the exploration behaviors of dDG lesioned, dCA3 lesioned, dCA1 lesioned, and control rats using the same testing apparatus, stimuli, and procedures used in the Goodrich-Hunsaker et al. (2005) study. Overall, dDG lesions impaired metric spatial information processing. Dorsal CA3 lesions disrupted metric representations. Dorsal CA1 lesions disrupted both topological and metric representations.

We hypothesized that the hippocampus subregion lesioned rats (dDG, dCA3, dCA1) would not disrupt topological spatial information processing. Previous research has shown that the PC, not the dHPC, mediates topological spatial information processing (Goodrich-Hunsaker et al., 2005). However, the present findings partially support this hypothesis. Dorsal CA1 lesioned rats spent less time exploring the displaced objects after a topological shift than dDG lesioned, dCA3 lesioned, and control rats. However, dCA1 lesioned rats still displayed preference for the novel, displaced objects over the familiar, non-displaced objects. Therefore, dCA1 lesions did not destroy topological representations. These data indicate that topological information is supported by dCA1, but that dCA1 appears not to be exclusively necessary, since dCA1 lesioned rats' exploration time with the displaced objects over the non-displaced object was heightened. Dorsal DG and dCA3 are not necessary for topological spatial information processing. As stated previously, the PC mediates topological spatial information on the same topological task (Goodrich-Hunsaker et al., 2005). Altogether, these data add to our understanding concerning possible PC and dHPC interactions. However, future studies are still needed to better characterize the neuroanatomical connections between the dHPC and PC, specifically for topological spatial information processing.

We also predicted that the hippocampus subregion lesioned rats (dDG, dCA3, dCA1) would not respond similarly on the metric task. Previous research has shown that even though lesions of the full dHPC disrupted spatial pattern separation (e.g., the orthogonalization of two spatial cues) of the hippocampus subregions only dDG lesions resulted in impairments for spatial pattern separation processes (Gilbert & Kesner, 2006; Gilbert, Kesner, & DeCoteau, 1998; Gilbert, Kesner, & Lee, 2001). Spatial pattern separation deficits were not observed with dCA3 or dCA1 lesions. This hypothesis is supported by the results of the present study. Dorsal DG lesioned rats spent more time exploring the familiar, non-displaced objects than exploring the same objects after a metric displacement. Dorsal DG lesions completed disrupted metric representations, as they were impaired on the metric task compared to dCA3 lesioned, dCA1 lesioned, and control rats. Dorsal CA3 and

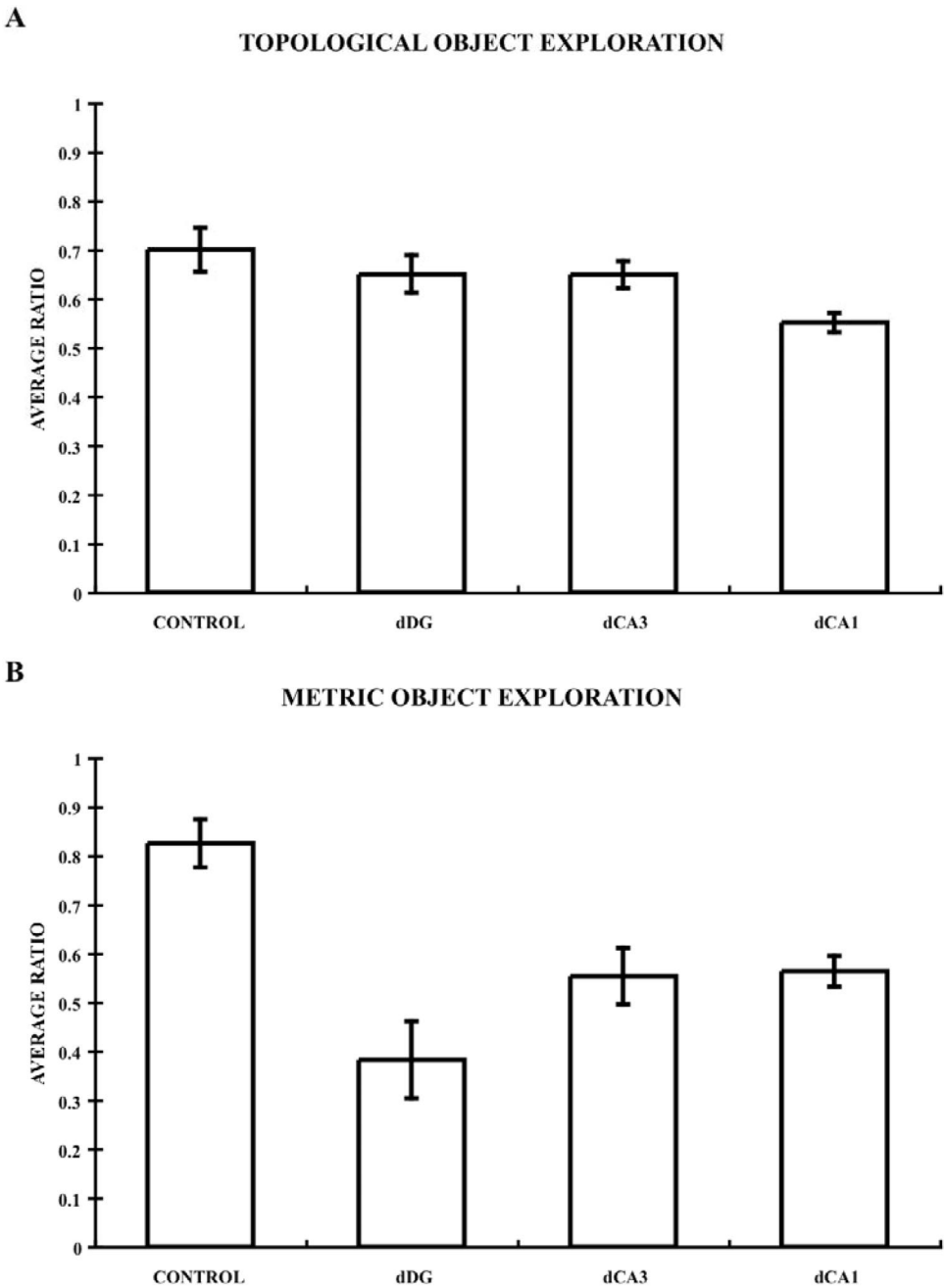

Figure 5. (A) Topological task. Graphed is an average ratio ± *SE* for Sessions 3 and 5 of exploration time that the animals spent with the displaced objects during the reconfiguration session divided by the sum time of the displaced objects and non-displaced objects. Dorsal DG and dCA3, and controls, but not dCA1, showed preference to the displaced objects (.5 = no preference). (B) Metric task. Graphed is an average ratio ± *SE* of exploration time that the animals spent with the objects during the reconfiguration session divided by the sum time during the final habituation session and reconfiguration session. Dorsal DG lesioned animals were impaired in object re-exploration as compared to controls, dCA3, and dCA1 (.5 = no preference). Dorsal CA3 and dCA1 were also impaired in object re-exploration as compared to controls.

dCA1 lesioned rats were also impaired compared to controls, but dCA3 and dCA1 lesioned rats' exploration differed from dDG lesioned rats' exploration. Dorsal CA3 and dCA1 lesioned rats spent equal amount of time exploring the familiar, non-displaced objects and novel, displaced objects. Dorsal CA3 and dCA1 lesioned impaired, but did not completely disrupt metric representations. These data suggest contrasting roles of dDG, dCA3, and dCA1 for metric spatial information processing.

The results from the metric task are consistent with previous research that states that the mnemonic function of the hippocampus is to process metric and metric-like spatial information. Specifically, orthogonalization or separation of similar but overlapping spatial information amidst noise is essential for proper memory consolidation and retrieval within the hippocampus (Gilbert et al., 1998; Guzowski, Knierim, & Moser, 2004; Mizumori, Ragozzino, & Cooper, 1999; Muller, Kubie, & Ranck, 1987; Nadel, 1994; Nitz & McNaughton, 2004). In particular, previous research from Gilbert et al. (Gilbert & Kesner, 2006; Gilbert, Kesner, & DeCoteau, 1998; Gilbert, Kesner, & Lee, 2001) found that rats with dDG lesions were impaired on a delayed-match-to-place task with differing levels of metric interference. The results of the present experiment—dDG lesioned rats displayed a stronger deficit for metric object re-exploration than dCA3 and dCA1 lesioned rats—are supported by these results. These data are also supported by Leutgeb, Leutgeb, Moser, & Moser (2007) who revealed that dDG place fields are more sensitive to discrete changes in the environment or pattern separation as compared to dCA3 fields recorded in parallel. Therefore, the dDG is vital for spatial information processing via pattern separation of sensory inputs to generate metric representations, whereas dCA3 and dCA1 are not as critical for metric spatial information processing.

Previous anatomical research also supports the results of metric task. In particular, prior research has indicated that the DG and, more specifically, the mossy fiber output to CA3, mediates pattern separation (Gilbert et al., 1998; Kesner et al., 2004; Marr, 1971; Rolls, 1996; Shapiro & Olton, 1994). Furthermore, it is suggested that the mossy fiber pathway to CA3 is important for encoding, whereas the perforant path from the entorhinal cortex to CA3 is important for retrieval (Lassalle, Bataille, & Halley, 2000; Lee & Kesner, 2004), thus reinforcing the role of the DG for pattern separation during encoding within CA3. Anatomically the DG granular cell projections via the mossy fibers converge onto the pyramidal cells in CA3 (i.e., one CA3 cell receives approximately 50 mossy fiber inputs (Rolls, 1996). The mossy fiber connections from the DG granular cells to CA3 pyramidal cells are comparably sparse, but powerful (Amaral & Witter, 1995; Rolls, 1996; Treves & Rolls, 1994; Witter, 1993). The recurrent collaterals within CA3 and perforant path projection from the entorhinal cortex into CA3 provides a greater number of the connections within CA3, as compared to the mossy fiber connections to the CA3 dendrites. As the second and third synapses along the trisynaptic loop, CA3 functions to complete the encoding of the already orthogonalized inputs. CA3 also initiates retrieval via the Schaffer collateral output that then continues along to CA1 where the retrieval process is completed via the subiculum output to the entorhinal cortex. Overall, research suggests that input into the DG granular cells via the perforant path is orthogonalized and categorized and information redundancy is removed by the time the information converges into CA3 pyramidal cells (Rolls, 1996; Treves & Rolls, 1994).

To conclude, lesions to dDG, dCA3, and dCA1 impair metric representations differently. Dorsal DG lesions eliminated metric representations, whereas dCA3 and dCA1 lesions marginally disrupted metric representations. It is thought that metric information is formed by dDG via orthogonalization or pattern separation and then the metric representation is transmitted to dCA3 and dCA1 along the trisynaptic loop. Lesions to dCA1 impaired, but did not abolish topological representations. Even though previous studies suggest that the PC mediates topological representations, it is possible that communication between dCA1 and the PC are necessary for topological spatial information processing (Goodrich-Hunsaker et al., 2005; Rogers & Kesner, 2006). Finally, the present data add to a growing body of literature suggesting functional dissociations and interactions among the hippocampal subregions.

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Received June 25, 2007
Revision received August 6, 2007
Accepted September 4, 2007 ■