

Article

Disconnection between Rat's Left and Right Hemisphere Impairs Short-Term Memory but Not Long-Term Memory

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Abstract: Split-brain experiments, which have been actively conducted since the twentieth century, have provided a great deal of insight into functional asymmetry and inter-hemispheric interactions. However, how communication between the left and right hemispheres directly contributes to memory formation is still poorly understood. To address this issue, we cut the rat commissural fibers prior to performing behavioral tests, which consisted of two short-term and two long-term memory tasks. The result showed that cutting the commissural fibers impairs short-term memory but not long-term memory. This suggests that the left-right hemispheric interaction through the commissural fibers contributes to the appropriate formation of short-term memory, but not that of long-term memory. Our findings would help to elucidate dynamic memory formation between the two hemispheres and contribute to the development of therapeutics for some neurological diseases which cause a reduction in the inter-hemispheric interaction.



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Keywords: commissural fiber; hemispheric interaction; short-term memory; long-term memory; rat

1. Introduction

The so-called “split-brain” experiment, which mainly involves cutting the Corpus Callosum (CC) connecting the left and right hemisphere, has been actively conducted since the 1950s [1], starting with the interocular transfer experiment by Roger Sperry [2]. These studies revealed that commissural fibers such as the CC exist not only to support physical connection between hemispheres, but also for the transmission of information between hemispheres [1]. However, previous studies have focused only on functions underlying motion, language, and perceptual modality. Details of the role of inter-hemispheric interactions in other higher brain functions such as memory formation are still poorly understood.

Functional left-right hemispheric asymmetries in the human brain, such as left-sided language ability and right-sided spatial cognitive ability, are well-known [3]. However, this feature is not specific to humans. Many behavioral and neurological studies [4–8] have suggested the existence of left/right hemispheric differences in various animal species, including rodents [9–14]. In these studies, one of the brain regions that has been particularly investigated is the hippocampus, and so far, differences in the gene [10,15], molecular composition [16], and morphology [17,18] between the left and right rodent hippocampi have been revealed. Furthermore, the existence of functional left/right hemispheric differences have also been demonstrated in several animals. For example, the left and right avian hippocampi play different roles in spatial cognition [19]. In rodents, Shipton and his colleagues demonstrated that the optogenetic silencing of the left Cornu Ammonis 3 (CA3) alone impaired performance in a hippocampus-dependent long-term memory task, while the unilateral silencing of either the left or right CA3 caused short-term memory deficit in hippocampus-dependent tasks [12]. In addition, our previous study [13] and the study by Jordan et al. [9] confirmed differences in environment-dependent neural activity

between the left and right hippocampal structures (for a detailed review of other left-right differences in the hippocampus, see [20]). These findings indicate that there are some differences in the functions of the left and right hippocampi. However, it is still unclear whether the left and right hemisphere, including the functionally lateralized hippocampus, interact with each other to form memories.

To address this issue, we cut the rat commissural fibers, including hippocampal commissure (HC) that connects the left and right hippocampi, and examined how inter-hemispheric interaction contributes to the formation of short-term and long-term memories.

2. Materials and Methods

2.1. Animals

“Experimental subjects were male Wistar albino rats (total $n = 18$; Shimizu Laboratory Supplies, Kyoto, Japan) that were 11 weeks old at the time of 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 21:00 h. The rats were randomly assigned to the sham group and the Cut 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 (approval code: A21007)” [14].

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). The commissural fibers were cut by inserting the tip of a razor blade (LR03NB, FEATHER Co. LTD., Osaka, Japan) and making two reciprocations along the AP axis. For the sham group, the blade was inserted slightly above the commissural fibers (AP: -0.5 mm from bregma; ML: 0.0 mm from bregma; DV: -2.0 mm from dura) [21]. The blade was subsequently moved slowly to -5.0 mm AP and two reciprocations were made. For the cut group, the blade was inserted into the commissural fibers, including the HC (AP, -0.5 mm from bregma; ML, 0.0 mm from bregma; DV, -4.0 mm from dura). The blade was then moved as in the sham group. Hemostatic agents (Abiten, 103010265, ZERIA Pharmaceutical Co. LTD., Tokyo, Japan) were used during the cutting of the commissural fibers to prevent massive bleeding due to vascular cutting. All rats were allowed to recover for seven days and were handled for 5 min each day. All rats were housed individually to prevent injuries at the surgical site by aggressive behavior between cage mates.

2.3. Behavioral Test

All rats were tested in two short-term memory tasks and two long-term memory tasks. On the day of the behavioral test, the home cage was moved to the experimental room 2 h before the start of the test for habituation. All rats were tested using one task each day. All tests were counterbalanced.

2.3.1. Spontaneous Alternation Test (SAT)

The SAT is a test to measure short-term memory, and the ability to alternately enter the three arms of the Y-shaped apparatus in sequence indicates that the short-term memory ability is normal. In other words, it is necessary to temporarily retain which arm the individual is currently in and which arm it entered on the previous opportunity. In individuals with impaired short-term memory, this alternation rate is expected to be decreased.

“For this test, a Y-maze was used. It was made of transparent acrylic plates, and 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., Wood Dale, 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" [14].

2.3.2. Novel Preference Test (NPT)

The NPT is a test to measure short-term memory. After exploration in phase 1, in which one of the three arms of the Y-shaped apparatus is blocked, if the time spent in the novel arm is longer than the chance level in phase 2, in which all arms can be explored, it indicates that the short-term memory ability is normal. In individuals with impaired short-term memory, the time spent in the novel arm is expected to be decreased.

"For this test, 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" [14]. Behaviors were recorded using the camera, and the total number of arm entries and the percentage of time spent in the Novel arms were calculated by the software program.

2.3.3. Object Location Test (OLT)

The OLT is a test to measure long-term memory. In phase 1, the individual memorizes the positions of the two objects, and 24 h later in phase 2, the contact time to the object whose position has been changed is evaluated. A high rate of contact time to the changed object indicates that long-term memory is normal. In individuals with impaired long-term memory, the rate is expected to be decreased.

"For this test, a 45 cm × 60 cm × 45 cm box made of white Styrofoam boards was used. In order to allow the rats to determine which direction to take in the apparatus, a large square-shaped mark was displayed on one rectangular surface using a tape which was 5 cm in width, and a cross-shape mark was presented on the opposite rectangular surface. First, rats were allowed to explore the empty apparatus for two hours for habituation. The next day, the two rectangular parallelepiped blocks (5 cm × 5 cm × 10 cm) made of wood were placed 5 cm away from one plane. The two blocks were placed 25 cm apart from one another. Subsequently, rats were gently placed at the center of the apparatus, and they were allowed to explore for 10 min. 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 rats were allowed to explore the box again for three minutes. 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) was calculated" [14].

2.3.4. Plus-Maze Test (PMT)

The PMT is a test to measure long-term memory. The individual learns the position of the reward in the four arms of the cross-shaped apparatus for seven days. In individuals with impaired long-term memory, the rate is expected to be decreased.

For this test, the Plus-maze was used. It was made of transparent acrylic plates, and comprised of four 75 cm long, 10 cm wide, and 40 cm high arms. A plastic dish was placed at the end of each arm. First, rats were allowed to explore the empty apparatus for two hours for habituation. The next day, the “correct arm” was randomly assigned among the four arms, and one small pellet was placed in the small dish which was located in this arm. The rats were then gently placed at one of the three arms (Start arm), and they were allowed to explore until their four limbs entered into one of the arms. The Start arm was randomly assigned among the three arms for each trial. After entering any arm other than the correct arm, they were allowed to explore the arm until they reached the end of the arm and three seconds spent. However, after entering the correct arm, they were removed after having eaten the pellet. The rats were returned to their home cages and five minutes later the next trial was started. After each trial, the apparatus was carefully cleaned with a towel containing 70% ethanol. The Entry arms per trial were recorded for each rat. The test comprised 10 trials per day for seven days (day 1–7). On day 8, as a prove test, the rats were allowed to explore freely for 1 min in the apparatus where no reward was set up. The time spent in the correct arm on day 8 was calculated.

2.4. Histology

“The day after the completion of all behavioral tests, the rats were deeply anesthetized with an overdose of sodium pentobarbital (220 mg/kg, Kyoritsuiseiyaku Corporation, Tokyo, Japan) and were transcardiacally 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 (100 μ m) using a microslicer (DTK-3000, Dosaka EM Co. Ltd., Kyoto, Japan) and mounted the sections on slides. [14] Subsequently, cresyl violet solution was used as a background stain to identify the site where the plastic piece was inserted, using a microscope (Axioplan 2 Imaging, Carl Zeiss Microscopy, LLC, White Plains, NY, USA). Brain regions were identified according to the Rat Brain Atlas [21].

2.5. Data Analysis

Data analyses were performed with BellCurve for Excel (Social Survey Research Information Co. Ltd., Tokyo, Japan). Experimental data are shown as means \pm standard error of mean (SEM). Two-way analysis of variance (ANOVA), followed by post-hoc Tukey–Kramer method, was used to analyze the results of the PMT. All other results were analyzed using a one-way ANOVA test.

3. Results

3.1. Histology

The surgery was performed as shown in Figure 1a. No individual died due to excessive bleeding during the surgery. Histological procedures were performed after all behavioral tests. The area through which the blade passed is shown in Figure 1b. Observation of the brain sections confirmed that there was no damage in the sham group, and the commissural fibers were cut correctly in the cut group (Figure 1c). Three animals in the cut group were excluded from the statistics, because the cuts had reached the intra-hippocampus and a part of hippocampal structures were damaged.

3.2. Behavioral Test

The SAT (Figure 2a) and the NPT (Figure 2d) were used to measure short-term memory. In the SAT, the one-way ANOVA showed a significant effect for the alternation rate (both $n = 9$, $F_{(1,16)} = 10.31$, $P = 0.0054$), and the cut group was significantly lower than that for the sham group (Figure 2b). On the other hand, the one-way ANOVA showed no significant effect for the entry number (both $n = 9$, $F_{(1,16)} = 0.090$, $P = 0.77$) (Figure 2c). In the NPT, the one-way ANOVA showed a significant effect for the Novel arm rate (both

$n = 9$, $F_{(1,16)} = 15.62$, $P = 0.0017$), and the cut group was significantly lower than that for the sham group (Figure 2e). On the other hand, the one-way ANOVA showed no significant effect for the entry number (both $n = 9$, $F_{(1,16)} = 16.00$, $P = 0.42$) (Figure 2f).

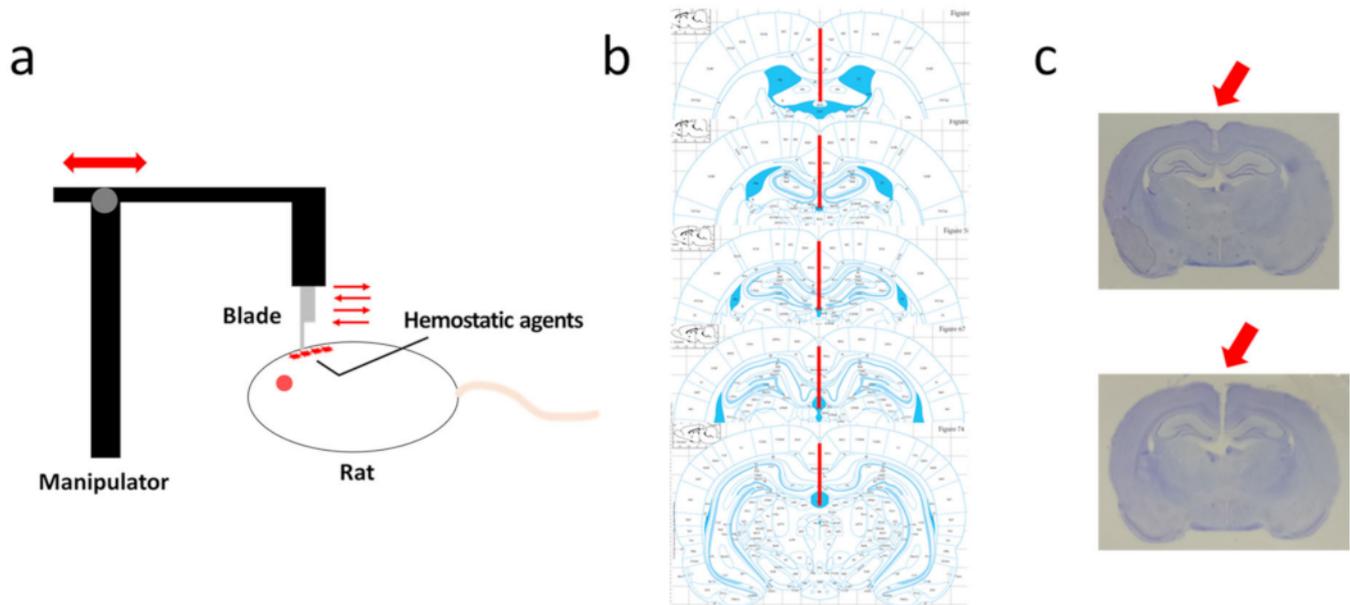


Figure 1. (a) Schematic diagram of the surgery. The blade was moved back and forth twice, and hemostatic agents were used to handling the bleeding. (b) The area through which the blade passed. The red line indicates the cut area. There was little or no difference in the size of the cut area among individuals. The brain atlas shows, from top to bottom, $AP = -1.08$, $AP = -2.04$, $AP = -3.00$, $AP = -4.08$, $AP = -5.04$. (c) Images of sections showing the cutting site (the red arrowhead) for the sham group (top) and the cut group (bottom).

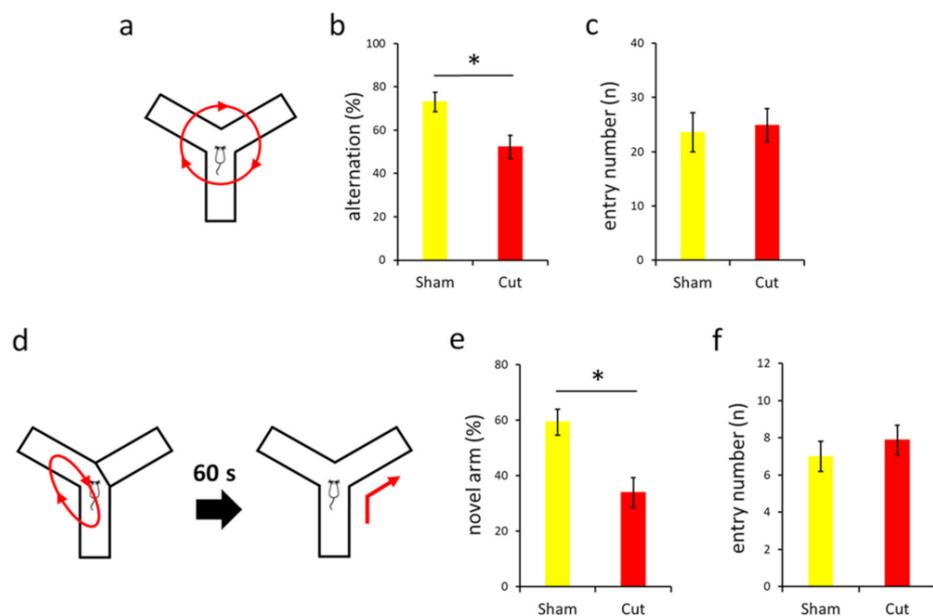


Figure 2. The results of short-term memory tasks. (a) Experimental apparatus used in the SAT. (b) Alternation rate in the SAT. (c) Total entry number in the SAT. (d) Experimental apparatus used in the NPT. (e) Novel arm rate in the NPT. (f) Total entry number in the SAT. Yellow and red bars represent the sham group ($n = 9$) and the Con group ($n = 9$), respectively. All measures are shown as means \pm SEM and * indicates $P < 0.05$. SAT, spontaneous alternation test; NPT, novel preference test.

The OLT (Figure 3a) and the PMT (Figure 3c) were used to measure long-term memory. In the OLT, the one-way ANOVA showed no significant effect for the Discrimination Index (both $n = 9$, $F_{(1,16)} = 0.040$, $P = 0.85$) (Figure 3b). In the PMT, the two-way and the one-way ANOVA showed no significant effect for both the accuracy on days 1–7 (both $n = 9$, main effect $F_{(1,112)} = 0.68$, $P = 0.41$; interaction $F_{(6,112)} = 0.68$, $P = 0.67$) (Figure 3d) and the correct arm rate on day 8 (both $n = 9$, $F_{(1,16)} = 0.46$, $P = 0.51$) (Figure 3e), respectively.

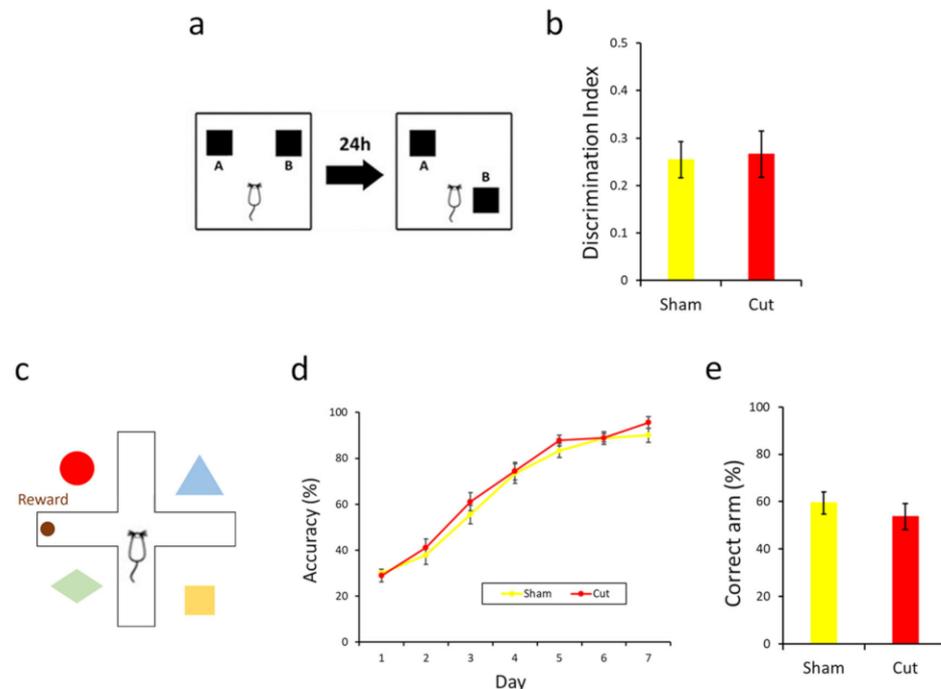


Figure 3. The results of long-term memory tasks. (a) Experimental apparatus used in the OLT. (b) Discrimination Index based on the novel location rate in the OLT. (c) Experimental apparatus used in the PMT. (d) Accuracy on days 1–7 in the PMT. (e) Correct arm rate on day 8 in the PMT. Yellow and red bars represent the sham group ($n = 9$) and the cut group ($n = 9$), respectively. All measures are shown as means \pm SEM. OLT, object location test; PMT, plus-maze test.

4. Discussion

The aim of this study was to investigate how the interaction between the left and right hemisphere contributes to the formation of short-term and long-term memories.

In the present study, the commissural fibers that connect the left and right hemisphere were cut. Thanks to the use of a very thin blade during the cutting operation, the histological results showed that the commissural fibers were cut accurately and that other areas, such as the cortex, were not damaged. Cutting of the commissural fibers affected the alternation rate in the SAT and the novel arm rate in the NPT (Figure 2b,e), but on the other hand, it did not affect the entry number in the SAT and the NPT (Figure 2c,f). These results indicate that only the function of memory could be properly assessed by the present tasks, because locomotion/exploratory behavior was not affected despite the impaired short-term memory performance. In summary, our results suggest that cutting of the commissural fibers impairs short-term memory.

On the other hand, cutting of the commissural fibers affected neither the Discrimination Index based on the novel location rate 24 h after sample presentation in the OLT nor the daily accuracy over a period of seven days in the PMT (Figure 3b,d). In addition, there was no significant difference in the prove test on day 8, and both groups memorized the correct arm sufficiently. In summary, our results suggest that cutting of the commissural fibers does not impair long-term memory.

Similar results from multiple tasks that are considered to require different cognitive skills, as in the present experiment, suggest that factors common to these tasks, that is, short-term memory and long-term memory, are likely to be the true factors influencing the results of the present experiment. Thus, the interaction between the left and right hemisphere may play an important role in the formation of short-term memory, and not long-term memory. According to the study by Shipton et al. [12], the silencing of excitatory neurons in the right or left CA3 using optogenetics impaired short-term memory, while the silencing of the left CA3, and not the right CA3, impaired long-term memory. Based on their findings and our experimental results, the left and right hemispheres interact with each other via the commissural fibers to control the formation of short-term memory; on the other hand, only the left hemisphere contributes to long-term memory formation.

Previous studies demonstrated that inter-hemispheric functional connectivity in the human brain is impaired by the complete section of CC [22], and split-brain patients have various dysfunctions [1]. Although these findings suggest the importance of inter-hemispheric communication and inter-hemispheric interactions via commissural fibers, such as CC, in various functions, the contribution of the commissural fibers to memory formation is poorly understood. The present study might help to improve our understanding of the role of the commissural fibers in memory formation.

In the rodent brain, many brain regions are arranged next to the other in the left and right hemisphere, and most of these regions communicate mainly through the anterior phalanx and CC. In the hippocampus, left/right CA3 communication occurs mainly through the HC [23]. Therefore, the results we obtained in this study may represent the result of the inhibition of the interaction between the left and right hippocampi via the HC, rather than the result of the inhibition of the hemispheric interaction by the disconnection of the entire commissural fibers. However, as a limitation, it is not possible to determine from the results which of brain regions affected the behavior, because several other regions such as the prefrontal cortex may be involved in memory formation in addition to the hippocampus. The results show only that “interaction between the left and right hemisphere” is involved in short-term memory.

It would be better if only the HC could be cut, but this has some methodological difficulties. (1) In rats, it is difficult to operate on the HC, which is located under the CC, without damaging the CC at all. (2) When cutting the commissural fibers with a blade, injuring the large blood vessel that runs through the midline is inevitable, causing fatal hemorrhage, and considerable training is required just to cut both the CC and HC as in this case. For these reasons, physically cutting only the HC is nearly impossible in rats. One alternative would be to use a species that is genetically deficient in the commissural fibers, such as the BTBR mice [24,25]. However, this approach might be inappropriate because it does not exclude the possibility of compensation by other brain regions or neural circuits, and it would need to be performed in wild-type animals. Future studies are expected to experiment with methods that do not damage CC and blood vessels, for example, HC-specific photoinhibition using optogenetics. Furthermore, it is still unclear at which point in time the inter-hemispheric interaction contributes to memory acquisition, consolidation, and recall. It may be also possible that there are some differences in the mechanisms of hemispheric interaction in the memory formation process between the two long-term memory tests we used in this study, targeted recall after 24 h (OLT) and learning over seven consecutive days (PMT). Nevertheless, the results of this study may serve as a roadmap for the direction of such future research.

Therefore, considering the results of the present study, the next step in future research should be to solve these problems with more advanced experimental methods to selectively excite or inhibit interaction between the left and right hippocampi. In addition, the actual manner of the inter-hemispheric communication in various brain regions should be clarified in the future. As an alternative perspective, in the present study, the experiments were conducted with all subjects uniformly being male Wistar rats in order to avoid the influence of other factors, such as estrogen, which has been reported to affect memory formation in

the hippocampus [26]. It may need to be generalized by experiments using female rats or subjects from other species. In addition, although the rats used in this study were housed alone after surgery, effects on memory have been reported to be found in rats housed singly compared to those housed in groups [27], and this point may need to be examined in the future.

These studies will contribute to the elucidation of the fundamental cause of psychiatric and developmental disorders that show inter-hemispheric [28,29] or long-distance inter-regional loss of connectivity [30] and partial volume loss in the corpus callosum [31], and to the development of treatments for these disorders.

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Informed Consent Statement: Not applicable.

Data Availability Statement: Publicly available datasets were analyzed in this study. This data can be found here: <https://github.com/YukitoshiSakaguchi/symmetry-1359137>.

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