Master's Thesis of Natural Science

The Roles of the Fasciola Cinereum in Object-Place Recognition

객체 장소 인식에 대한 소대회의 역할

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Graduate School of Natural Sciences
Seoul National University
Brain and Cognitive Science Major

Eun Young Lee

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Inah Lee

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Graduate School of Natural Sciences
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Eun Young Lee

Confirming the master's thesis written by
Eun Young Lee
February 2020

Chair	이 석 호	(Seal)
Vice Chair	이 인 아	(Seal)
Examiner	이 용 석	(Seal)

Abstract

The fasciola cinereum (FC) is a subregion of the hippocampus, sharing the distal border of CA1. A previous study found that the FC receives afferent projections from the lateral entorhinal cortex and perirhinal cortex, and projects to the dentate gyrus in the hippocampus (Park et al., 2019). Because of these anatomical connections, we expected that the FC may be involved in processing non-spatial information and its association with the place. To test this functional hypothesis, we conducted spontaneous object exploration tasks with rats with FC lesions and sham surgery. Specifically, rats were tested for their capability in object location memory (object location task), object-place association memory (object-in-place task), and novel object recognition memory (novel object preference task). First, rats sampled two identical objects appearing at the same locations across three sampling phases (5 min/phase) and were tested if they recognized the change of the objects' locations in the test phase. In the object-in-place task, rats sampled two/three different objects at a fixed location across the sampling period and were expected to notice if one/two of the objects were swapped with the familiar object. To test the novel object recognition, rats sampled two identical objects during the sample phases and should notice when one of the objects was replaced with a novel one during the test phase either 5 min or 1 h after the last sample phase. The result indicated that the FC lesion rats showed impairments in both the object location task and the object-in-place task, but not in the novel object preference task. Based on the results, it is suggested that the FC plays an important role in recognizing object-place paired associates, but not in object recognition per se.

Keywords: Hippocampus, episodic memory, fasciola cinereum, object recognition, object-place associative memory

Student Number: 2018-20782

Table of Contents

Chapter 1. Introduction

1.1. Hippocampus and episodic memory

Previous studies demonstrated that the hippocampus plays a critical role in episodic memory to recollect personal experiences (Scoville and Milner, 1957, O'keefe and Nadel, 1978, Aggleton and Brown, 1999, Eichenbaum and Cohen, 2004, Squire et al., 2004). Episodic memory processing requires integration of the what, where and when components of a memory (Nyberg et al., 1996, Clayton and Dickinson, 1998, Eichenbaum and Fortin, 2005). In particular, "what+where" conjunctive representations are a key component of the hippocampus regarding episodic memory (Gilbert and Kesner, 2002, Gilbert and Kesner, 2003, Deshmukh and Knierim, 2011). Since it is well known that the hippocampus receives "what" and "where" information through the cortical areas (Suzuki et al., 1997, Burwell, 2000, Amaral and Witter, 1995, Knierim, 2006), investigating how this information is processed in the hippocampus is important for understanding episodic memory. However, recent studies showed that "what" and "where" information might not be processed separately along the dorsal and ventral streams in the medial temporal lobe, unlike what has been known conventionally (Zhu et al., 1995a, Zhu et al., 1995b, Young et al., 1997, Wan et al., 1999). Therefore, we conducted three different spontaneous object exploration tasks to determine how the hippocampus processes this information.

1.2. The medial temporal lobe memory system

It is well known that the hippocampus receives information on external stimuli through the medial entorhinal cortex (MEC) and the lateral entorhinal cortex (LEC). Historically, it was believed that the information that comes from the perirhinal cortex (PER) to the LEC is non-spatial (objects, temporal, emotion), and that from the postrhinal cortex (POR) to the MEC is spatial

(place, specific location, orientation) (Eichenbaum et al., 2007, Ranganath and Ritchey, 2012, Raslau et al., 2015, Yonelinas and Ritchey, 2015). However, this two-way information processing (spatial/non-spatial pathway) theory showed contradictions and limitations when compared to several studies (Knierim et al., 2014; Deshmukh and Knierim, 2011; Wan et al., 1999; Young et al., 1997; Zhu et al., 1995). Specifically, the LEC showed increased *c-fos* expression in an object-context recognition task (Wilson et al., 2013a). The function of the LEC was involved not only in non-spatial processes, but also in spatial processes (Van Cauter et al., 2013). Furthermore, recent studies reported that research on the anatomical connections of the cortical areas and the parahippocampal regions showed different results from the conventional studies. It has been confirmed that many of the outputs of the POR are distributed throughout the LEC (Doan et al., 2019). In the same study, it was found that the superficial layer of the LEC received the majority of the input of the POR. As these contradictions were reported, the need for a new theory has been suggested. In relation to these issues, my thesis will focus on examining a new neural hippocampal circuit that may be involved in processing the non-spatial information associated with place memory.

1.3. The fasciola cinereum

The fasciola cinereum (FC) is a small region of the hippocampus. Its anatomical characteristics and functions are largely unknown. Previous research found that the FC has intrinsic projection and receives projections from the lateral entorhinal cortex (LEC) and perirhinal cortex (PER) (Figure 1), where cortical areas play an important role in processing non-spatial information to the hippocampus and object familiarity recognition. The roles of the PER and the hippocampus are well known for recognition memory (Brown and Aggleton, 2001, Squire and Zola-Morgan, 1991, Winters et al., 2004). Furthermore, the major output of the FC is the dentate gyrus (DG), which is involved in object-place associative memory (Barbosa et al., 2012, Hunsaker

et al., 2008, Hunsaker and Kesner, 2008). The connected brain areas of the FC are highly related to object recognition, associative memory, and spatial novelty detection. The results of a previous FC lesion study showed that the FC is essential for the acquisition of novel visual–contextual memory, but not for the retrieval of familiar visual contextual memories (Park et al., 2019). We hypothesize that the FC processes non–spatial information including the visual scene and may play key roles in object–place associative memory.

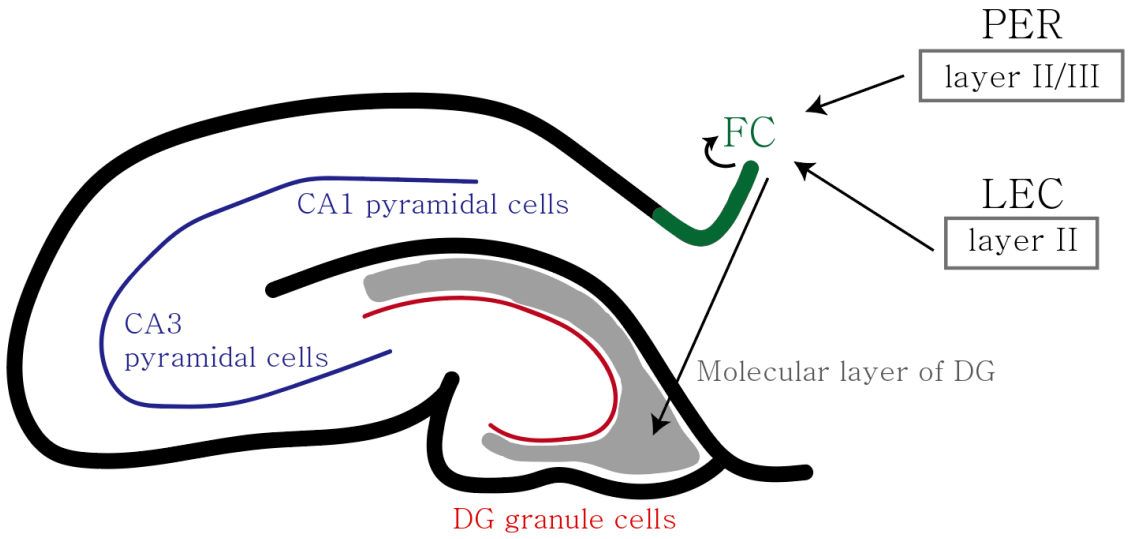


Figure 1. Schematic illustration of anatomical connection of the FC

Chapter 2. Methods

2.1. Subjects

Thirty adult male Long–Evans rats, weighing 360–480g on the first day of the spontaneous object exploration task, were used as subjects. The rats were divided into two groups: the FC lesion group (n = 17) and the sham surgery control group (n = 13). They were housed individually under a 12h light/12h dark cycle (the light phase was 8:00–20:00h). All experiments were conducted during the light cycle. Food was restricted to maintain a normal weight. All animal procedures were performed in compliance with the Institutional Animal Care and Use Committee of Seoul National University.

2.2. Surgery

For colchicine and saline injections, a glass pipette (Marienfeld, Denmark) was made using a vertical pulling machine (PC–10, Narashige) at 67.8℃. The glass pipette was connected to a 1 μl Hamilton syringe (Hamilton, NV, USA) and backfilled with silicon oil (Sigma Aldrich, MO, USA). Sterile saline or colchicine was loaded into the glass pipette immediately before the injection was administered. The rat was anesthetized with sodium pentobarbital (Nembutal, 70 mg/kg) and anesthesia was maintained by iso–fluorane (0.5–2% isoflurane mixed with 100% O2; Piramal critical care, MO, India) during the surgery. The temperature of the rat was preserved with a warm–pad at 35–37℃. After the skull was exposed, the bregma and lambda of the skull were measured. The glass pipette was vertically injected on the 3.5 mm posterior to the bregma along the midline, 3.5 mm below the dura. Subsequently, 0.05 μl of the colchicine or saline was injected by using a syringe pump (KD Scientific, MA, USA) through mechanical pressure (0.166 μl/min).

2.3. Apparatus

Spontaneous object exploration tasks took place in an acrylic open-top arena (70 x 70 x 60 cm). The floor of the arena was covered with brown kraft wrapping paper and the paper was replaced in every session to reduce the odor cue of the floor. All sessions were recorded with an overhead camera (Logitech HD Pro Webcam C920). The stimuli objects were made of glass, hardened wood, and plastic (Figure 2). Copied objects were used for the test phase. Ferrite magnets were attached to the underside of the platform to fix the objects. The size of the objects varied from 5 x 5 x 8 cm to 4.5 x 4.5 x 14 cm.

Figure 2. Object stimuli used for spontaneous object exploration tasks. (a) Object location task, (b) Object-in-place task 1, (c) Object-in-place task 2, (d) Novel object preference task (1h delay), (e) Novel object preference task (5m delay)

2.4. Behavioral testing

After being handled for three days, rats had a sham or lesion surgery. A six-day recovery period was allowed for rats, after which they started four days of platform habituation. Four days after the end of the habituation period, rats were tested on five different spontaneous object exploration tasks every second day. Each object exploration task comprised three sample phases and a test phase separated by three-minute delays. During the delay periods, objects were cleaned with 70% ethyl alcohol, and the brown paper on the platform floor was replaced to remove olfactory cues.

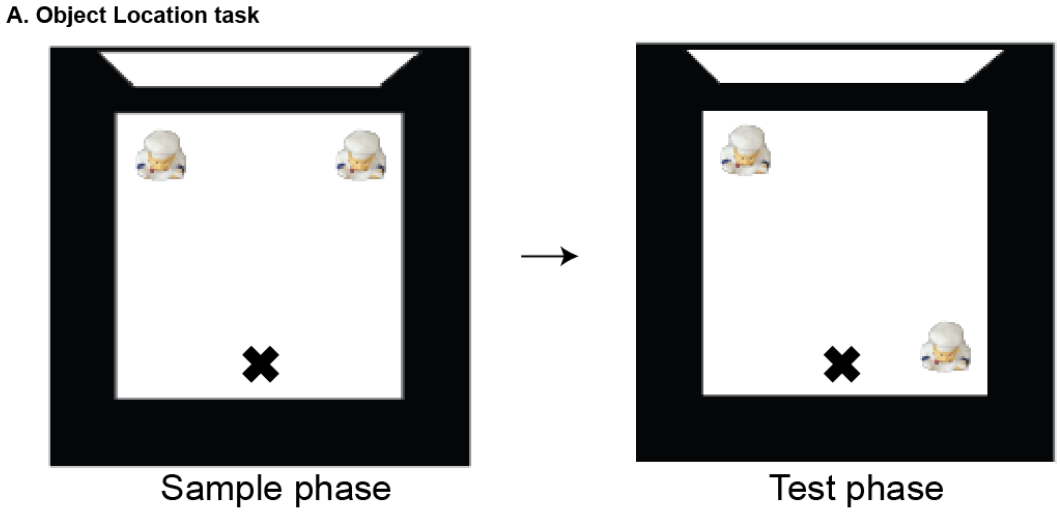
Task Number	Name	Delay (Sample-Test)	Number of object	Novel object appearance in test phase	Nature of object change	Object-location change	Nature of location change
1	Object location	3 min	2	X	Same -> Same	O	New location
2-1	Object-in-place 1		3		Same -> Same	O	Object swap at old location
2-2	Object-in-place 2		2		Different -> Same	X	Object replacement at old location
3-1	Novel object preference (1 h delay)	1 h	2	O	Same -> Different	X	
3-2	Novel object preference (5 min delay)	5 min	2		Same -> Different	X	

Table 1. Summary of the spontaneous object exploration tasks

Platform habituation

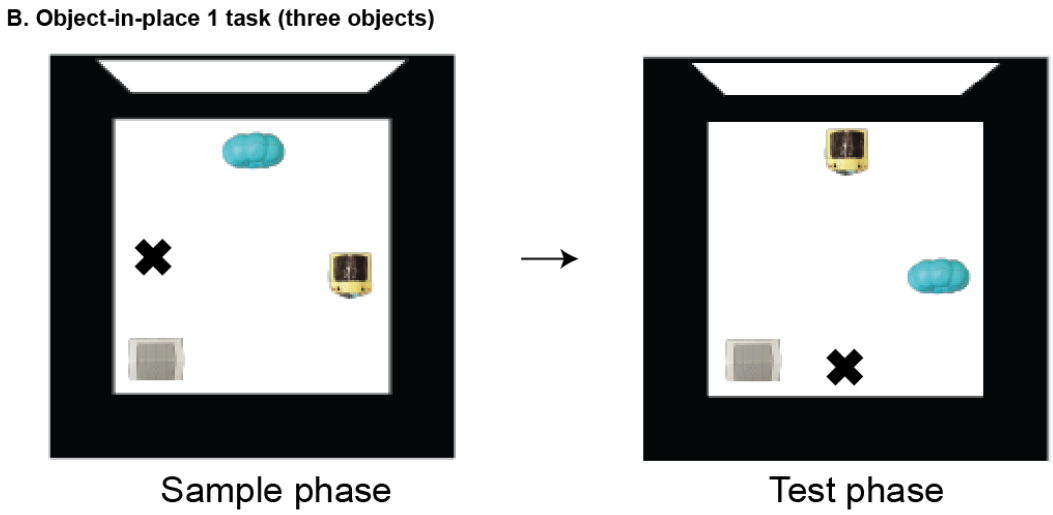
During the four days of platform habituation, rats were habituated to the platform for 15 min per day with no object or food. The rat was introduced to the platform at random positions every day. All animal behaviors were recorded for the behavior analysis.

Object location task



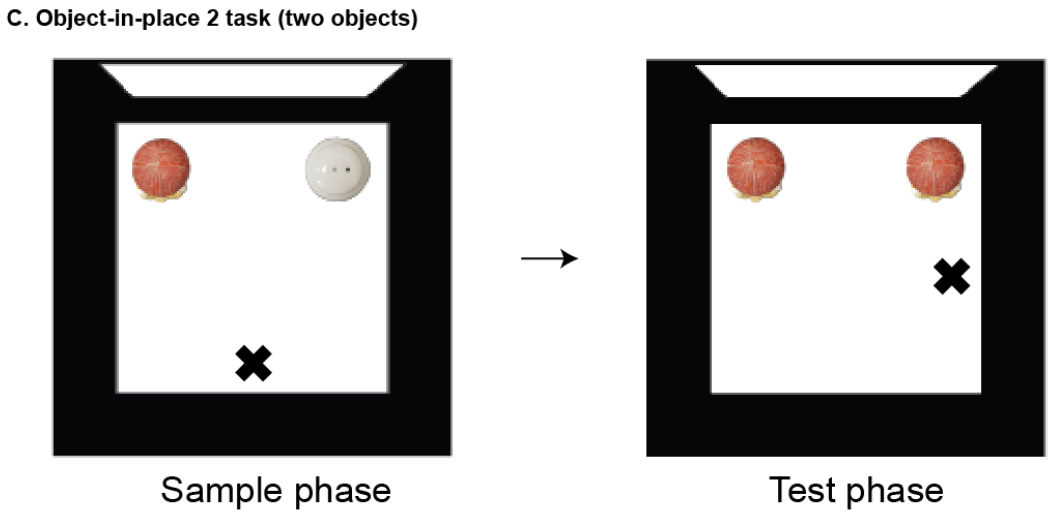
Rats were tested for their ability to detect an object’s spatial novelty. During the three sample phases, two identical objects were presented on the north-east and north-west corners. Animals were allowed to move freely on the platform for five minutes and taken off the platform for the three-minute delay. In the test phase, the rats were released onto the platform at the same location as in the sample phases. The objects were copied objects from the sample phase but placed diagonally from each other. The object that was displaced to the novel location in the test phase was counterbalanced between rats. Therefore, both objects were familiar, but the location of the object was novel. X indicates the release point of the rat.

Object-in-place task 1 (three objects)



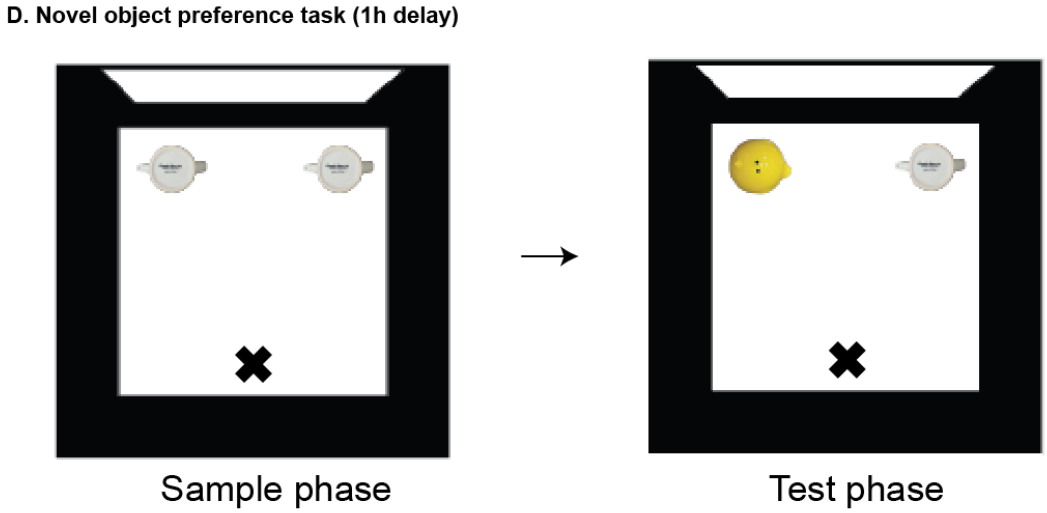
In the sample phase, three different objects were placed on the platform. Rats were allowed to explore the objects for five minutes. The entry point of the rats was consistent during the sample phases. In the test phase, two of the three objects were swapped with each other. The starting point of the rat was changed from the sample phases. The rats were removed from the platform at the same point at which they entered. The position of the objects in the sample phase and the pair objects swapped in the test phase were counterbalanced between rats. X indicates the release point of the rat.

Object-in-place task 2 (two objects)



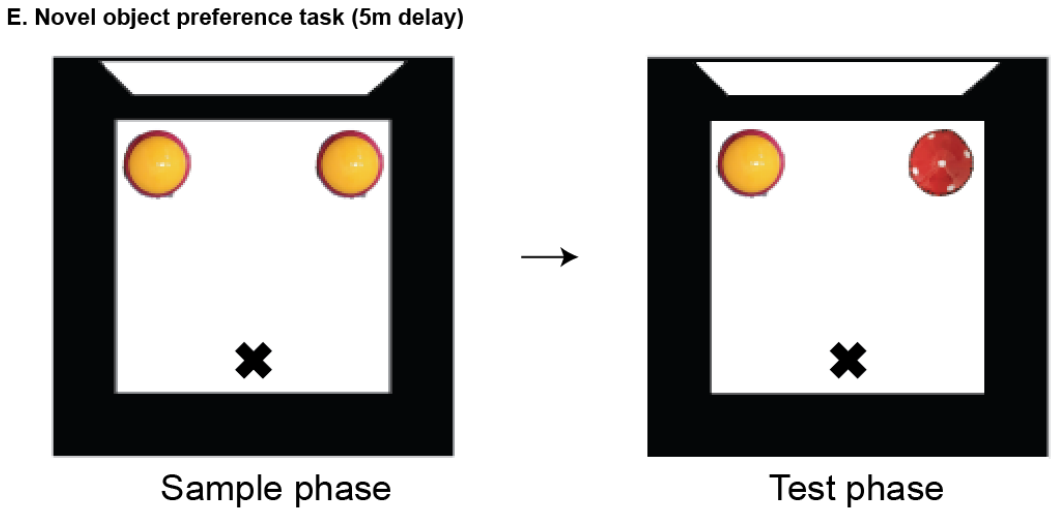
Two different objects were shown in the sample phases and placed at the north corners of the wall. The starting point in the behavioral apparatus was the same during the sample phases and it was counterbalanced between rats. In the test phase, the white object was replaced with the red object that was shown in the sample phases. The entry point in the sample and test phases differed. Thus, the two objects were familiar, but the object-place relationship was changed. X indicates the release point of the rat.

Novel object preference (1h delay)



Rats were exposed to two identical objects, which were placed near the north-east and north-west corners of the platform. The rats entered at the same place on the platform during the sample phases and test phase. The retention interval between the third sample phase and the test phase was one hour. During the one-hour delay, rats stayed in their home cage. In the test phase, one of the objects was replaced with a novel object. The location of the novel object was counterbalanced by rats. X indicates the release point of the rat.

Novel object preference (5m delay)



The procedures for the sample phases were the same as those in the novel object preference (1h delay) task. However, the last delay period was changed to five min. The object used as a familiar object in the test phase was copied objects used in the sample phase. Rats were released at the same location on the platform during the sample phases and test phase. X indicates the release point of the rat.

2.5. Behavioral measures and statistical analyses

All sessions were video recorded and analyzed with Ethovision XT 13 software. The duration of the animal behaviors (grooming, rearing, sniffing, staying, defecation) was calculated manually. Exploratory behavior was defined as the animal sniffing the object. Previous studies that performed spontaneous object exploration tasks excluded the data if the total exploration time was insufficient less than the criteria (Langston and Wood, 2010, Barker and Warburton, 2011). However, all the animal data were used for analysis in this study. The discrimination index was calculated as the difference between the novel object sniffing time and familiar object sniffing time divided by the total exploration time of the novel and familiar objects (Ennaceur and Delacour, 1988).

Statistical data were presented with a box plot. Group comparisons used non-parametric tests (Wilcoxon rank-sum test, Mann-Whitney U test, Friedman test). All the statistical analyses used a significance level of 0.05.

Chapter 3. Results

3.1. Histology

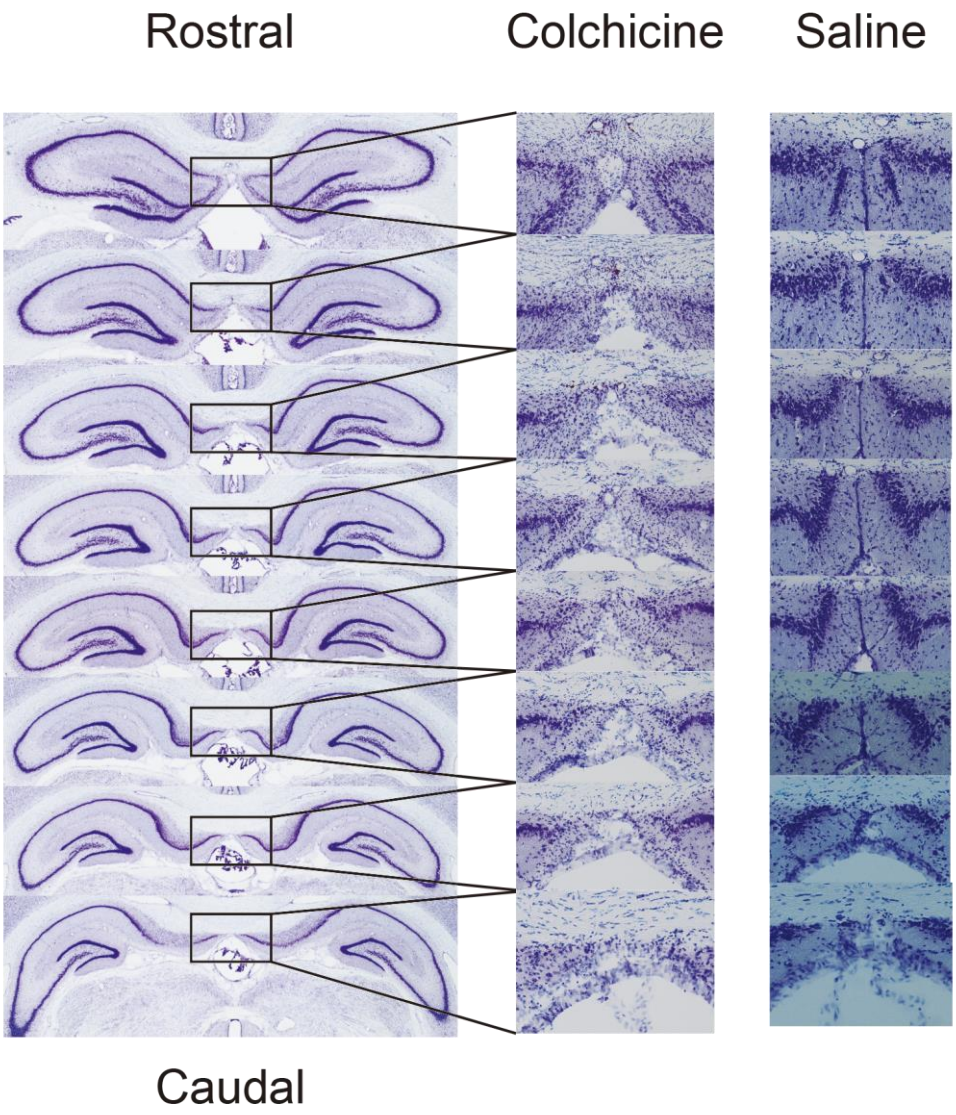


Figure 3. Colchicine or saline injection into the FC. Coronal sections are arranged rostrocaudally

3.2. Task 1: Spatial novelty detection

The FC is necessary for the object's spatial novelty detection

The purpose of the spatial novelty detection task was to assess the animals' ability to recognize the displacement of the familiar object. The same four objects were used for the task and the location of one of the familiar objects was changed in the test phase (Figure 4A).

Object location task

Recognition during test phase

Figure 4B shows the object exploration time for the control group and the FC lesion group in the object location task. The Wilcoxon signed-rank test showed a significant difference between the displaced object and non-displaced object exploration time of the control group, but no significant difference in the FC lesion group. For the displaced object discrimination index, the Mann-Whitney U test revealed a significant difference between the control group and the FC lesion group (Figure 4C).

Total exploration time during the sample and test phases

Figure 5A shows the total exploration time during the test phase. There was no significant difference between the control group and the lesion group. The total exploration time decreased significantly during the three sample phases (Figure 5B). However, the total object exploration time showed no significant difference between groups. These data indicate that the FC lesion rats had impairments in recognizing the spatial novelty of the object.

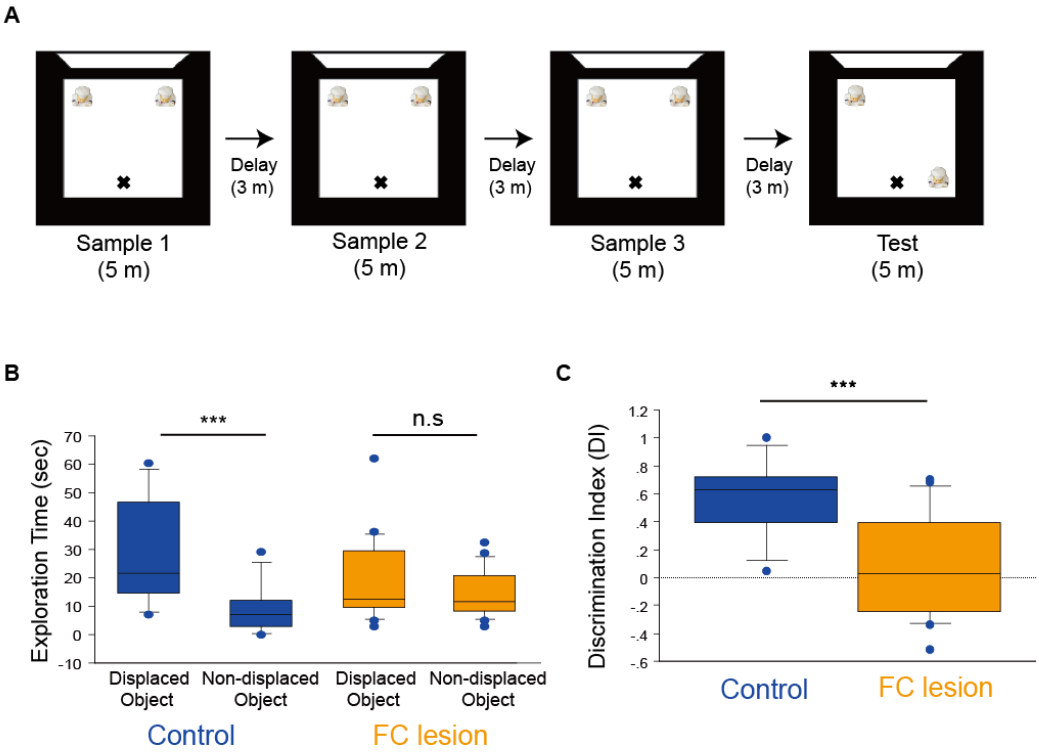


Figure 4. Object location task. (A) Behavior paradigm of the object location task. (X indicates the starting locations of the rat during the sample and test phases of the object location task.) (B) Exploration time of the displaced and non-displaced object during the test phase by the control group and lesion group. (C) Discrimination index of the control group and the lesion group during the test phase (***p<.001).

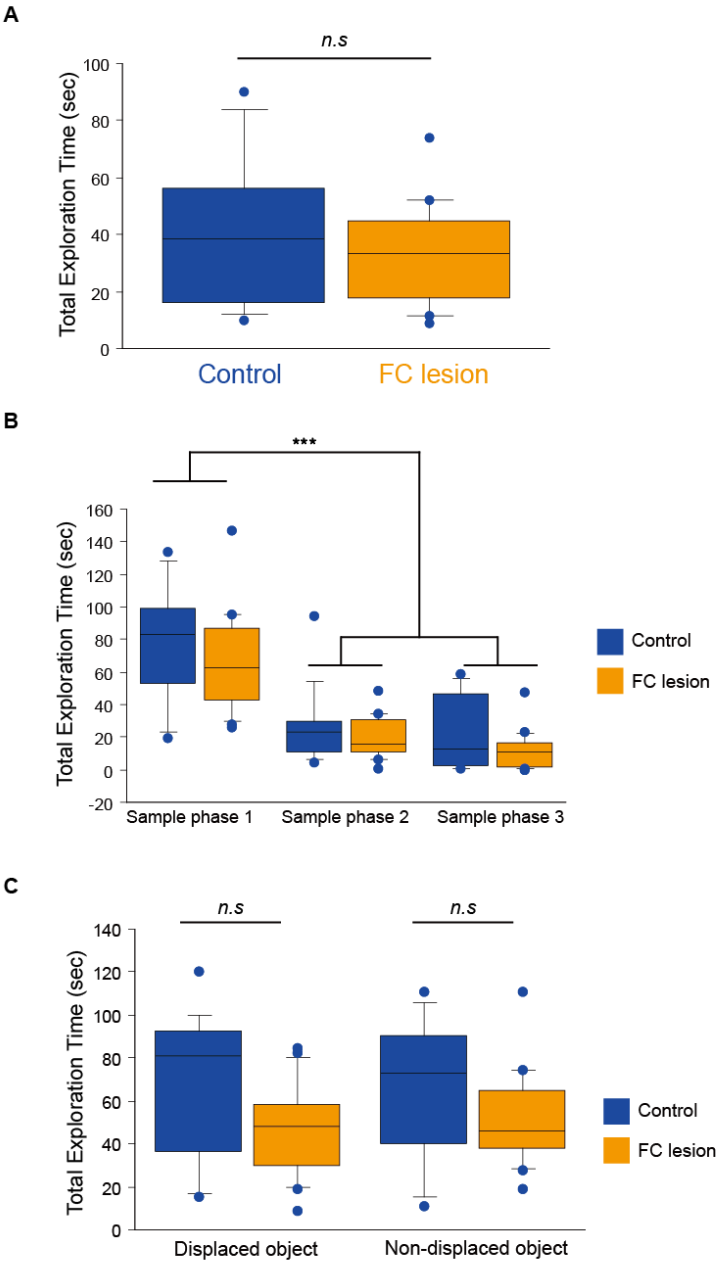


Figure 5. Total exploration time (displaced object exploration time + non-displaced object exploration time) of the object location task during the test phase and sample phases. (A) Total exploration time during the test phase of the control group and the experimental group. (B) Total exploration time of the control group and experimental group during the three sample phases (***p<.001). (C) The median of the exploration time during the three sample phases of the displaced and non-displaced objects.

3.3. Task 2: Object-place associative memory

The FC is required for object-place associative memory

Object-place association tasks were conducted to determine whether the FC is important for object-place associative memory or not. Familiar objects were used in the test phase, but the object was displaced to the old location (Figures 6A and 8A).

1) Object-in-place task 1

Recognition during test phase

The exploration time of the displaced object and the non-displaced object was significantly different in the control group but not in the lesion group (Figure 6B). The performance of the control group was significantly higher than the FC lesion group (Figure 6C). The Mann-Whitney U test revealed a significant difference between the control and experimental groups.

Exploration time during the sample and test phases

Figure 7A shows the total exploration time during the test phase. The Mann-Whitney U test showed no significant differences between the two groups (Figure 7A). The total exploration time of the third sample phase decreased significantly compared to the first sample phase and the second sample phase (Figure 7B). Moreover, the total exploration time of the displaced and non-displaced objects showed no significant difference between the two groups during the sample phases (Figure 7C). These data suggest that the FC is required for object-place associative memory.

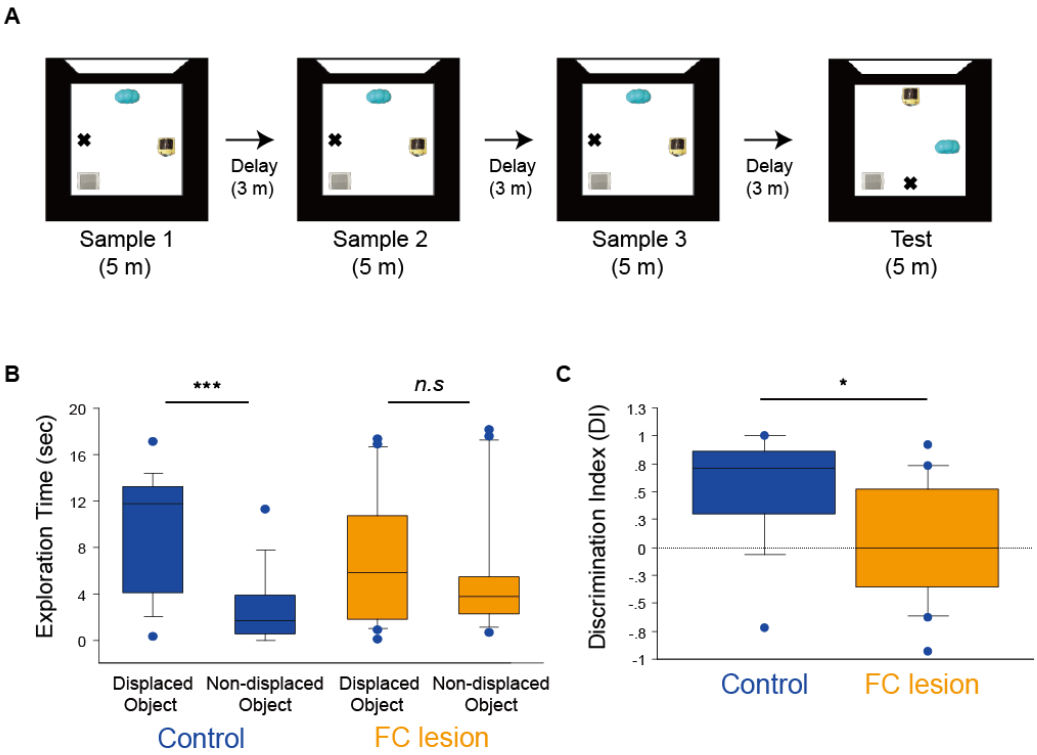


Figure 6. Object-in-place task 1. (A) Behavior paradigm of object-in-place task 1. (X indicates the starting locations of the rat during the sample and test phases of object-in-place task 1.) (B) Object exploration time of the control and lesion groups in the test phase. (C) Discrimination index of the two groups during the test phase (*p<.05, ***p<.001).

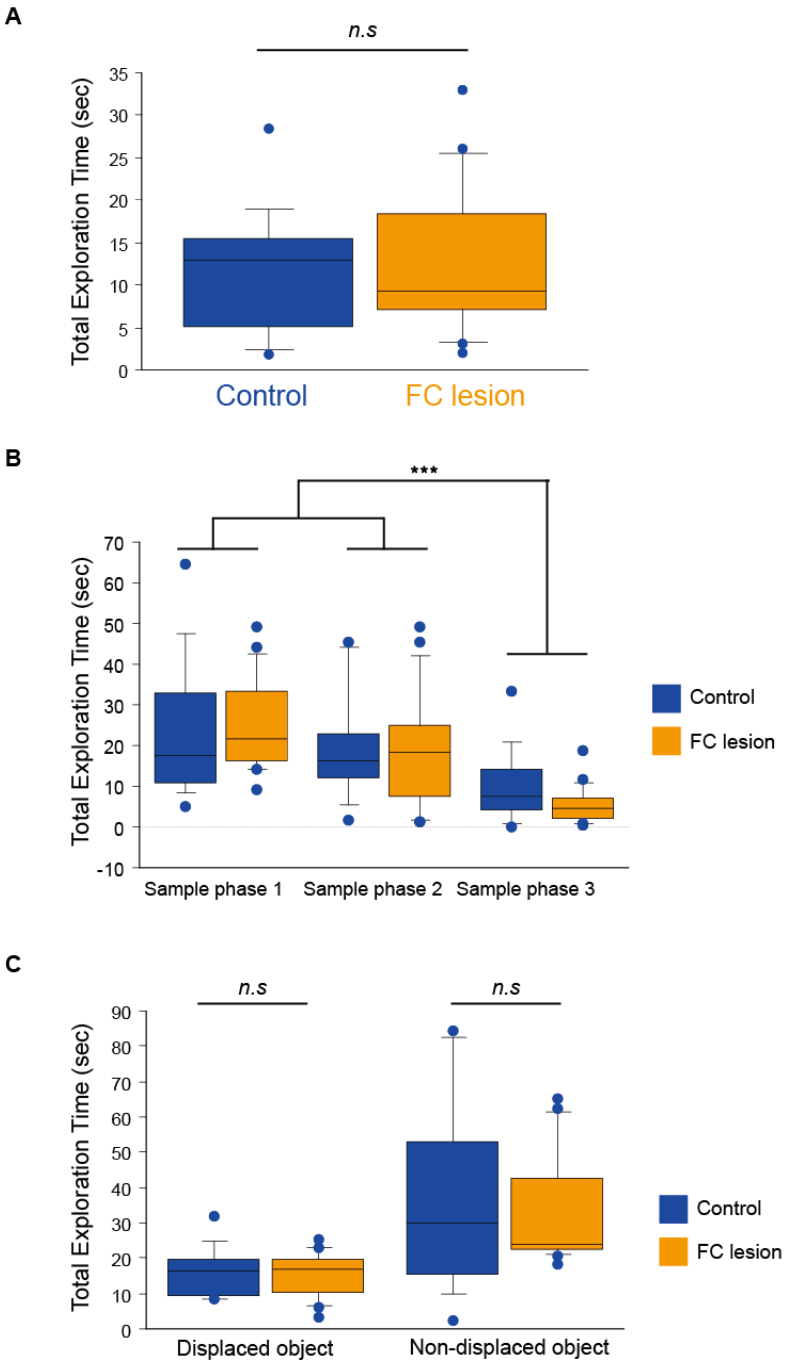


Figure 7. Total exploration time of object-in-place task 1. (A) Exploration time of the displaced and non-displaced objects by the control group and lesion group during the test phase. (B) Total exploration time during the three sample phases. (C) The median of the total exploration time of the three sample phases by displaced object and non-displaced object (***p<.001).

2) Object-in-place task 2

Recognition during the test phase

The control group indicated a significant difference in exploration time between the novel object and the familiar object, but there was no significant difference in the FC lesion group (Figure 8B). The discrimination index showed significant differences between the control group and lesion group using the Mann-Whitney U test (Figure 8C).

Exploration time during the sample and test phases

Figure 9A provides the total exploration time of the control group and the experimental group during the test phase. There were no significant differences between the groups according to the Mann-Whitney U test analysis (Figure 9A). The box plot indicates that there were significant differences between sample phase 1 and sample phases 2 and 3 (Figure 9B). The exploration time of the novel object and familiar object showed no significant differences in the two groups (Figure 9C). These data suggest the FC plays an important role in object-place associative memory.

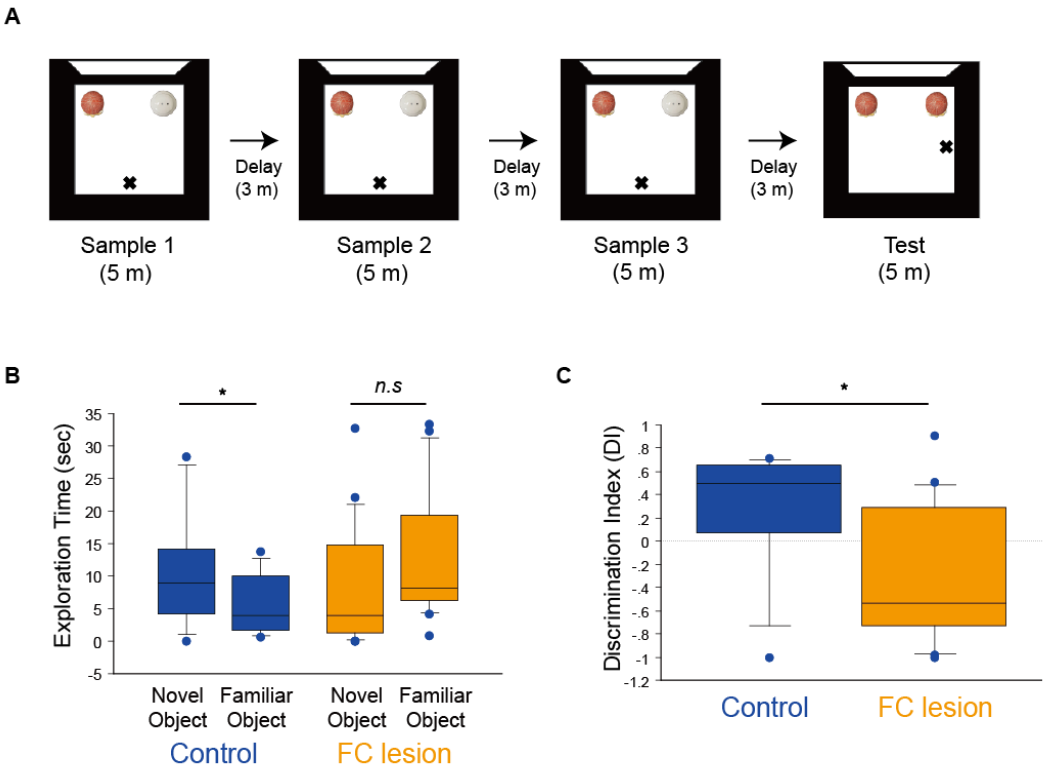


Figure 8. Object-in-place task 2. (A) Behavior paradigm of object-in-place task 2. X indicates the release point of the rat. (B) Exploration time in the test phase. (C) Performance of the animals during the test phase (*p<.05)

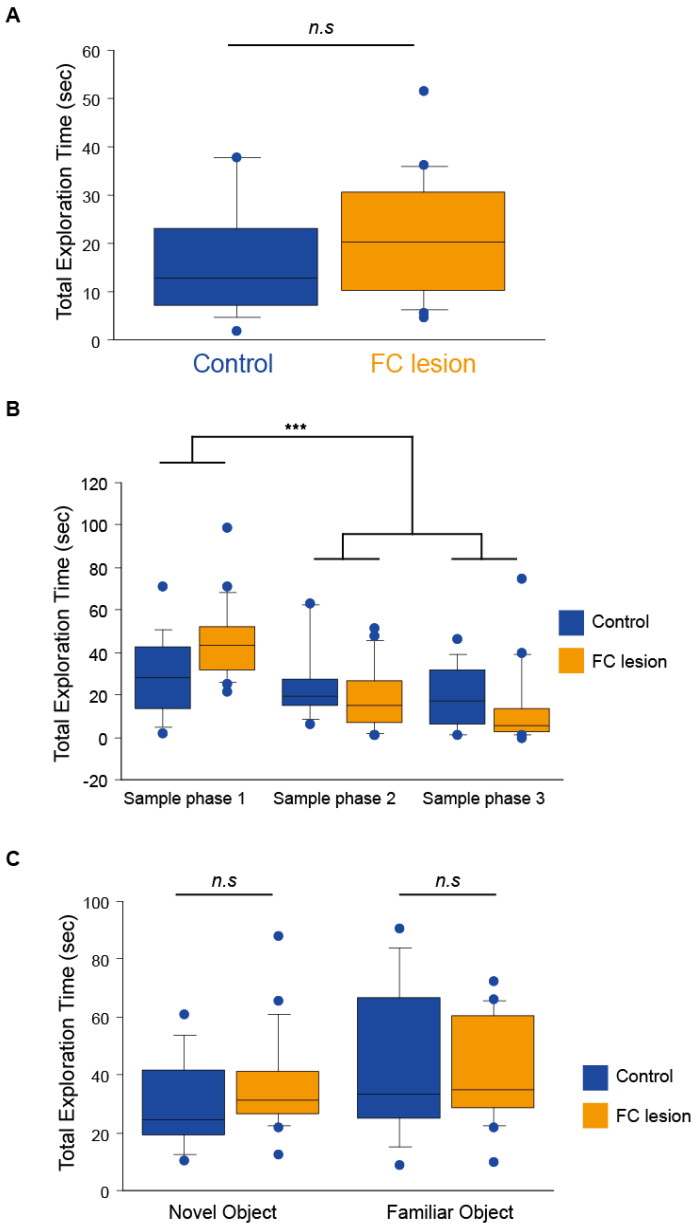


Figure 9. Total exploration time of the animals during object-in-place task 2. (A) Total exploration time in the test phase. (B) Total exploration time during the three sample phases. (C) The average of the total exploration time during the sample phases (***p<.001).

3.4. Task 3: Object novelty detection

The FC is not involved in novel object recognition

Novel object preference tasks were performed to investigate the object novelty detection role of the FC. The starting point of the animals was the same during the sample phases and test phase. The object identity was changed in the test phase and the experimenter measured the exploration time of the animals (Figures 10A and 12A).

1) Novel object preference task (1h delay)

Recognition during the test phase

The control group and the experimental group showed significant differences between the novel object and the familiar object exploration time (Figure 10B). There was no impairment in the control group and the experimental group (Figure 10C).

Exploration time during the sample and test phases

The total object exploration time of the two groups showed no significant difference in the test phase (Figure 11A). The Friedman test revealed significant differences between the control group and the experimental group. Furthermore, the Wilcoxon signed-rank test indicated that sample phase 1 showed significant differences compared to sample phases 2 and 3 (Figure 11B). There was no significant difference in the total exploration time of the novel and familiar objects during the sample phases (Figure 11C).

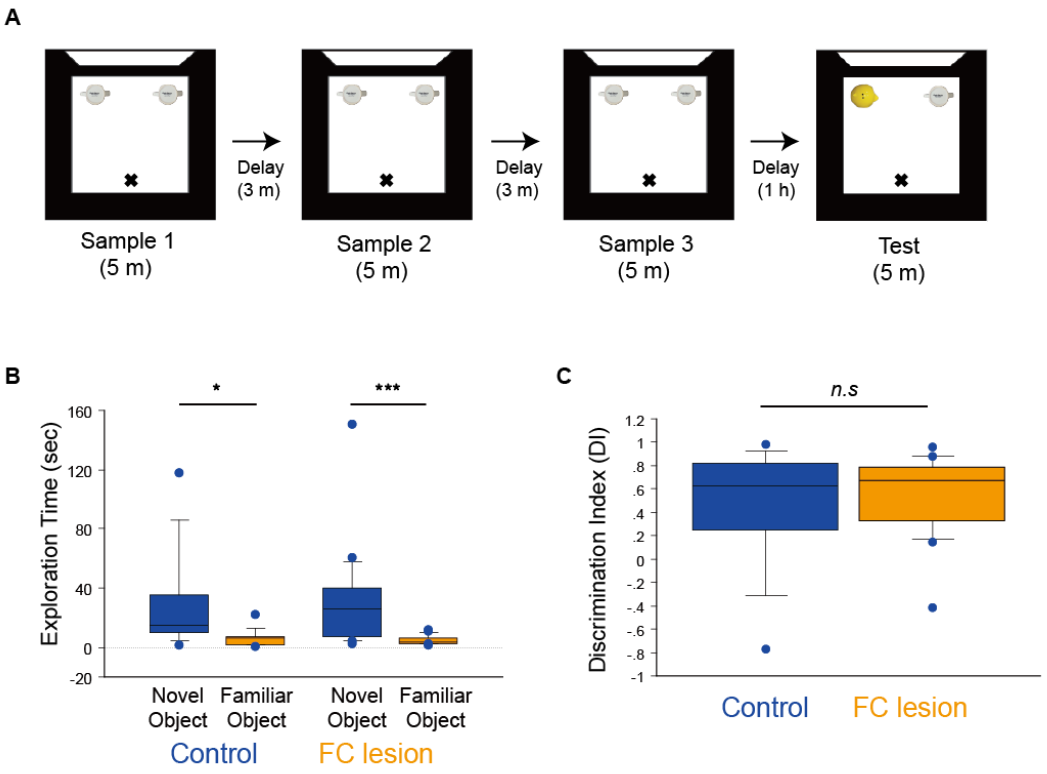


Figure 10. Novel object preference (1h delay) task. (A) Behavior paradigm of the novel object preference (1h delay) task. X indicates the release point of the rat. (B) Exploration time during the test phase. (B) Performance in the test phase (***p<.001)

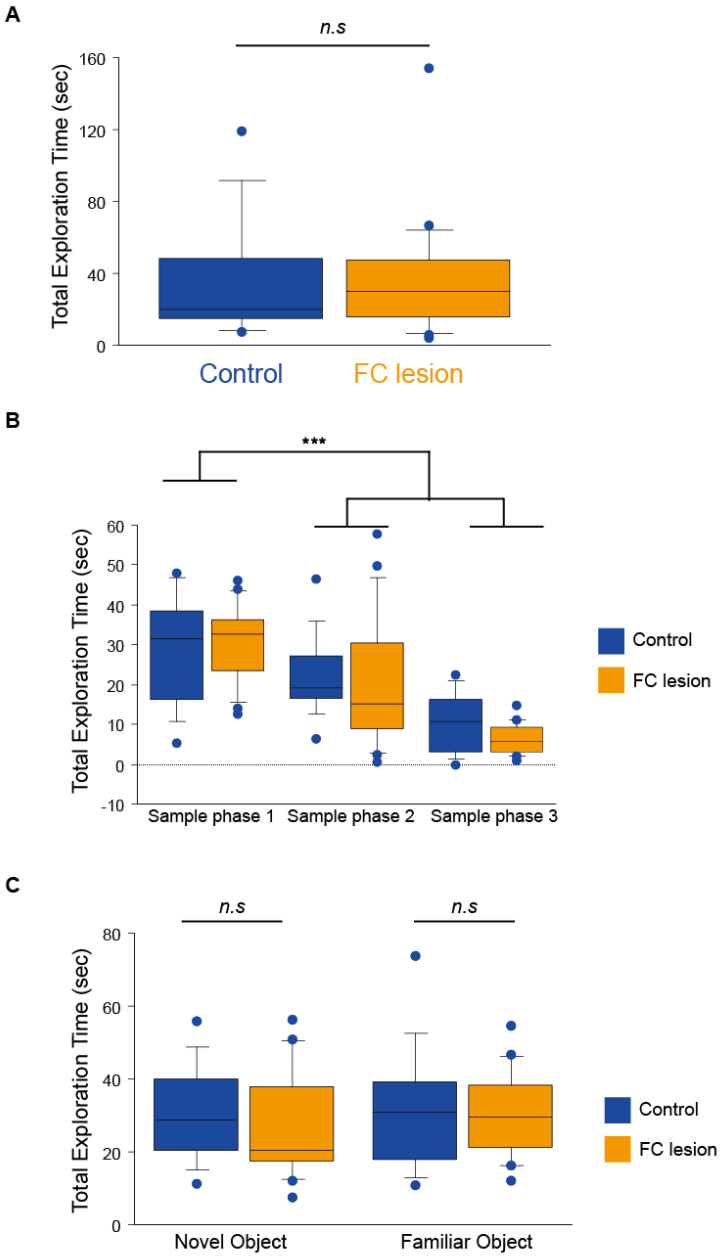


Figure 11. Total exploration time of the animals. (A) Total exploration time in the test phase. (B) Total exploration time during the three sample phases. (C) The average of the total exploration time during the sample phases (***p<.001)

2) Novel object preference task (5m delay)

Recognition during the test phase

The box plot presents the significant difference between the novel object and the familiar object in the control group and the experimental group (Figure 12B). All animals showed intact performance in the novel object preference task (Figure 12C).

Exploration time during the sample and test phases

The total exploration time showed no significant difference between the control and experimental groups, which means there is no surgical condition effect on animals' activity (Figure 13A). The total exploration time of sample phase 3 decreased significantly compared to sample phases 1 and 2 (Figure 13B). Finally, the novel object exploration time and familiar object exploration time showed no significant difference in both groups. Together, the novel object preference tasks results imply that the FC is not involved in object novelty detection.

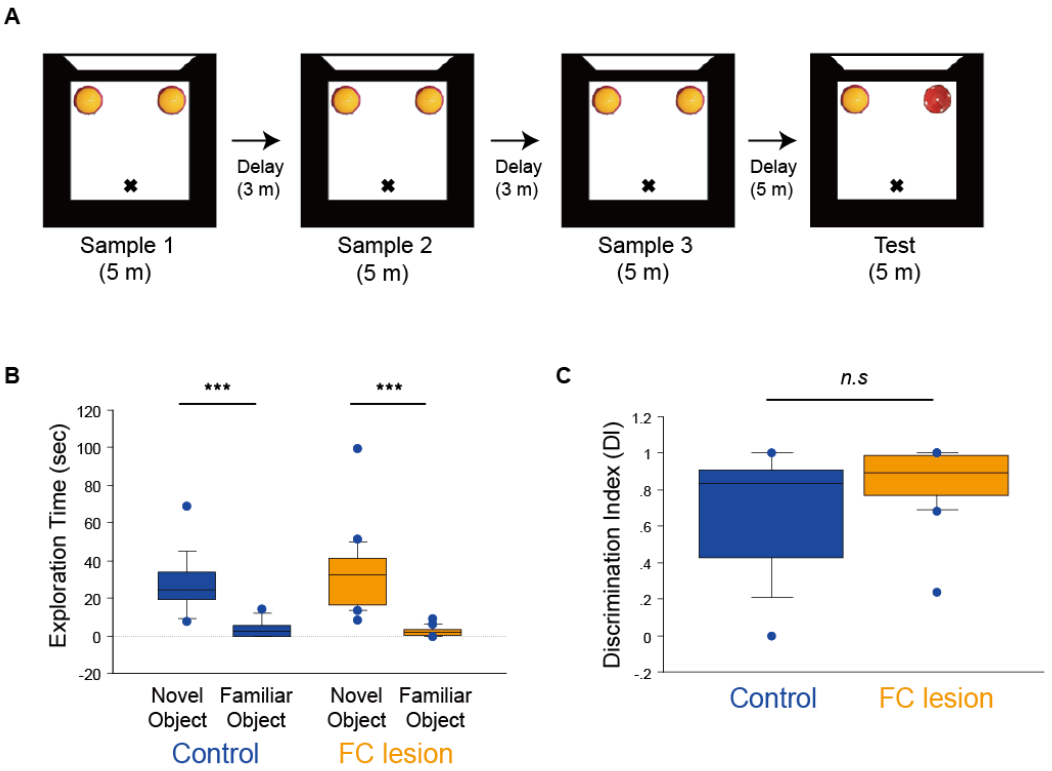


Figure 12. Novel object preference (5m delay) task. (A) Behavior paradigm of novel object preference (5m delay) task. X indicates the release point of the rat. (B) Exploration time in the test phase. (C) Performance in the test phase. (***p<.001)

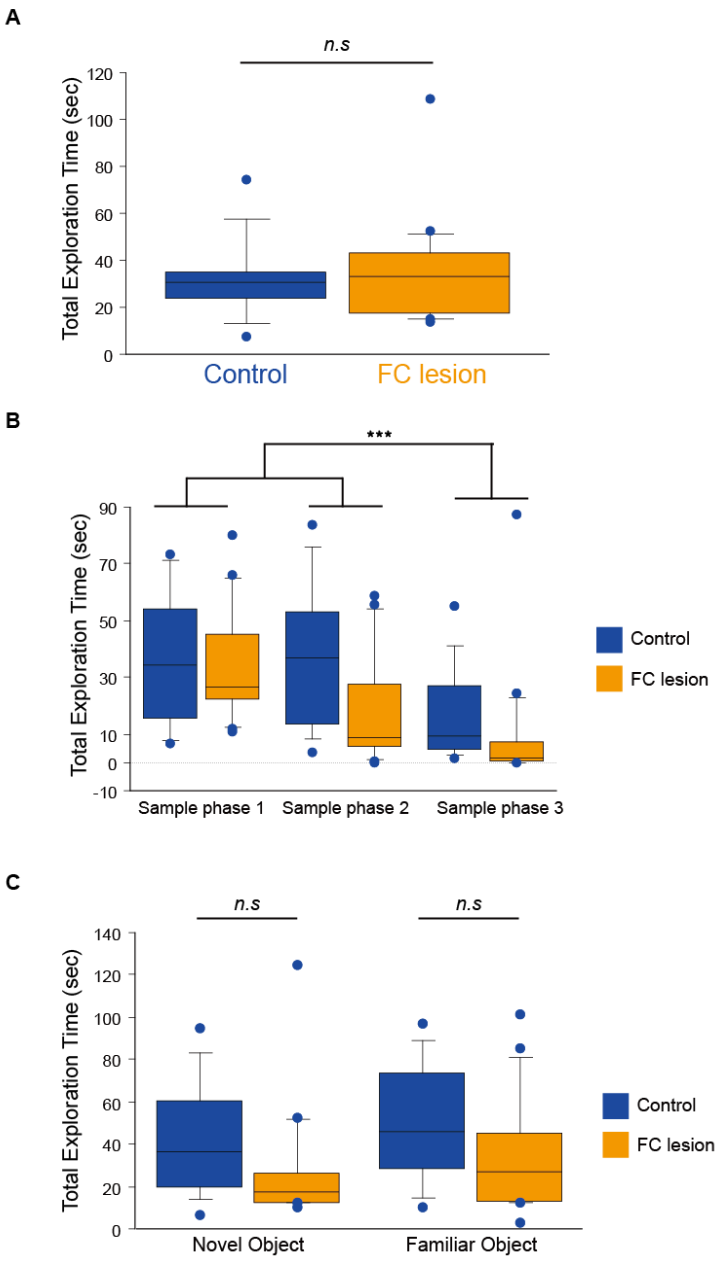


Figure 13. Total exploration time of the novel object preference (5m delay) task. (A) Total exploration time in the test phase. (B) Total exploration time in the three sample phases. (C) The mean of the total exploration time during the sample phases (***p<.001)

Chapter 4. Discussion

The main finding of the study is that the ablation of the FC significantly impaired object location memory and object-place associative memory. However, there was no effect of FC lesions on the performance of the novel object preference task following a 5-min and 1-hour delay. Previous studies demonstrated that the hippocampus is required for object-place association memory and object location memory (Barker and Warburton, 2011, Langston and Wood, 2010). We identified for the first time that the FC is an important component of a neural system that functions to support object location memory and object-place associative memory.

4.1. Contradictions to the conventional medial temporal lobe memory system

We predicted that the FC would work as a non-spatial pathway and process the association memory with the DG because of the characteristics of the anatomical connectivity of the FC. However, the results showed that the rats with ablation of the FC were not impaired in recognizing the object's identity. Based on this result, we argue that the LEC is not required for processing non-spatial information itself but is involved in the place-associative memory. Previous studies found that the LEC processes the information by receiving the spatial information from the MEC to form episodic memory in the hippocampus (Wilson et al., 2013b, Deshmukh and Knierim, 2011). Moreover, it has been found that the LEC plays an important role in associative recognition memory with the integration of information that is related to objects, places, and context to form episodic memory (Wilson et al., 2013a). Tsao et al. reported that the LEC is involved in a hippocampal-cortical circuit for object-place memory (Tsao et al., 2013). Together, spatial and non-spatial information is processed by the interaction of the MEC and the LEC at

the entorhinal cortex level (Van Cauter et al., 2013). The conventional dichotomy of the medial temporal lobe memory system, which is the "what" pathway and the "where" pathway, should be revised (Knierim et al., 2014). Our data suggest that the LEC may be involved in associative memory by processing the non-spatial information by integrating the spatial information.

4.2. Investigation of a new functional neural circuit of the FC

The anatomical neural circuit of the FC was investigated for the first time in 2019 (Park et al., 2019). The FC receives inputs from layer II of the LEC and layer II/III of the PER and projects strong output to the DG. Furthermore, intrinsic connectivity was found within the FC (Figure 14). However, there were no connections with CA1 and CA3. We suggest that the FC processes information with a certain pathway of the parahippocampal area and works with the DG related to the visual contextual novelty detection and pattern separation. A recent study conducted by Park et al. provided evidence that the FC-DG pathway contributes to the acquisition of the novel contextual behavior, but not to retrieval, which is hippocampal memory. In this study, we presume that the FC-DG connection and intrinsic FC circuit may play a role in object-place associative memory because the DG is important for object-place associative memory (Hunsaker et al., 2008). The DG lesion rats showed impairment in the spatial discrimination of the objects. The functional circuit of the FC should be studied in more detail in future studies. The anatomical connectivity and other functional neural circuits of the FC for episodic memory also need to be investigated.

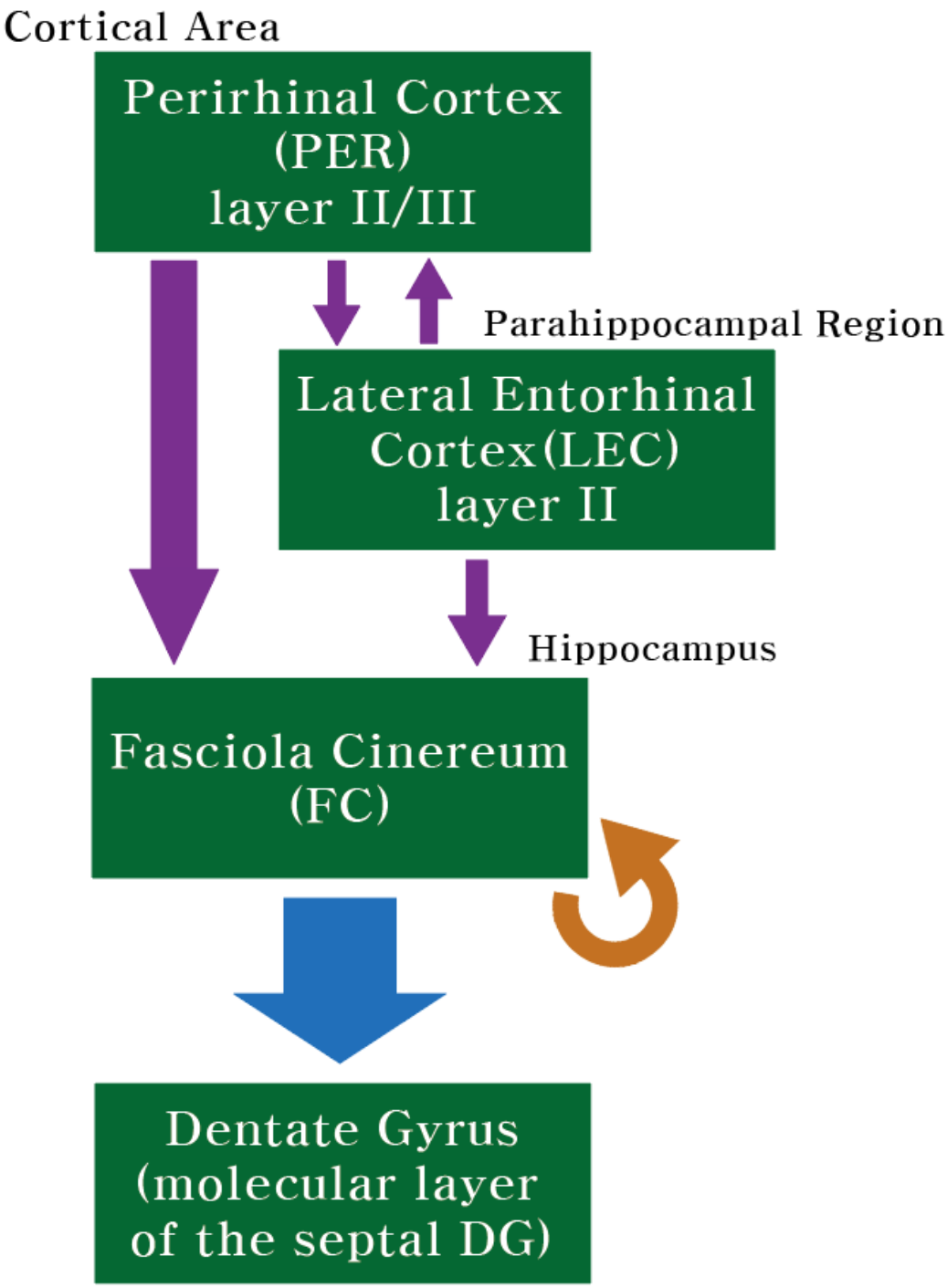


Figure 14. Schematic illustration of anatomical connections of the FC. Purple arrow: input of the FC. Blue arrow: output of the FC. Orange arrow: intrinsic connection

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국문 초록

서울대학교 자연과학대학
뇌인지과학과
이은영 (Eun Young Lee)

소대회는 해마의 하위 영역으로 CA1 과 인접해있는 영역이다. 이 영역은 측면 내후각 피질의 II 층과 비주위의 피질 II/III 층으로부터 구심성 신경을 받고 치아이랑으로 원심성 신경을 보내며 내재적 연결성을 가지고 있다. 이러한 해부학적 연결을 고려해 보았을 때 소대회는 비공간적 정보와 장소와 연합된 기억을 처리 할 것이라는 가정을 도출했다. 해부학적 기능을 검증하기 위하여 소대회 병변 쥐와 손상 되지 않은 쥐를 사용하여 자발적 물체 탐색 과제를 수행하도록 하였다. 자발적 물체 탐색 과제로는 물체 위치 기억, 물체-공간 연합 기억, 새로운 물체 기억 세 가지를 검사하였다. 물체 위치 기억 과제에서는 쥐는 먼저 두 가지 동일한 물체가 동일한 위치에 있는 환경을 세번 씩 오분 동안 경험 한 뒤, 검정 시행에서 두 물체 중 한 물체의 위치를 이동하여 이동한 물체를 인식할 수 있는 지 확인 해 보았다. 물체-공간 연합 기억 과제에서는 두 개 혹은 세 개 물체를 올려놓은 뒤 검정 시행에서 물체의 위치가 서로 바뀌어진 것을 인식하는 지 확인하고자 하였다. 마지막으로 새로운 물체 기억 과제에서는 동일한 위치의 동일한 물체 두 가지를 보여준 뒤 검정 시행에서 동일한 위치에 놓여 있지만 새로운 물체를 쥐에게 보여줌으로써 쥐가 새로운 물체를 인식할 수 있는 지 확인하였다. 행동 결과로는 소대회를 손상시킨 쥐 그룹에서 물체 위치 기억과 물체-공간 연합 기억을 수행해야하는 과제에서 장애를 보였으나 새로운 물체 기억 과제에서는 장애를 보이지 않았다. 이 연구의 실험 결과를 통해 소대회가 물체 인식에 관여하는 것이 아니라 물체와 공간간의 연합 기억에 관여 한다는 사실을 알 수 있었다.

주요어: 해마, 일화 기억, 소대회, 물체 인식, 물체-장소 연합 기억

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