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Left-right functional difference of the rat dorsal hippocampus for short-term memory and long-term memory

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ABSTRACT

The existence of left-right hemispheric differences has been suggested not only in humans but also in rodents. In recent studies, left-right anatomical and functional differences of the rodent hippocampus have been revealed. However, there is only one report investigating the left-right difference for short-term memory (STM), and the left-right difference for long-term memory (LTM) is not consistent among previous studies. Therefore, we examined the effects of unilateral hippocampal lesion and stimulation on the formation of STM and LTM in rats. Our results showed that the right, but not the left, hippocampal lesion impaired STM performance, evaluated by the alternation rate in the spontaneous alternation test and the novel-arm choice rate in the novelty preference test. In addition, electrical stimulation of the left, but not the right, hippocampus immediately before the tests impaired STM performance. On the other hand, the left, but not the right, hippocampal lesion impaired the LTM performance, evaluated by the discrimination index in the object recognition test. In addition, the stimulation of the left, but not the right, hippocampus impaired LTM performance. These results suggest that both the left and right hippocampi are involved in STM formation, and the right hippocampus has a facilitating role while the left hippocampus has a suppressing role for STM. On the other hand, LTM may be driven correctly only by the left hippocampus with appropriate level of neural activity. The left and right hippocampi of rodents may work in different mechanisms depending on the demand for STM and LTM.

1. Introduction

Left-right hemispheric differences in the brains of humans, such as left-sided language areas and right-sided spatial cognitive ability, are well-known [1]. However, this feature is not specific to humans, and many behavioral studies [2–4] have suggested the existence of left-right hemispheric differences in various animal species such as toads [5], chicks [6], dolphins [7], and horses [8]. For example, honeybees could recall short-term memory (STM) of odour association when tested using their right antennae, conversely long-term memory (LTM) was accessed mainly via the left antenna, suggesting the time-dependent shift from right to left antenna [9]. More recently, left-right anatomical [10–13] and functional [14–19] differences have been reported in the rodent hippocampus. In particular, the findings of the study by Shipton et al. [16] were highly suggestive, demonstrating that the optogenetic silencing of the left CA3 alone impaired LTM performance in the reward exploration task, whereas the unilateral silencing of either the left or right CA3 caused STM deficits in the spontaneous alternation task and the spatial novelty preference task. However, unlike the results of Shipton et al. [16], previous studies have reported that the right hippocampus contributes predominately to LTM tasks, such as the Barnes maze test [17] and the active avoidance test [19], and the unilateral advantage of the left or right hemisphere in LTM is not consistent among the studies. On the other hand, right hippocampal dominance in STM has been suggested in humans [20]. In rodents, however, there is no such study except Shipton et al. [16], and follow-up experiments are needed. Therefore, it is necessary to investigate this complex left-right hemispherical functional separation for STM and LTM with further experiments. In addition to the functional inhibition of the unilateral hippocampus that has been reported in the previous studies [11–16], functional facilitation may contribute to elucidating the functional separation of the left-right hippocampus in rodents.

In the present study, we confirmed the reproducibility and consistency of the left-right hippocampal difference in STM and LTM by the hippocampal lesion experiment. In addition, we investigated how the activation of the unilateral hippocampus by electrical stimulation affects the performance of STM and LTM. From these experiments, we obtained data on the actual role of the left and right hippocampi for STM and LTM formation.

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2. Materials and methods

2.1. Animals

Experimental subjects were 42 male Wistar albino rats (Shimizu Laboratory Supplies, Kyoto, Japan) that were aged 9 weeks old at the time of the surgery. The rats were individually housed in cages with free access to food and water under a light-dark cycle, with the light period between 08:00 and 20:00 h. The rats were randomly assigned to the lesion group and the stimulation group. All experiments were performed in accordance with the Guidelines for Animal Experiments at Doshisha University and with the approval of the Animal Research Committee of Doshisha University.

2.2. Surgery

One week before the experiment, the rats were anesthetized with isoflurane (2.5 %, 2.5 L/min) via an anesthetic vaporizer (MK-AT200, MUROMACHI KIKAI Co. LTD., Tokyo, Japan).

In the lesion group (for both STM and LTM experiments), electrical lesions were made by passing anodal direct current (1 mA, 30 s) using a lesion-making device (53500, UGO BASILE SRL, Gemonio, VA, Italy) and a stainless bipolar electrode (150-μm diameter, UB-9007, UNIQUE MEDICAL Co., LTD., Tokyo, Japan). The electrode was inserted into the right or left dorsal hippocampus (DH) ((1) AP, −3.0 mm from bregma; ML, ± 2.0 mm from bregma; DV, −3.0 mm from dura; (2) AP, −4.0 mm; ML, ± 3.0 mm; and DV, −3.0 mm; (3) AP, −5.0 mm; ML, ± 4.0 mm; and DV, −3.0 mm). Brain regions were identified according to the Rat Brain Atlas [21]. For sham lesions, the electrode was lowered to the same coordinates, but no current was passed.

In the stimulation group (for both STM and LTM experiments), a head device for electrical stimulation was mounted on the rats' skull. A bipolar electrode was prepared with coated tungsten wire (300-μm diameter, UNIQUE MEDICAL Co. LTD., Tokyo, Japan; the coating is peeled off to 0.5 mm from the tip). The electrodes were inserted into the bilateral, right, or left DH (AP, −3.0 mm from bregma; ML, ± 2.0 mm from bregma; DV, −3.0 mm from dura) and were fixed with dental cement and screws. All rats were allowed to recover for 7 days and were handled for 5 min each day.

2.3. Stimulation

Electrical stimulation for 10 min was performed in the left and right stimulation groups 10 min before each behavioral test started. The electrodes were connected to the isolated stimulator (Model DS3, Brain Science Idea Co. Ltd., Osaka, Japan) and the train/delay generator (Model DG2A, Brain Science Idea Co. Ltd., Osaka, Japan). The stimulation parameters were 100 μA, 130 Hz, and 90 μs. In the Sham group, the electrodes were connected to the stimulator, but no current was passed.

In addition, to confirm that the stimuli used in this experiment properly activated neurons in the hippocampus, an additional 6 rats (named Stim group, n = 3; Sham group, n = 3) were similarly stimulated for 10 min under free-moving conditions.

2.4. Behavioral tests

In both the lesion and the stimulation experiments, there were two meta-groups, STM- and LTM-task. The rats of STM-task groups (Sham, L-lesion, and R-lesion) were tested in two short-term memory tasks, the spontaneous alternation test (SAT) and the novelty preference test (NPT). All rats were tested using one task each day. The rats of LTM-task groups (Sham, L-lesion, and R-lesion) were tested in a long-term memory task, the object location test (OLT). On the day of each behavioral test, the home cage was moved to the experimental room 2 h before the start of the test for habituation.

2.4.1. Spontaneous alternation test

For the SAT, a T-shaped maze was used. It was made of transparent acrylic plates. It was comprised of three arms which were each 75 cm long, 10 cm wide, and 40 cm high. Rats were gently placed at the tip of one of the three arms (Start arm). They were then allowed to explore the maze for 10 min. The Start arm was chosen randomly for each rat. After each test, the apparatus was carefully cleaned with a towel containing 70 % ethanol. This was done to prevent the exploratory behavior of other rats from being influenced by olfactory stimuli produced by the previous rats. Behaviors were recorded using a camera (BSW32KM03SV, BUFFALO INC., Aichi, Japan) mounted directly above the apparatus, and the total number of alternations and entries into each of the three arms were calculated by a software program (ANY-maze software, Stoelting Co., IL, USA). The alternation rate was calculated using the following equation: (number of entries into the arm not entered in the preceding two entries)/((total number of entries into all the arms) − 2). Rats were considered to have entered an arm when all four of the animal's paws were located in that arm.

2.4.2. Novel preference test (NPT)

For the NPT, a Y-maze was used. It was made of transparent acrylic plates and comprised of three 75 cm long, 10 cm wide, and 40 cm high arms. First, one of the arms (named "Novel arm") was blocked with an opaque acrylic plate. Subsequently, rats were gently placed at the Start arm (one of the two unblocked arms) and they were allowed to explore the two unblocked arms (named "Familiar arms") for 5 min. Afterwards, the rats were moved to their home cages for one minute, then the plate blocking the Novel arm was removed and the rats were placed at the Start arm again and were allowed to explore all three arms for three minutes. The Start arm and Novel arm were chosen randomly for each rat. After each test, the device was rotated 120 degrees in a randomly selected direction and carefully cleaned with a towel containing 70 % ethanol. Behaviors were recorded using the camera, and the percentage of time spent in the Novel arm and the entries into each of the three arms were calculated.

2.4.3. Object location test

For the OLT, a 45 cm × 60 cm × 45 cm box made of white styrofoam boards was used. First, rats were allowed to explore the empty apparatus for two consecutive days (two hours per day) for habituation. On the third day, the two rectangular parallelepiped blocks (5 cm × 5 cm × 10 cm) made of wood were placed 5 cm away from one plane. Subsequently, rats were gently placed at the center of the apparatus, and they were allowed to explore for 10 min (Note that the rats of the stimulation groups were stimulated for 10 min just prior to this exploration.). After the rats were returned to their home cages, one block (named "Novel block") was placed in another corner of the device, and one of the previously presented blocks (named "Familiar block") was placed at the same position as before. After 24 h (the fourth day), the rats were allowed to explore the box again for three minutes (Note that the rats of the stimulation groups were stimulated for 10 min just prior to this exploration). After each test, the apparatus was carefully cleaned with a towel containing 70 % ethanol. Behaviors were recorded using the camera, and the total time during which the rat's nose touched the Familiar and Novel blocks and the discrimination index (DI, (Novel time − Familiar time)/(Novel time + Familiar time)) were calculated.

2.5. Histology

In day following the completion of behavioral tests, the rats were deeply anesthetized with an overdose of sodium pentobarbital (220 mg/kg, Kyoritsuseiyaku Corporation, Tokyo, Japan) and were perfused with 0.01 M Phosphate Buffered Saline (PBS, Nacalai Tesque, Kyoto, Japan) and 4 % paraformaldehyde (PFA, Nacalai Tesque, Kyoto, Japan). The brains were then removed and stored in PFA overnight, before transferring them to 30 % sucrose. We obtained coronal brain

sections (50 μm) using a microslicer (DTK-3000, Dosaka EM Co. Ltd., Kyoto, Japan) and mounted them on slides, then cresyl violet solution was used as a background stain to detect the lesion area and the inserted site of the cannula with a microscope (Axioplan 2 Imaging, Carl Zeiss Microscopy, LLC, NY, USA) equipped with a camera (DFC300 FX, Leica Microsystems Inc., IL, USA). Brain regions were identified according to the Rat Brain Atlas [21]. The numbers of neurons in the cortex just above the hippocampus (AP, −3.0 mm from bregma; ML, ± 2.0 mm from bregma; DV, −1.5 mm from dura) were counted with ImageJ software (National Institutes of Health, Bethesda, MD, USA). The image editing method and the cell counting method were applied as previously described [14]. The threshold used for each image was set to 120–180 points, and the circularity values was set to 0.60–1.00 points.

2.6. Immunohistochemistry

We used a free-float method for immunohistochemistry. The sections of the Stim and Sham groups (AP = 3.50 mm) were blocked with a solution containing 5 % goat serum (G9023, Sigma-Aldrich, MO, USA) for 1 h. After washing in buffer, sections were incubated with rabbit anti-c-fos antibody (1:1000 dilution, sc-52, Santa Cruz Biotechnology, CA, USA), overnight, at 4 ℃. Then sections were washed and incubated with goat anti-rabbit immunoglobulin G (1:1000 dilution, ab150077, Abcam, Cambridge, UK) for 2 h at room temperature. Finally, the stained slices were mounted on slide glasses and coverslipped with the mounting reagent containing DAPI (Fluoro-KEEPER Antifade Reagent, Nacalai Tesque, Kyoto, Japan). Each section was scanned at 20 × magnification using the light microscope equipped with the camera. The numbers of c-fos-positive cells in hippocampal subregions (dentate gyrus (DG), CA3, and CA1) were counted with the ImageJ software. The image editing method and the cell counting method were applied as previously described [14]. The threshold used for each image was set to 80–100 points, and the circularity values was set to 0.80–1.00 points.

2.7. Data analysis

Data analyses were performed with BellCurve for Excel (Social Survey Research Information Co. Ltd., Tokyo, Japan). Experimental data are shown as means ± SEM. One-way analysis of variance (ANOVA), followed by post-hoc Tukey–Kramer method was used for all statistical comparisons.

3. Results

3.1. Histology

In the lesion experiment, we observed that the stereotaxic passing of an anodal direct current destroyed most DH structures. Fig. 1a shows a raw sample of an electrical lesion. Fig. 1e (for STM-task) and 2a (for LTM-task) indicate the lesion areas (minimum lesion areas, gray color; maximum lesion areas, black color) of the left and right lesion groups (n = 6 in each group). The extent of the lesion is shown with reference to the horizontal sections found in the Rat Brain Atlas [21]. Four rats whose lesions were over-destroyed (lesion was observed outside of the hippocampal structure) were excluded from analysis. The Sham lesion group had little-to-no damage in these areas. In addition, Fig. 1bc shows enlarged section images of the cortex just above the lesion area of the ipsi- and contra-lateral hemispheres, respectively. In both the left and right lesion groups, there was no significant difference between the number of neurons on the ipsi-lateral (n = 6) and the contra-lateral (n = 6) hemispheres (left; $F_{(1, 10)} = 0.029$, $P = 0.87$, right; $F_{(1,}$

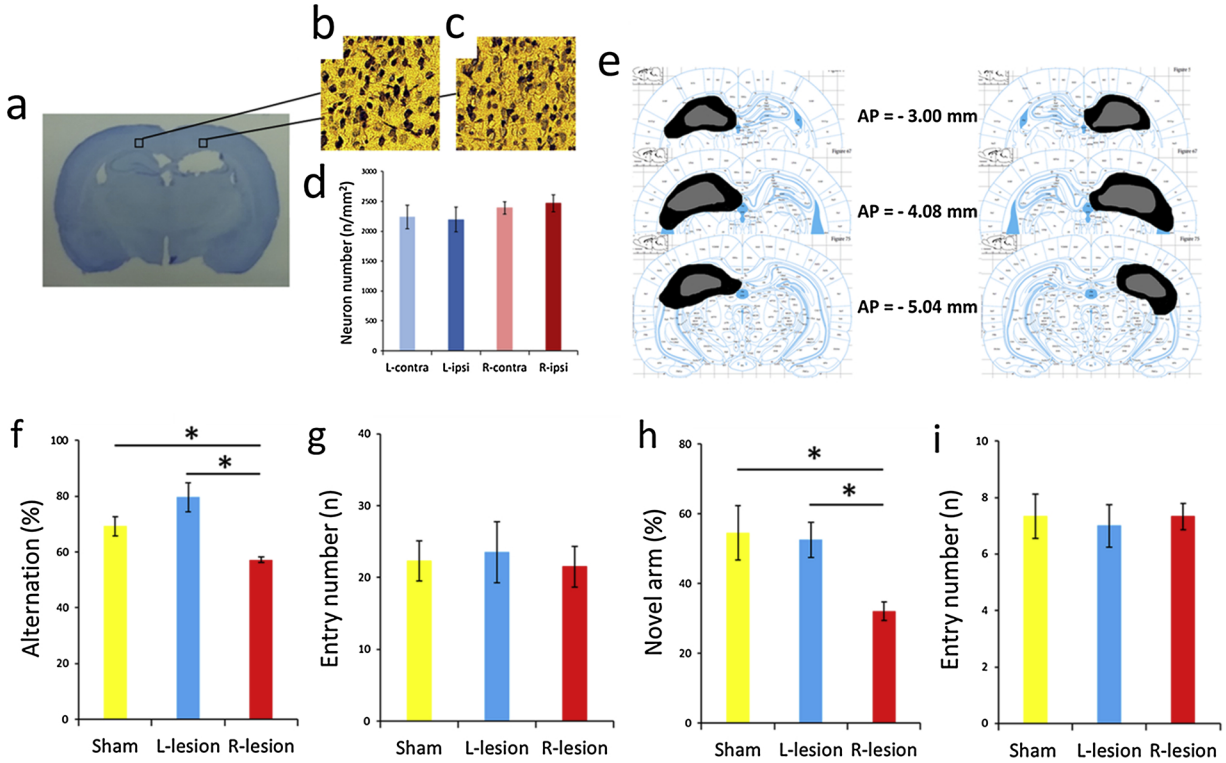

Fig. 1. Lesion experiment for STM. Images of sections showing the lesion sites for the (a) raw sample, and (b) maximum (black) and minimum (gray) lesion areas of the left (n = 6, left side three figures) and right lesion (n = 6, right side three figures) groups. A 10 × raw sample of the cortical area (AP = 3.00) located just above the hippocampus in (c) ipsi-lateral hemisphere (lesion side) and (d) contra-lateral hemisphere (opposite side). (e) The number of neuron in the ipsi- and contra-lateral hemisphere. (f–h) The results of STM tasks. (f) Alternation rate in the SAT. (g) Total entry number in the SAT. (h) Novel arm rate in the NPT. (i) Total entry number in the NPT. Yellow, blue, and red bars represent the Sham (n = 6), the left (L) lesion (n = 6), and the right (R) lesion (n = 6) groups, respectively. All measures are shown as means ± SEM and * indicates $P < 0.05$. STM, short-term memory; SAT, spontaneous alternation test; NPT, novel preference test.

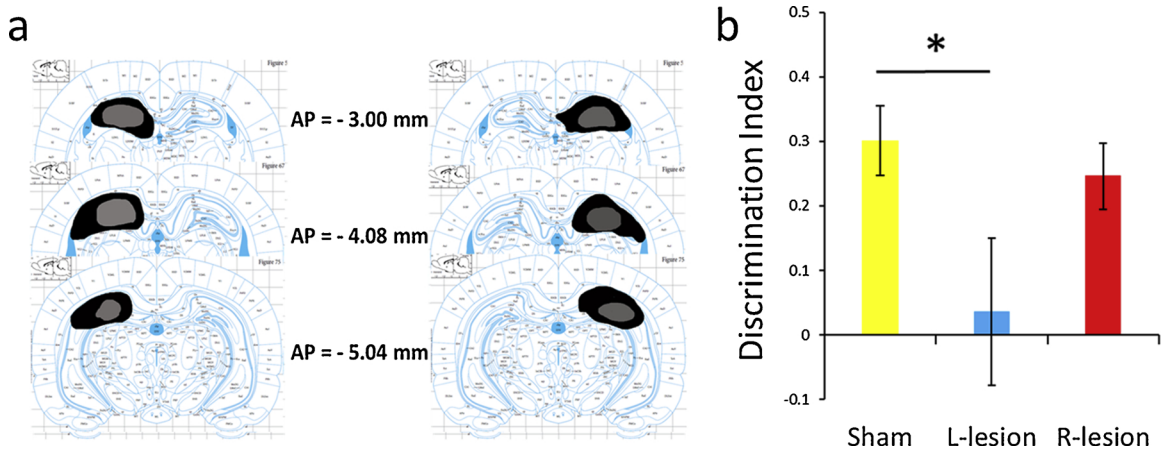

Fig. 2. Lesion experiment for LTM. (a) Maximum (black) and minimum (gray) lesion areas of the left (n = 6, left side three figures) and right lesion (n = 6, right side three figures) groups. (b) The results of LTM task. The DI 24 h after the sample presentation in the OLT. Yellow, blue, and red bars represent the Sham (n = 6), the left (L) lesion (n = 6), and the right (R) lesion (n = 6) groups, respectively. All measures are shown as means ± SEM and * indicates P < 0.05. LTM, long-term memory; DI, discrimination index; OLT, object location test.

$_{10)}$ = 0.22, P = 0.65) (Fig. 1d).

In the stimulation experiment, we observed that the electrode tip was accurately placed into the intra-hippocampus. Figs. 4a, 4 b/5 a, and 4 c/5 b show the raw section sample, and the insertion site of each individual of the left group and right group, respectively (n = 6 in each group). In addition, in order to confirm that stimulation with the parameters used in this experiment can definitely activate hippocampal neurons, the expression of c-fos protein, an activation marker of neurons, was quantified 1.5 h after performing stimulation for 10 min. Fig. 3a shows the electrode insertion site (n = 3) and Fig. 3b shows raw samples of c-fos expression in the DG, CA3, and CA1 of the Stim and Sham groups. Fig. 3c shows the number of positive cells in each subregion. Compared to the Sham group, the number of positive cells in the Stim group was significantly higher in the DG ($F_{(1,\ 4)}$ = 178.21, P = 0.0030), CA3 ($F_{(1,\ 4)}$ = 98.83, P = 0.0050), and CA1 ($F_{(1,\ 4)}$ = 158.08, P = 0.0023).

3.2. Behavioral tests

In all rats, no epileptiform behaviors such as convulsions, rotations, sudden stops, and jumping were observed.

3.2.1. STM in the lesion experiment

The SAT and the NPT were used to measure STM. In the lesion experiment, in the SAT, the one-way ANOVA showed a significant effect for the alternation rate ($F_{(2,\ 15)}$ = 11.48, P = 0.00094) (Fig. 1f). The post-hoc comparisons revealed that the right lesion group (n = 6) was significantly lower than that for the Sham group (n = 6) or for the left lesion group (n = 6) (P = 0.0047 and P = 0.0042, respectively). There was no significant difference between the Sham group and the left lesion group (P = 0.052). On the other hand, the one-way ANOVA showed no significant effect for the total entry number ($F_{(2,\ 15)}$ = 0.11, P = 0.90) (Fig. 1g). In the NPT, the one-way ANOVA showed a

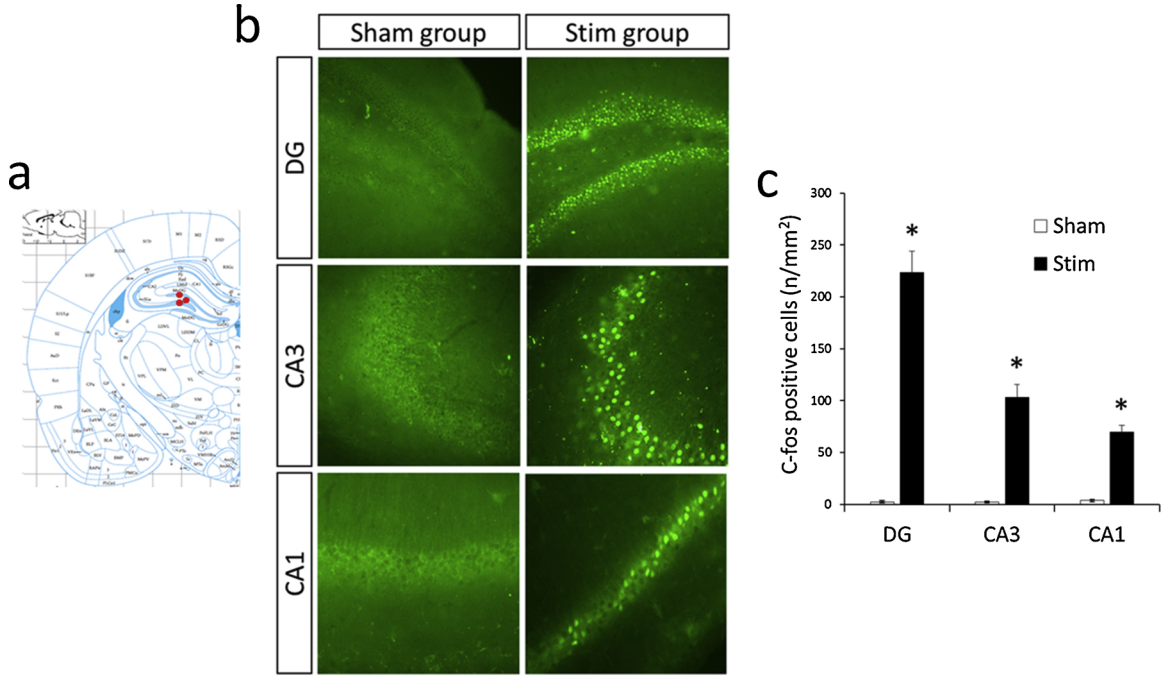

Fig. 3. C-fos expression by the electrical stimulation. (a) Insertion sites of the stimulation electrode (the Stim group, n = 3). (b) Raw sections of DG, CA3, and CA1 of the Sham and the Stim groups. (c) Number of the c-fos positive cells. White and black bars represent the Sham (n = 3) and the Stim groups (n = 3), respectively. All measures are shown as means ± SEM and * indicates P < 0.05.

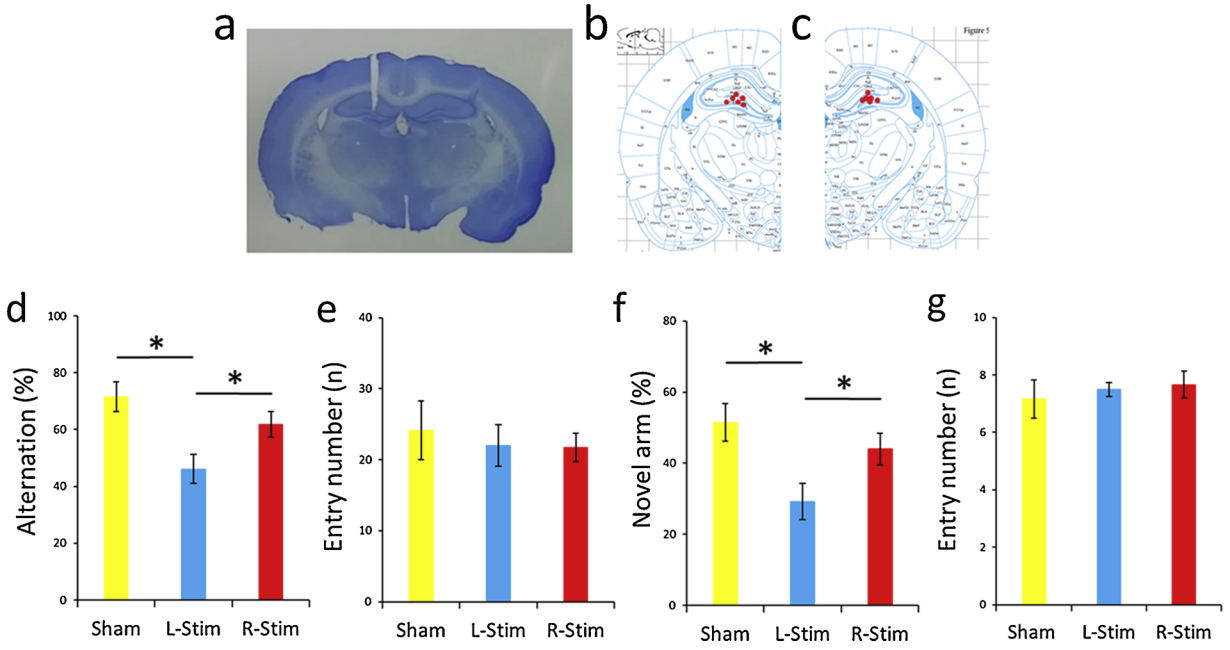

Fig. 4. Stimulation experiment for STM. (a–c) Insertion site of the stimulation electrode. Images of sections showing the insertion site for the (a) raw sample, (b) individual insertion sites of the left stimulation group (n = 6), and (c) individual insertion sites of the right stimulation group (n = 6). (d–f) The results of the STM tasks. (d) Alternation rate in the SAT. (e) Total entry number in the SAT. (f) Novel arm rate in the NPT. (g) Total entry number in the SAT. Yellow, blue, and red bars represent the Sham (n = 6), the left (L) stimulation (n = 6), and the right (R) stimulation (n = 6) groups, respectively. All measures are shown as means ± SEM and * indicates $P < 0.05$. STM, short-term memory; SAT, spontaneous alternation test; NPT, novel preference test.

significant effect for the novel arm rate ($F_{(2, 15)} = 5.60$, $P = 0.015$) (Fig. 1h). The post-hoc comparisons revealed that the right lesion group (n = 6) was significantly lower than that for the Sham group (n = 6) or for the left lesion group (n = 6) (P = 0.0033 and P = 0.0053, respectively). There was no significant difference between the Sham group and the left lesion group (P = 0.40). On the other hand, the one-way ANOVA showed no significant effect for the total entry number ($F_{(2, 15)} = 0.096$, $P = 0.91$) (Fig. 1i).

3.2.2. LTM in the lesion experiment

The OLT was used to measure LTM. The one-way ANOVA showed a significant effect for the DI ($F_{(2, 15)} = 3.81$, $P = 0.045$) (Fig. 2b). The post-hoc comparisons revealed that the left lesion group (n = 6) was significantly lower than that for the Sham group (n = 6) (P = 0.031). There was no significant difference between the Sham group and the right lesion group (P = 0.26), and between the left lesion group and the right lesion group (n = 6) (P = 0.080).

3.2.3. STM in the stimulation experiment

In the stimulation experiment, in the SAT, the one-way ANOVA showed a significant effect for the alternation rate ($F_{(2, 15)} = 8.07$, $P = 0.0042$) (Fig. 4d). The post-hoc comparisons revealed that the right lesion group (n = 6) was significantly lower than that for the Sham group (n = 6) or for the left lesion group (n = 6) (P = 0.0047 and P = 0.0042, respectively). There was no significant difference between the Sham group and the left lesion group (P = 0.052). On the other hand, the one-way ANOVA showed no significant effect for the total entry number ($F_{(2, 15)} = 0.25$, $P = 0.79$) (Fig. 4e). In the NPT, the one-way ANOVA showed a significant effect for the novel arm rate ($F_{(2, 15)} = 9.27$, $P = 0.0024$) (Fig. 4f). The post-hoc comparisons revealed that the right lesion group (n = 6) was significantly lower than that for the Sham group (n = 6) or for the left lesion group (n = 6) (P = 0.0033 and P = 0.0053, respectively). There was no significant difference between the Sham group and the left lesion group (P = 0.40). On the other hand, the one-way ANOVA showed no significant effect for the total entry number ($F_{(2, 15)} = 0.33$, $P = 0.72$) (Fig. 4g).

3.2.4. LTM in the stimulation experiment

In the OLT, the one-way ANOVA showed a significant effect for the DI ($F_{(2, 15)} = 6.17$, $P = 0.011$) (Fig. 5c). The post-hoc comparisons revealed that the left stimulation group (n = 6) was significantly lower than that for the Sham group (n = 6) or for the right stimulation group (n = 6) (P = 0.026 and P = 0.0076, respectively). There was no significant difference between the Sham group and the right stimulation group (P = 0.38).

4. Discussion

The purpose of the present study was to elucidate how the left and right hippocampi contribute to the formation of STM and LTM.

4.1. Left-right differential roles for STM

In the lesion experiment, only the right hippocampal lesion impaired both the alternation rate in the SAT (Fig. 1f) and the novel arm preference in the NPT (Fig. 1h). The lesion areas were not extended beyond the hippocampal structure (Fig. 1e). In addition, there was no significant difference in the number of neurons in the cortex located just above the dorsal hippocampus between the ipsi-lateral (hippocampal lesion side) and contra-lateral hemisphere (Fig. 1d). Considering the cortical involvement in the formation of both STM and LTM [22,23], it was necessary to confirm the cortical damage, but the present result shows that the lesion method we used had a specific effect on the hippocampal structure without affecting cortical neurons. Moreover, there was no significant difference in the number of entries in the SAT and in the NPT between the Sham group and left/right lesion groups (Fig. 1gh), this suggests that rats had no motor impairment by the hippocampal lesion. Therefore, these results indicate that the right hippocampus predominantly contributes to the formation of STM required for the present tasks. Our results differ from those of the results by Shipton et al. [16], which showed that unilateral optogenetic inactivation of both left and right mice CA3 alone during hippocampus-dependent STM tasks impairs the task performance, and suggests that

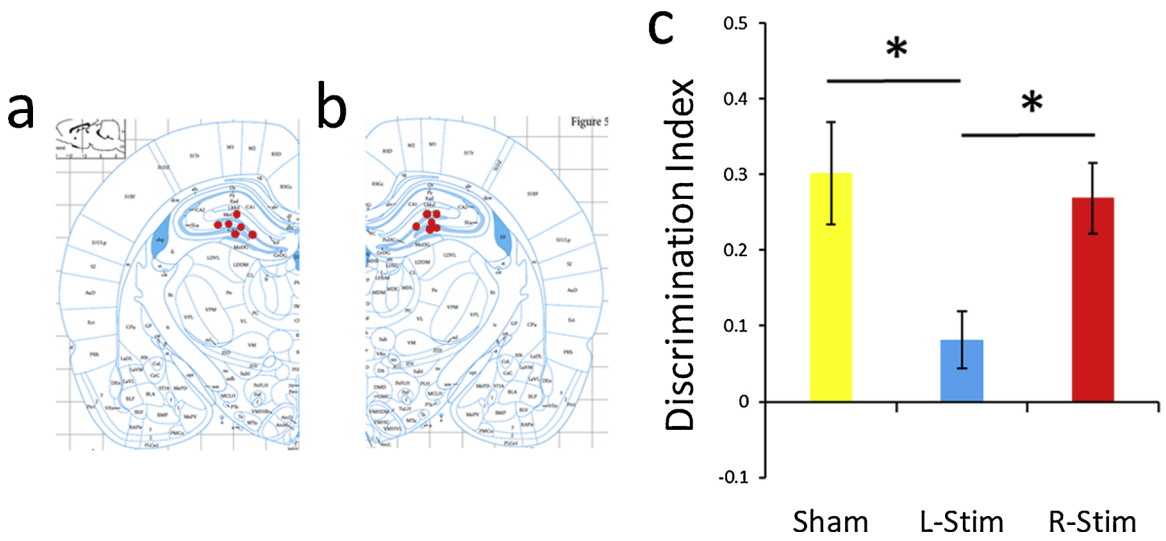

Fig. 5. Stimulation experiment for LTM. (a and b) Insertion site of the stimulation electrode. (a) Individual insertion sites of the left stimulation group (n = 6) and (b) those of the right stimulation group (n = 6). (c) The results of the LTM task. The DI in the OLT. Yellow, blue, and red bars represent the Sham (n = 6), the left (L) stimulation (n = 6), and the right (R) stimulation (n = 6) groups, respectively. All measures are shown as means ± SEM and * indicates P < 0.05. LTM, long-term memory; DI, discrimination index; OLT, object location test.

both the left and right hippocampi contribute to STM formation. Such different results might be due to the difference in animal species (rat vs. mouse), target brain region (whole hippocampus vs. CA3), and/or the difficulty of the tasks. On the other hand, in the stimulation experiment, the electrical stimulation of the left hippocampus before testing of the tasks impaired both the alternation rate in the SAT (Fig. 4d) and the novel arm preference in the NPT (Fig. 4f). The insertion sites of the electrode were properly placed in the intra-hippocampus (Fig. 4bc) and the stimulation induced an increase in the number of c-fos positive cells in all the hippocampal subregions (DG, CA3, and CA1) (Fig. 3c). Moreover, there was no significant difference in the number of entries in the SAT and in the NPT between the Sham group and left/right lesion groups (Fig. 4eg), this suggests that rats had no motor impairment by the hippocampal stimulation. Therefore, these results indicate that hyper-excitation of neuronal activity in the left hippocampus inhibited the formation of STM. Taken together, the results of our two experiments suggest that the right hippocampus has a facilitating role for the formation of STM, whereas the left hippocampus has a suppressive role for the formation of it. The left and right hippocampi may utilize the interhemispheric interaction via the hippocampal commissure and interact to excite or inhibit one another during STM formation.

4.2. Left-sided specialization for LTM

In the lesion experiment, only the left hippocampal lesion impaired the DI in the OLT (Fig. 2b). The lesion areas were not extended beyond the hippocampal structure (Fig. 2a). These results indicate that the left hippocampus predominantly contributes to the formation of LTM, agreed with the result of Shipton et al. [16]. Additionally, in the stimulation experiment, the electrical stimulation of the left hippocampus before testing of the tasks impaired the DI in the OLT (Fig. 5c). The insertion sites of the electrode were properly placed in the intra-hippocampus (Fig. 5ab). These results indicate that hyper-excitation of neuronal activity in the left hippocampus inhibited the formation of LTM. Taken together, the results of our two experiments suggest that unlike the results of the STM tasks, only one side (left) of the hippocampus is expected to contribute to LTM. This means that hemispheric interaction might be unnecessary for LTM formation. In addition, it is considered that a refined mechanism that requires an appropriate level of neural activity in LTM formation process. This may be because excessive synchronous firing of cell populations incorporates unnecessary information into the episode, thereby disrupting the accuracy of LTM.

Our results are consistent with Shipton et al. [13], but inconsistent with the previous studies showing that the right hippocampus contributes predominately to the LTM tasks, such as the Burns maze task [17] and the active avoidance task [19]. This contradiction may be due to the different types of reinforcer, i.e., the negative/avoiding vs. positive/approaching stimuli, such as Belcheva et al. (foot shock) [19] and Shinohara et al. (light exposure) [17] vs. Shipton et al. (food reward) [16] and Jordan et al. (novel object exploration) [15]. The serotonin involvement in the dorsal hippocampal asymmetry [19], the asymmetrical contribution of left/right ventral hippocampus to cope with anxiety [14], and the functional asymmetry in the dorsal hippocampus may depend on emotional types as well as the memory types (STM/LTM) and should be considered in the future research. The accumulation of further findings on left-right differences of hippocampal functions and interhemispheric interactions will contribute to clarifying the actual state of functional divisions and coordination between two hemispheres.

CRediT authorship contribution statement

Yukitoshi Sakaguchi: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Investigation, Funding acquisition. **Yoshio Sakurai:** Supervision, Writing - review & editing, Funding acquisition.

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