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Lesions of the lateral entorhinal cortex disrupt non-spatial latent learning but spare spatial latent learning in the rat (*Rattus norvegicus*)

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The current study examined the function of the lateral entorhinal cortex (LEC) in a non-spatial latent learning task and a spatial latent learning task. Latent learning is the acquisition of neutral information that does not immediately influence behavior, but can be recalled and utilized when it becomes relevant to the animal. Based on previous research, it was predicted that the LEC would be necessary for latent learning of non-spatial information, but would not be necessary for latent learning of spatial information. Forty-two male Sprague Dawley rats (*Rattus norvegicus*) were either given pre-training neurotoxic lesions restricted to the LEC or were given sham (SH) lesions. The rats were then trained and tested on two latent learning tasks: the Latent Cue Preference (LCP) task which assesses single-cue (non-spatial) latent learning and a spatial latent learning task utilizing a Barnes maze. Results showed that rats with LEC lesions were impaired on the non-spatial LCP task compared to SH rats, but showed no impairment on the spatial latent learning task. Therefore, the LEC appears to be selectively involved in processing non-spatial latent learning and does not process, or is at least not necessary for, spatial latent learning. These findings indicate a specific role of the LEC in information processing and provide new information about the function of the entorhinal cortex.

Key words: Latent learning, latent cue preference, spatial, non-spatial, lateral entorhinal cortex

The entorhinal cortex (EC) is part of the major input-output pathway between association cortical areas and the hippocampus (Amaral and Witter 1989), and is involved in a variety of learning and memory tasks, including reinforced spatial learning (Aggleton et al. 2000, Fyhn et al. 2004, Steffenach et al. 2005), nonspatial learning (Jarrard et al. 2004, Hargreaves et al. 2005), inhibitory avoidance learning (Izquierdo and Medina 1993, Izquierdo et al. 1993, Pereira et al. 2001), and latent inhibition (Coutureau et al. 1999, Coutureau et al. 2002). The EC itself is composed of two major bands (medial and lateral), with the medial entorhinal cortex (MEC) connecting the postrhinal cortex to the hippocampus and the lateral entorhinal cortex (LEC) connecting the perirhinal cortex to the hippocampus (Burwell 2000). The postrhinal-MEC-hippocampus circuit has been proposed to process "where" (spatial) information, whereas the perirhinal-LEC-hippocampus circuit has been proposed to process "what" (non-spatial) information about the environment (for review see Eichenbaum and Lipton 2008). This proposal stems from the specific connectivity of the MEC and LEC (Kerr et al. 2007, Agster and Burwell 2009), as well as the presence of spatial information processing grid cells (Hafting et al. 2005) and boundary cells (Savelli et al. 2008, Solstad et al. 2008) in the MEC.

Evidence from recent lesion, cellular recording, and fMRI studies have provided more evidence of this functional dissociation between the MEC and the LEC. For example, Van Cauter and colleagues (2012) examined the effects of lesions of the MEC and LEC on spatial navigation tasks and object exploration tasks. Van Cauter and others (2012) found that MEC lesions impaired performance on the spatial water maze task and a path integration task but produced no deficits in the non-spatial object exploration tasks. Conversely, lesions of the LEC produced no deficits on the spatial navigation tasks but did produce deficits in

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the object exploration tasks. Deshmukh and Knierim (2011), on the other hand, recorded cellular activity in the MEC and LEC as rats foraged for food in an open field maze filled with discrete objects. Not surprisingly, Deshmukh and Knierim (2011) found that neurons in the MEC showed strong spatial selectivity even in the absence of the objects, while neurons in the LEC showed very little spatial selectivity when the objects were removed from the open field. However, the neurons in the LEC showed strong firing to the objects themselves, indicating they were processing the sensory information about the objects rather than spatial information. Furthermore, Schultz and coauthors (2012) recently demonstrated that this functional dissociation between the MEC and LEC does not appear to be limited to rats. Schultz and colleagues (2012) used fMRI scans on human participants as they performed a working memory task that involved either the recall of spatial information (scenes) or non-spatial information (faces). The results indicated that the pathway involving the MEC was more active during the recall of the spatial information, while the pathway involving the LEC was more active during the recall of the non-spatial information.

This proposed dissociation of function for the LEC and MEC has important implications for latent learning. Latent learning is the acquisition of neutral information that does not immediately influence behavior but can be recalled when it becomes relevant to the animal (Blodgett 1929, Tolman and Honzik 1930). Recent lesion studies examining the brain structures that underlie latent learning have demonstrated that the EC, but not the hippocampus, is necessary in both the acquisition and expression of latent learning. For example, Stouffer and White (2007) and Stouffer (2010) used the Latent Cue Preference (LCP) task (an adaptation of the Conditioned Cue Preference task, which has been shown to not be sensitive to changes in locomotor activity due to lesions or drug administration; Ortmann 1985, Hiroi and White 1991, White and McDonald 1993) to demonstrate that the EC was required for both the acquisition and expression of latent learning of non-spatial information. These permanent and temporary lesions were centered in the LEC, but spread to the MEC as well. On the other hand, Gaskin and White (2007, 2010) examined the role of the EC in a spatial latent learning task that used pre-exposure trials in a radial arm maze. The lesion coordinates used by Gaskin and White (2007, 2010) were centered more in the MEC, which resulted in impairments for both the acquisition and expression of spatial latent learning. However, no study has yet been conducted examining the effects of lesions of the EC on both a spatial and non-spatial latent learning task.

The purpose of the present study was to evaluate the prediction that the LEC is selectively involved in processing non-spatial latent learning, which would correspond to the proposal that the LEC specifically processes "what" information about environmental stimuli rather than spatial information. The LCP task has been utilized previously (Stouffer and White 2005, 2006, 2007, Stouffer 2010) to assess non-spatial latent learning. In the LCP task, rats are given training trials in which they are exposed to an irrelevant stimulus (water) in one compartment of a 3-compartment box. During this acquisition phase of the latent learning, the movement of the rats in the LCP box is restricted and the visibility to all external cues is blocked, which cre-

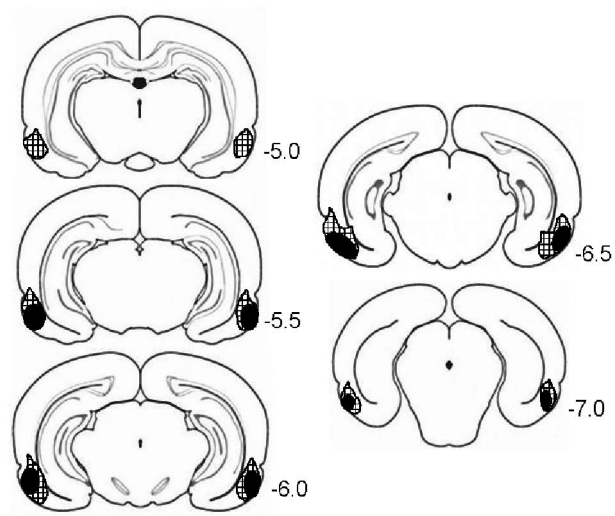

Fig. 1. An illustration of the approximate maximum (cross-hatched) and minimum (black) damage to the lateral entorhinal cortex (LEC) produced by the NMDA infusions. Initial infusion volumes of 0.08 µL were placed at −5.3 A/P, +/− 6.8 M/L, −8.2 D/V. Infusion volumes of 0.05 µL were then placed at −5.8, +/−7.0, −7.8; −6.3, +/−5.8, −8.4; and −6.3, +/−6.4, −7.8. Final infusion volumes of 0.08 µL were placed at −6.7, +/−6.4, −8.0. Infusion cannulas were initially lowered 0.2 mm below the D/V coordinate and then were quickly raised dorsally 0.4 mm halfway through the infusion. Cannulas were then left in place for 4 min post-infusion. All coordinates are relative to bregma. Modified from Paxinos G, Watson C, The Rat Brain in Stereotaxic Coordinates (5th Edition). Figures 75, 79, 83, 87, 91, Copyright (c) 2005, with permission from Elsevier.

ates an environment in which spatial learning does not take place (McDonald and White 1995, White and Ouellet 1997). The rats are then given a compartment preference test in which they are water-deprived to determine if they are able to recall the latently acquired association between the presence of the water and the compartment. This type of learning is behaviorally (Stouffer and White 2005) and neurologically (Stouffer and White 2006, 2007) different than a conditioned cue preference.

A total of 42 male Sprague-Dawley rats (*Rattus norvegicus*, Ace Animals, Boyerstown, PA) were used in the study. The rats were 3 months old at the beginning of the study, and were housed in single hanging cages with wire-mesh floors. The cages were kept in a temperature-controlled room (20°C) that was on a 12-h light/dark cycle. The rats had free access to food (LabDiet Prolab Animal Diet) and water throughout the experiment, unless otherwise noted in the procedure. Prior to any training, the rats were given either bilateral *N*-methyl-D-aspartate infusions (NMDA; 10 mg/mL, dissolved in normal saline) at a rate of 0.05 μL/min into the LEC (n=22) or were given sham lesion surgeries (SH; n=20) in which the infusion cannulas were lowered into the LEC but no NMDA was delivered. The caption for Figure 1 provides the lesion coordinates derived from Paxinos and Watson (2005), as well as the volumes of NMDA infused. All surgeries were conducted under isoflurane anesthesia (5% induction and 2.5% maintenance), and were followed by administration of a topical analgesic (benzocaine 20%) during recovery. All experimental procedures were reviewed and approved by the Bloomsburg University Institutional Animal Care and Use Committee.

Following a minimum of 10 days for recovery, 10 of the LEC rats and 10 of the SH rats were randomly selected to be trained on the LCP task (Stouffer 2010). The LCP task used four LCP boxes created by using modified Coulbourn Instruments Rat Arenas (E63-20) constructed with black Plexiglas walls (40 cm wide × 40 cm deep × 40 cm high). A gray plastic drop pan (Coulbourn Instruments, E63-20-DP) created the floor of each box, which was removed and cleaned between trials. Each box consisted of three compartments that were created by two opaque Plexiglas partitions. The two partitions had door openings (7 cm wide × 8 cm high) that were blocked during training trials, but were unblocked during the compartment preference test. Compartments 1 and 3 (15 cm wide × 40 cm deep × 40 cm high) served as the water-paired and unpaired compartments, counterbalanced, while the middle Compartment 2 (10 cm wide × 40 cm deep × 40 cm high) served as the neutral start compartment during the compartment preference test. The walls of Compartment 1 in two of the boxes were painted with 2.5 cm thick white stripes, while the walls of Compartment 3 were kept solid black. This pattern was reversed in the other two boxes. The walls of Compartment 2 were painted gray in all four boxes. A 50-ml water bottle was attached to the front of the outside of each box by a Velcro strip. The spout of each water bottle protruded through a hole (1.5 cm diameter) in the front wall of the box and rested about 8 cm above the floor in either Compartment 1 or 3. The location of the water bottles was counterbalanced in the boxes. Each box was equipped with a TruScan Photobeam sensor ring (Coulbourn Instruments, E63-22) that surrounded the arena and sat 2 cm above the floor of the arena. The photobeams in the sensor ring were spaced 2.5 cm apart, providing a 1.3 cm^2 spatial resolution, and provided information about the position of the rats every 0.5 second. Each photobeam sensor ring was connected to a TruScan Photobeam Linc (Coulbourn Instruments, E63-01HS), which relayed information to a Gateway E-series computer *via* a Habitest Port Expander Box (Coulbourn Instruments, L18-16XHS-10). Data from the photobeam sensors were processed using TruScan v2.01 software. Each of the LCP boxes was placed inside an open cubicle (132 cm wide × 55 cm deep × 80 cm high) along one wall of an experimental room (2.5 m × 4.3 m). The open cubicles created a white ceiling 40 cm above each box, blocking visibility to all external cues in the room.

In the LCP task, water-replete rats were given training trials in which they were placed into one side of the LCP box (Compartment 1 or 3) with access to water on one day for 30 min, and then were placed into the opposite side of the box with no access to water on the next day for 30 min. This 2-day procedure constituted one training trial, and the rats were given a total of three training trials over a 6-day period. After this 6-day training period, all rats were given a 24-h rest period, followed by a 23-h water-deprivation period. The rats were then given a 20-min compartment preference test in which they were placed in the neutral middle compartment at the start of the preference test and were allowed to explore all three compartments

with the water absent. The amount of time spent in each compartment was recorded using the TruScan v2.01 software. Immediately following the compartment preference test, all rats were given 30-min access to water, and the amount of water consumed was recorded in order to verify that the rats were water deprived during the compartment preference test and therefore motivated to seek out water.

All rats were then given a 7-day rest period. Following the rest period, all rats (n=20 SH; n=22 LEC) began the spatial latent learning task using a Barnes maze (Barnes 1979). The procedures for the spatial latent learning task were first described by Stouffer and Heisey (2013). The Barnes maze (Med Associates, ENV-562-R) used for the task consisted of a white round platform (122 cm in diameter) which contained 18 holes (9.5 cm in diameter) evenly spaced around the perimeter. The platform was elevated 1.5 m above the floor of the experimental room. The maze was surrounded by 13 white geometric shapes placed onto black curtains along the walls of the experimental room. A black Plexiglas escape box (Med Associates, ENV-562-R-GB) was able to be placed under any of the 18 hole locations. Mounted above the maze were two 500 watt halogen lights, a video camera, a circular fan (51 cm in diameter), and a rope-and-pulley system. The rope-and-pulley system allowed an opaque plastic bucket to be raised and lowered onto the platform from an adjacent laboratory room, where the video camera signal was displayed by a computer monitor.

The LEC and SH rats were assigned into one of two pre-exposure conditions (SpatialPX or MazePX), making sure that the rats that had been trained in the LCP task were evenly split between the two pre-exposure conditions. The rats in the SpatialPX condition (n=10 SH; n=12 LEC) were placed onto the Barnes maze and were allowed to explore the maze and the surrounding spatial cues for 20 min. The rats in the MazePX condition (n=10 SH; n=10 LEC) were placed onto the maze and were allowed to explore the maze for 20 min without the spatial cues present. The MazePX condition was included to control for the effect that habituation to the maze may have had on performance. The room lights were dimmed and the lights and fan above the maze were kept off during the pre-exposure trials. Ten reinforced training trials (with spatial cues present) began the day after the pre-exposure trials, during which each rat was assigned one specific escape box location. To begin each training trial, the experimenter placed the rat under the bucket in the middle of the top of the maze, turned on the halogen lights and fan (creating an aversive environment), and then left the room. The experimenter then raised the bucket using the rope-and-pulley system, started a stopwatch, and observed the rat on the monitor in the adjacent room. The rat was allowed to search for the hidden escape box for a maximum of 2 min. If the rat did not find the escape box within 2 min, the experimenter entered the room and led the rat to the escape box, where it was allowed to remain for 30 s. The experimenter then turned off the halogen lights and fan and returned the rat to its home cage. Each rat performed two trials per day for 5 days, with a daily inter-trial-interval of 15–20 min. The amount of time required by the rats to climb down into the escape box (escape latency) and the number of times the rats looked down into incorrect hole locations (incorrect nose pokes) were recorded on each training trial. If a rat looked into an incorrect hole, then left and came back to look into the same incorrect hole location, it was counted at two separate incorrect nose pokes.

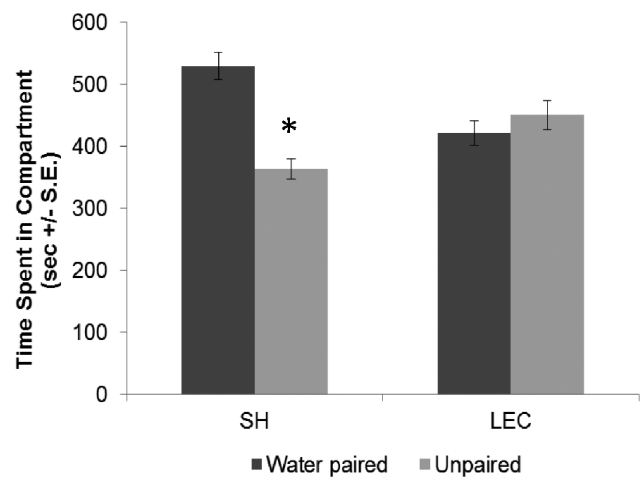

Fig. 2. The compartment preference times in the Latent Cue Preference (LCP) task, which assesses non-spatial latent learning. Rats given sham-lesions (SH) showed a significant preference for the compartment that previously contained water, indicating that they were able to form the association between the visual compartment cue and the presence of water while they were water-replete and then express that learning when they were water-deprived. However, rats given lateral entorhinal cortex (LEC) lesions showed no compartment preference during the test trial, indicating that this non-spatial latent learning was disrupted. * P<0.05.

All rats were then perfused and their brains were extracted for histological examination using thionin staining. Figure 1 illustrates the minimum and maximum lesions of the LEC. After examination, three of the LEC rats were removed from the data analyses due to misplaced or incomplete lesions. A 2 × 2 (Lesion × Compartment) mixed ANOVA was then performed (using IBM SPSS software) on the compartment preference times of the remaining LEC (n=9) and SH (n=10) rats for the LCP task (see Fig. 2). The ANOVA revealed a significant main effect of compartment ($F_{1,17}$=6.735, P=0.019), and a significant Lesion × Compartment interaction effect ($F_{1,17}$=13.507, P=0.002). However, there was no significant main effect of lesion type. Scheffe *post-hoc* tests on the significant Lesion × Compartment interaction showed that while the SH rats spent significantly more time in the water-paired compartment than the unpaired compartment (P<0.05), the LEC rats showed no significant compartment preference, indicating that the LEC lesions produced an impairment in non-spatial latent learning.

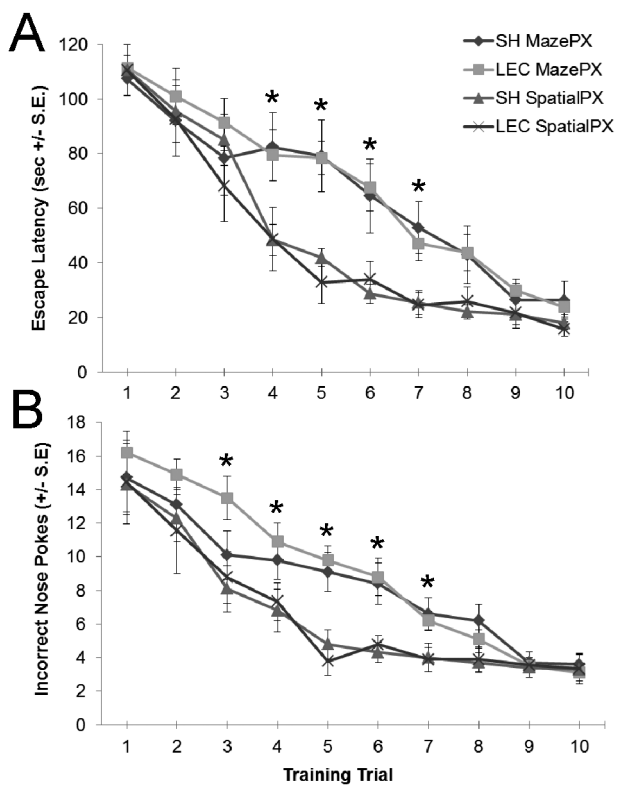

Fig. 3. The escape latencies (A) and number of incorrect nose pokes (B) made by the four groups of rats on the spatial latent learning task using the Barnes maze. The rats with sham lesions (SH) or lesions of the lateral entorhinal cortex (LEC) that were given the spatial pre-exposure procedure had significantly faster escape latencies (A) and significantly fewer incorrect nose pokes (B) than the LEC and SH-lesioned rats given the maze pre-exposure procedure. This indicates that the presence of the bilateral LEC lesion did not disrupt the rats' spatial latent learning abilities. * P<0.05.

In addition, a 2 × 4 (Lesion × Trial) mixed ANOVA was performed on the amount of water each of the two lesion groups consumed during the three training trials and the post-preference test consumption period. The ANOVA revealed a significant main effect of trial ($F_{3,51}$=448.866, P<0.001), but the main effect of lesion type and the Lesion × Trial interaction were not significant (post-preference test consumption means: SH = 13.4 ml, LEC = 14.2 ml). Scheffe *post-hoc* tests on the main effect of trial revealed that all rats consumed more water during the post-preference test consumption period than during each of the training trials (P's<0.05). The water consumption during the each of the three training trials was not significantly different from each other. This pattern of results indicates that all rats were water-deprived during the compartment preference test and were motivated to seek out water. Therefore, the different compartment preference patterns of the two lesion groups were not due to differences in water consumption during training or motivation to consume water during testing.

Next, a 2 × 2 × 10 (Lesion × Pre-exposure × Trial) mixed ANOVA was performed on the escape latencies of the SH MazePX, SH SpatialPX, LEC MazePX, and LEC SpatialPX groups on the Barnes maze task (see Fig. 3A). The ANOVA revealed a significant main effect of trial ($F_{9,315}$=68.057, P<0.001), a main effect of pre-exposure type ($F_{1,35}$=14.836, P<0.001), and a significant Pre-exposure × Trial interaction effect ($F_{9,315}$=4.155, P<0.001). However, the main effect of lesion type was not significant, nor were the Lesion × Trial, Lesion × Pre-exposure, and the Lesion × Pre-exposure × Trial interaction effects. Scheffe *post-hoc* tests on the significant Pre-exposure × Trial interaction effect showed that rats given the SpatialPX condition had significantly faster escape latencies on Trials 4, 5, 6, and 7 compared to the rats given the MazePX condition (P's<0.05). The two pre-exposure conditions were not different on any other trials. These results indicate that pre-exposure to the spatial cues surrounding the Barnes maze had a beneficial effect on escape latency performance for rats regardless of whether they had SH or LEC lesions, indicating intact spatial latent learning in both lesion groups.

Finally, a 2 × 2 × 10 (Lesion × Pre-exposure × Trial) mixed ANOVA was performed on the number of incorrect nose pokes made by the SH MazePX, SH SpatialPX, LEC MazePX, and LEC SpatialPX groups (see Figure 3B). The ANOVA revealed a significant main effect of trial ($F_{9,315}$=51.462, P<0.001), a significant main effect of pre-exposure type ($F_{1,35}$=19.444, P<0.001), and a significant Pre-exposure × Trial interaction ($F_{9,315}$=2.295, P=0.017). However, the main effect of lesion type was not significant, nor were the Lesion × Pre-exposure, Lesion × Trial, and Lesion × Pre-exposure × Trial interaction effects. Scheffe *post hoc* tests on the significant Pre-exposure × Trial interaction showed that rats given the SpatialPX condition had significantly fewer incorrect nose pokes on Trials 3, 4, 5, 6, and 7 compared to the rats given the MazePX condition (P's<0.05). The two pre-exposure conditions were not different on any other trials. This pattern of results indicates that the rats showed improved searching accuracy when given the spatial pre-exposure regardless of lesion type, again indicating intact spatial latent learning in both lesion groups.

The pattern of these results shows a clear dissociation of function within the LEC. Pre-training NMDA lesions of the LEC impaired performance on the LCP task, which assesses latent learning for non-spatial environmental stimuli. However, lesions restricted to the LEC did not disrupt the same rats' latent learning of a spatial map during a pre-exposure period, or the expression of that spatial map during reinforced training trials on the Barnes maze task. This appears to be the first evidence from a lesion study that the LEC is specifically involved in processing non-spatial latent learning and is not involved in, or is at least not necessary for, processing spatial latent learning. These results appear to support the proposal that the LEC is specifically involved in processing non-spatial information about the sensory qualities of environmental stimuli and is not involved in processing spatial information about environmental stimuli. Furthermore, the current findings demonstrate that this specificity of function also applies when the environmental stimuli are considered neutral, as they are in latent learning tasks.

One major limitation of the current study is the difference in motivation types between the two tasks used. The expression of latent learning in the LCP task involves appetitive motivation (seeking out the water during the compartment preference test), while the expression of latent learning in the Barnes maze task involves aversive motivation (escaping from the aversive environment created by the lights and fan). However, it is unlikely that the differential involvement of the LEC in the two tasks is due to these motivation differences. Motivation in both appetitive and aversive tasks is usually attributed to the ventral hippocampus (Bannerman et al. 2004, Stouffer and White 2006, 2007), amygdala (Balliene and Killcross 2006, Savage and Ramos 2009, Morrison and Salzman 2010), nucleus accumbens (Salamone 1994), hypothalamus (Balińska 1968, Destrade and Cazala 1979), and the periaqueductal gray (Cazala et al. 1985). A detailed review of the literature did not provide any indication that the LEC is differentially involved in appetitive versus aversive tasks, although the anatomical connectivity between the amygdala and the LEC (McDonald and Mascagni 1997) does create this possibility. A second limitation of the current study is that there is no information on whether the LEC is involved in the acquisition or expression (or both) of latent learning in the LCP task. Stouffer and White (2007) demonstrated that the EC was involved in both the acquisition and expression of non-spatial latent learning in the LCP task. Therefore, we can only assume that the same holds true with the LEC subregion. However, this was not examined in the current study. A third limitation of the current study is that there is no direct information on the role of the MEC in the non-spatial and spatial latent learning tasks. Due to the involvement of the MEC in reinforced spatial learning (Deshmukh and Knierim 2011, Van Cauter et al. 2012), the use of pre-training lesions would have potentially disrupted performance during the reinforced training trials in the Barnes maze task, making it impossible to determine if the MEC was involved during the latent learning (pre-exposure) phase of the task or during the reinforced training trials. However, based on the findings of Gaskin and White (2007, 2010), we can hypothesize that the MEC is specifically involved in processing spatial latent learning and would not be required for processing non-spatial latent learning. This is a topic that should be addressed in future experiments through the use of temporary inactivation of the MEC during the pre-exposure phase of the Barnes maze task.

The present findings provide an important insight into the potential functional difference between the LEC and the MEC. The EC is not only part of the input-output pathway between the hippocampus and

the cortex, but it is also centrally involved in specific types of learning and information processing. Therefore, it is vital to understand the different types of learning and information processing that are handled by the different subregions of the EC. By demonstrating that the LEC is specifically involved in processing non-spatial latent learning rather than spatial latent learning, we have provided some initial information about the specific function of the LEC which may lead to further understanding of other subregions.

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