

## Article

# Paradoxical Enhancement of Spatial Learning Induced by Right Hippocampal Lesion in Rats

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**Abstract:** The left–right hemispheric differences in some brain functions are well known in humans. Among them, savant syndrome has unique features, such as exceptional abilities in vision, memory, computation, and music, despite brain abnormalities. In cases of acquired savant and transient savant, brain damage or inhibition is often seen in the left hemisphere, suggesting a link between left hemispheric dysfunction and these talents. On the other hand, some functional left–right differences have been reported in rodent brains, and therefore, unilateral damage in rodents may also result in savant-like enhancements. In the present study, we examined the effects of hippocampal damage on spatial learning in rats with left, right, or bilateral hippocampal lesion. The results showed that learning performance was impaired in the bilateral lesion group, and there was no significant difference in the left lesion group, while performance was enhanced in the right lesion group. These results suggest that damage to the right hippocampus in rats may lead to savant-like enhancement in learning and memory. The construction of the savant model through these results will contribute to the neuroscientific elucidation of the paradoxical phenomenon observed in savants, that some abilities are enhanced despite their brain dysfunction.



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**Keywords:** spatial learning; hippocampus; rat; savant syndrome; hemispheric asymmetry

## 1. Introduction

Savant syndrome can describe a person who has a serious brain disorder but also has exceptional talent in functions such as vision, memory, computational tasks, and music [1–7]. For example, some people with savant syndrome have the ability to calculate the calendar to find the day of the week for a date tens of thousands of years in the future, some have the ability of eidetic imagery to remember the contents of thousands of books word for word accurately, and others have high spatial memory to remember a route they took once, even if it was a long time ago [8].

It is known that savants with such characteristics exist to a certain extent mainly among autistic people, comprising about 10% [7] or 1% [9] (autistic savant). Other types of savant have been reported, such as acquired savant, in which an ability is acquired through an accident or disease [6,10–13], and transient savant, in which a similar ability is demonstrated by temporarily suppressing a certain brain region using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) [14–16]. Importantly, a common feature of brain function in all of these savants is asymmetry between the left and right hemispheres, with left brain dysfunction together with right brain compensation [1,6,8,14,17,18]. For example, anatomical and functional hemispheric asymmetries and associated left hemispheric functional inhibition and right hemispheric functional enhancement have been frequently reported in autistic persons [19–28]. Frontotemporal dementia, in an acquired savant, causes atrophy or hypoperfusion of the left frontal lobe and anterior part of the left temporal lobe [29]. An American boy named Orlando Serrell

was able to perform calendar calculations after an accident damaged his left frontotemporal lobe [8,13]. In transient savants, TMS-induced functional inhibition of the left frontotemporal lobe leads to improved performance on a visual quantity estimation task [14]. In addition, functional inhibition of the left anterior temporal lobe and functional activation of the right anterior temporal lobe using tDCS showed visual memory enhancement [15]. Snyder et al. concluded that this savant-like enhancement was caused by a paradoxical hyperfunction of the right parietal lobe caused by inhibition of the left anterior temporal lobe [14]. In fact, it has been reported that the two hemispheres are usually well organized with an interhemispheric inhibition mechanism, in which the hemispheres send inhibitory signals to each other's contralateral hemisphere [30–32]. Kawamura et al. proposed the “Oshikuramanju hypothesis” (the term “oshikuramanju” in Japanese means “the way two persons try to expand their territory by pushing each other”) as the cause of savant syndrome, based on the observation that language functions in the left hemisphere compete with visuospatial functions in the right hemisphere [4]. The left temporal and frontal lobes in particular may be candidates for the mechanisms that underlie the exceptional functions of savants.

On the other hand, behavioral and neurological evidence of left–right asymmetry has been confirmed in a variety of non-human animal species [33–40]. Left–right differences have been investigated particularly intensively in the rodent brain, and the existence of anatomical and functional asymmetries in several brain regions has been revealed. One of the most repeatedly reported brain regions is the hippocampus, which is located in the temporal lobe and involved in learning and memory [41]. For example, asymmetrical differences in the gene level [42,43], molecular level [44], morphology [45–51], and cell numbers [52,53] between the left and right rodent hippocampi have been observed. In addition, functional left–right hemispheric asymmetries have also been revealed [54–62]. In rodents, in our previous work, we reported that lesions of the rat right hippocampus impaired short-term memory, while lesions of the left hippocampus impaired long-term memory [55]. We also reported results indicating that interhemispheric connections are necessary in short-term memory, but not in long-term memory, suggesting the existence of interhemispheric interactions [63]. Furthermore, according to the elegant experimental results by Shipton et al., “the optogenetic silencing of the left Cornu Ammonis 3 (CA3) alone impaired performance in the 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 [58,64]” [63]. These results were replicated in their follow-up studies [59].

These findings, taken together, suggest that similar neural mechanisms and enhanced memory function in the temporal lobes of the brains of people with savant syndrome may also be found in the hippocampus of rodents. However, although the effects of unilateral hemispheric dysfunction on behavior have been demonstrated, it remains to be elucidated whether or not such functional enhancement is also observed in the rodent brain, as in savant syndrome. Therefore, the causal relationship between unilateral hippocampal inhibition and enhanced memory and learning remains unclear.

To address this issue, in the present study, we investigated the changes in spatial memory learning induced by unilateral hippocampal lesions.

## 2. Materials and Methods

### 2.1. Animals

The experimental subjects were male Wistar albino rats (total  $n = 40$ ; 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 20:00 h. The rats were randomly assigned to the sham group, the right lesion group, the left lesion group, and the bilateral lesion 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) [63].

## 2.2. Surgery

All surgical procedures were performed based on our previous study [55]. 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 groups (for both the 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  $\mu$ m diameter, UB-9007, UNIQUE MEDICAL Co., Ltd., Tokyo, Japan) [55]. For lesion groups, the electrode was inserted into the right or left or bilateral dorsal hippocampus (DH) ((1) AP,  $-3.0$  mm from bregma; ML,  $\pm 2.0$  mm from bregma; DV,  $-3.0$  mm from dura; (2) AP,  $-4.0$  mm; ML,  $\pm 3.0$  mm; and DV,  $-3.0$  mm; (3) AP,  $-5.0$  mm; ML,  $\pm 4.0$  mm; and DV,  $-3.0$  mm). In the bilateral lesion group, current was passed to both sides of the DH (1)~(3), and in the left and right lesion groups, current was passed to only one side of the DH (1)~(3). Brain regions were identified according to the Rat Brain Atlas [65]. For sham lesions, the electrode was lowered to the same coordinates, but no current was passed. All rats were allowed to recover for 7 days and were handled for 5 min each day. They were housed individually to prevent injuries at the surgical site by aggressive behavior between cage mates [63].

## 2.3. Behavioral Test

On the day of the behavioral test, the home cage was moved to the experimental room 1 h before the start of the test for habituation.

### 2.3.1. Measurement of the Turning Direction Bias

To confirm that unilateral hippocampal lesions did not affect the turning direction in the apparatus, we conducted a measurement of the turning bias.

For this test, the T-maze was used as the experimental apparatus. It was made of transparent acrylic plates and comprised three arms that were each 75 cm long, 10 cm wide, and 40 cm high [63]. Prior to this test, habituation was conducted for 30 min per day for 2 consecutive days. On the day of the test, rats were gently placed at the tip of the start arm (the stem arm of the T-shape). The rats were free to select and enter either the left or right arm, and after reaching the tip of the selected arm, they were returned to their home cage. If the rat did not make a choice within 1 min, the trial was not recorded. This task was performed for 15 trials, every 5 min, for 2 consecutive days. In total, each rat was counted for 30 entries to the left or right.

### 2.3.2. Plus-Maze Test (PMT)

The PMT is a test to measure spatial learning and memory. The rats learn the position of the reward in the four arms of the cross-shaped apparatus for 7 consecutive days. In rats with impaired learning, the accuracy is expected to be decreased. All procedures in this experiment were performed based on our previous study [63].

For this test, the plus maze was used as the experimental apparatus. It was made of transparent acrylic plates and comprised 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 2 h for habituation [63]. The second day, the "correct" arm was randomly assigned among all arms, and a pellet as the reward was placed in the small dish that was located in this arm. The rats were then gently placed at one of the three other arms (the "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 5 min later, the next trial was started. After each trial, the apparatus was carefully cleaned with a towel soaked in 70% ethanol. Behaviors were recorded using a camera (BSW32KM03SV, Buffalo INC., Aichi, Japan) mounted directly above the apparatus, and the total numbers 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) [55]. Rats were considered to have entered an arm when all four of the animal's paws were located in that arm. The Entry arms per trial were recorded for each rat. The test comprised 10 trials per day for 7 days (Days 1–7). On Day 8, as a proving 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 was calculated on Day 8 [63].

#### 2.4. Histology

Histological procedures were performed based on our previous study [63]. The day after the completion of all behavioral tests, the rats were deeply anesthetized with an overdose of sodium pentobarbital (220 mg/kg, Kyoritsu-seiyaku Corporation, Tokyo, Japan) and were transcardially 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  $\mu$ m) using a microslicer (DTK-3000, Dosaka EM Co. Ltd., Kyoto, Japan) and mounted the sections on slides. Subsequently, cresyl violet solution was used as a background stain to identify the lesion area, using a microscope (Axioplan 2 Imaging, Carl Zeiss Microscopy, LLC, White Plains, NY, USA). Brain regions were identified according to the Rat Brain Atlas [63,65].

#### 2.5. Data Analysis

Data analyses were performed using 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) was used to analyze the results of the PMT on Days 1–7 [63]. When an interaction in two factors, Condition (groups) and Day, was detected, the simple main effect test, followed by the post hoc Tukey method, was conducted as a sub-test. The simple main effect test was used to perform multiple comparisons on one factor independent of the presence or absence of any interaction between the two factors. All other results were analyzed using one-way ANOVA, followed by the post hoc Tukey–Kramer method.

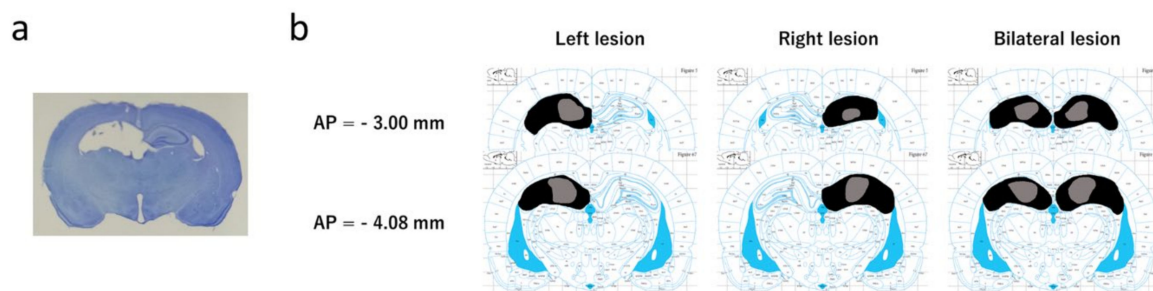
### 3. Results

#### 3.1. Histology

All surgeries were completed without any problems. None of the individuals died during the surgery or the recovery period. Histological procedures were performed after all behavioral tests. Figure 1a shows a raw sample of an electrical lesion. Figure 1b indicates the lesion areas (minimum lesion areas, gray color; maximum lesion areas, black color) of the left, right, and bilateral lesion groups ( $n = 10$  in each group). The extent of the lesion is shown with reference to the horizontal sections found in the Rat Brain Atlas [65]. The sham lesion group had little-to-no damage in hippocampal structures.

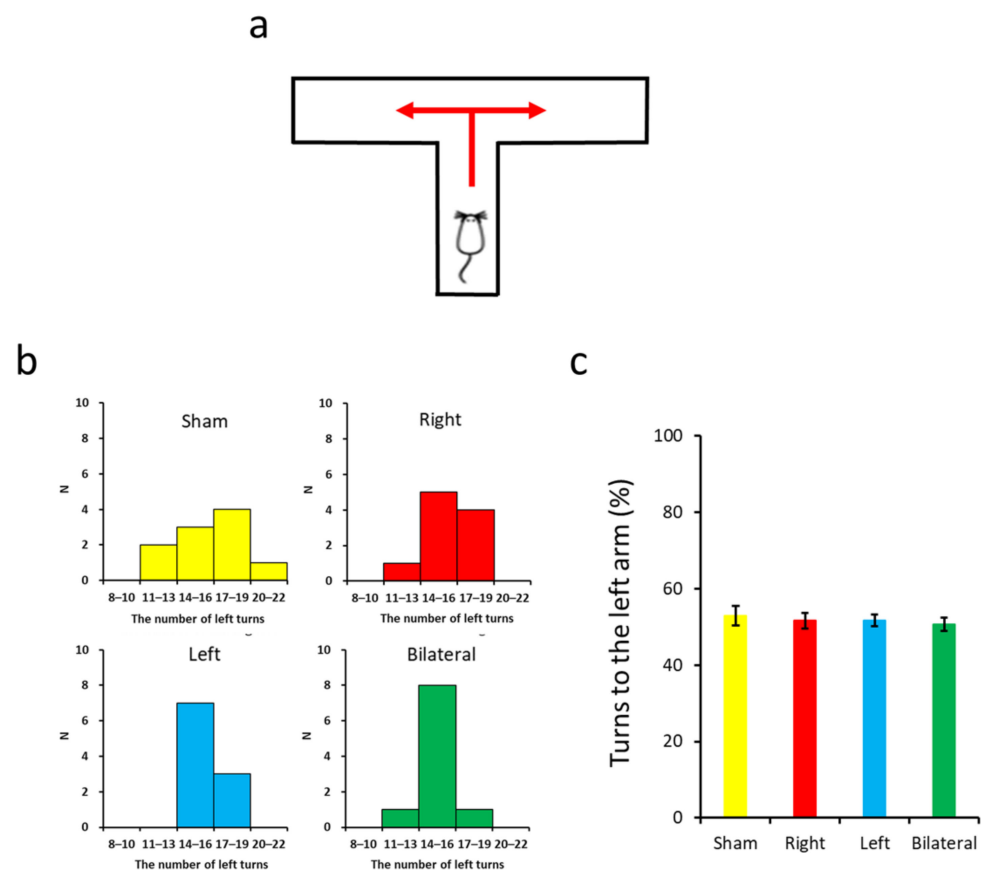
#### 3.2. Behavioral Tests

To determine whether lesions on one or both sides of the hippocampus affected the direction of turning, we measured the turning direction bias (Figure 2a).



**Figure 1.** Images of sections showing the lesion sites for the (a) raw sample, and (b) maximum (black) and minimum (gray) lesion areas of the left, right, and bilateral lesion groups (all  $n = 10$ ; AP =  $-3.00$  mm and AP =  $-4.08$  mm sections based on the Rat Brain Atlas [65]).

Figure 2b,c shows a histogram of the turning direction for each group (the number of left turns out of 30 trials) and the percentage for each group, respectively. The one-way ANOVA showed no significant effect on left and right turning directions in all groups (all  $n = 10$ ,  $F_{(3, 36)} = 0.24$ ,  $p = 0.86$ ) (Figure 2c).

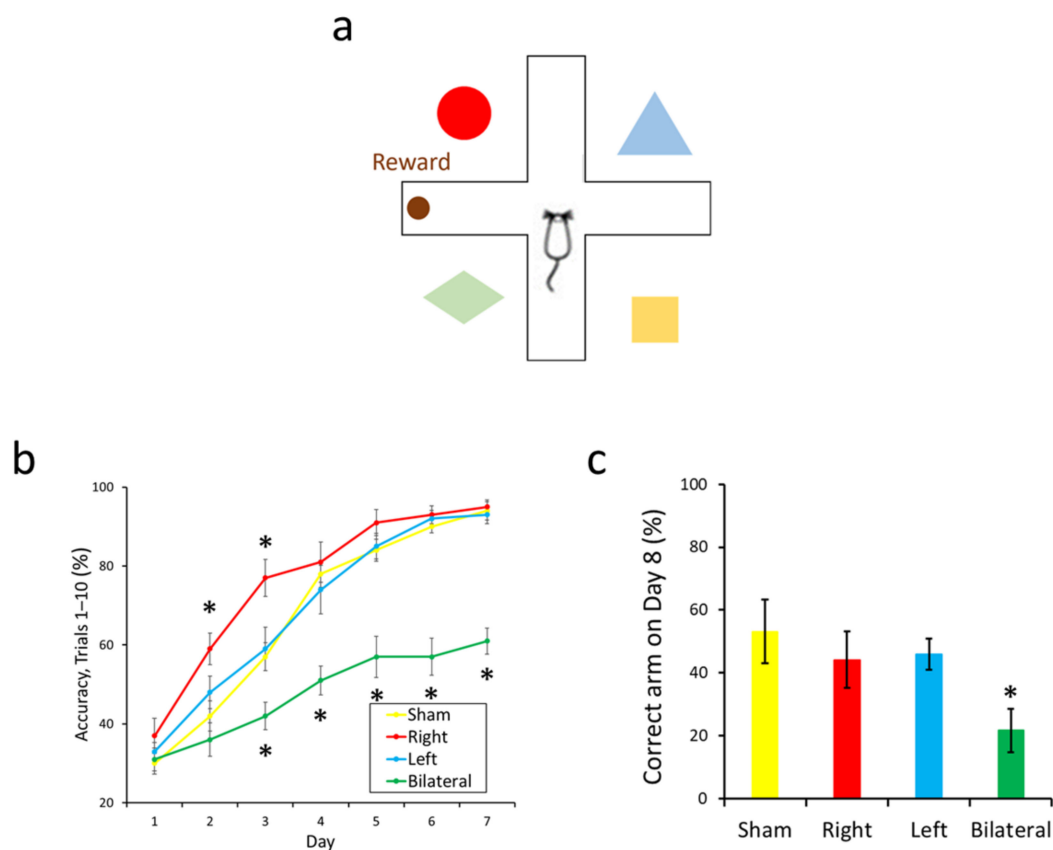


**Figure 2.** The results of measurement of the turning direction bias. (a) Experimental design used in this test. (b) The histogram of the turning direction for each group (30 trials in total for each individual). “N” indicates the number of individuals. (c) Turning rate to the left arm for each group. Yellow, red, blue, and green bars represent the sham group ( $n = 10$ ), the right lesion group ( $n = 10$ ), the left lesion group ( $n = 10$ ), and the bilateral lesion group ( $n = 10$ ), respectively. All measures are shown as means  $\pm$  SEM. Statistical analysis revealed no significant differences among the groups.

The PMT was used to measure learning and memory. Figure 3a shows the experimental design. A reward was placed in one of the four arms, and the rat learned the correct arm by following the locations of landmarks placed around the apparatus.

The two-way ANOVA showed a significant effect for the accuracy on Days 1–7 (all  $n = 10$ , Trials 1–10, main effect Condition  $F_{(3, 252)} = 83.06$ ,  $p < 0.001$ ; main effect Day  $F_{(6, 252)} = 129.81$ ,  $p < 0.001$ ; interaction Condition–Day  $F_{(18, 252)} = 3.59$ ,  $p < 0.001$ ). The simple main effect test showed a significant effect on Days 2–7 (Day 1  $F_{(3, 252)} = 0.77$ ,  $p = 0.51$ ; Day 2  $F_{(3, 252)} = 7.73$ ,  $p < 0.001$ ; Day 3  $F_{(3, 252)} = 16.52$ ,  $p < 0.001$ ; Day 4  $F_{(3, 252)} = 14.94$ ,  $p < 0.001$ ; Day 5  $F_{(3, 252)} = 18.44$ ,  $p < 0.001$ ; Day 6  $F_{(3, 252)} = 24.26$ ,  $p < 0.001$ ; Day 7  $F_{(3, 252)} = 21.92$ ,  $p < 0.001$ ). The post hoc comparison revealed significantly higher accuracy in the right lesion group compared to the sham group on Days 2 and 3, and significantly lower accuracy in the bilateral lesion group on Days 3 to 7. There was no significant difference in the left lesion group compared to the sham group (Figure 3b). The statistics and  $p$  values for these tests are summarized in Table 1.

The one-way ANOVA showed a significant effect for the rate of the time spent in the correct arm on Day 8 (all  $n = 10$ ,  $F_{(3, 36)} = 3.23$ ,  $p = 0.033$ ). The post hoc comparison revealed that there was a significantly lower rate in the bilateral lesion group compared to the sham group ( $p = 0.027$ ). There was no significant difference in the left and right lesion groups compared to the sham group (right lesion group,  $p = 0.83$ ; left lesion group,  $p = 0.91$ ) (Figure 3c).



**Figure 3.** The results of the plus-maze test. (a) Experimental design used in this test. (b) Percentage accuracy (the rate of selection of the correct arm during 10 trials) on Days 1–7. All 10 trials per day were combined. (c) Correct arm rate on Day 8 in the PMT. Yellow, red, blue, and green bars represent the sham group ( $n = 10$ ), the right lesion group ( $n = 10$ ), the left lesion group ( $n = 10$ ), and the bilateral lesion group ( $n = 10$ ), respectively. All measures are shown as means  $\pm$  SEM and \* indicates  $p < 0.05$ .

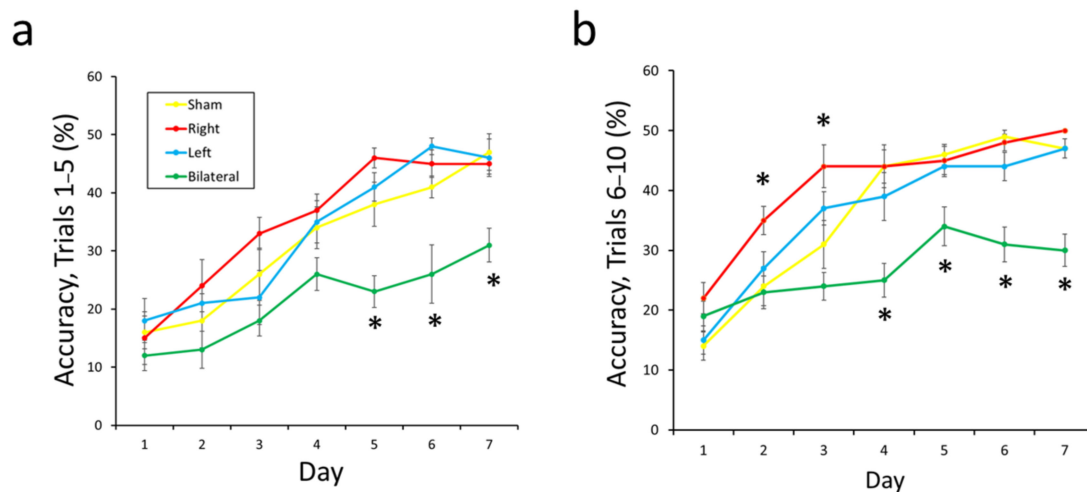
**Table 1.** Results of multiple comparisons for the accuracy (the rate of selection of the correct arm during 10 trials) on Days 1–7 (Trials 1–10).

		Statistics	<i>p</i> -Value	<i>p</i> < 0.05
Day 1	Sham–Right	1.40	0.51	
	Sham–Left	0.60	0.93	
	Sham–Bilateral	0.20	0.99	
Day 2	Sham–Right	3.41	0.0042	*
	Sham–Left	1.20	0.63	
	Sham–Bilateral	1.20	0.63	
Day 3	Sham–Right	4.01	<0.001	*
	Sham–Left	0.40	0.98	
	Sham–Bilateral	3.01	0.015	*
Day 4	Sham–Right	0.60	0.93	
	Sham–Left	0.80	0.85	
	Sham–Bilateral	5.41	<0.001	*
Day 5	Sham–Right	1.40	0.51	
	Sham–Left	0.20	0.99	
	Sham–Bilateral	5.41	<0.001	*
Day 6	Sham–Right	0.60	0.93	
	Sham–Left	0.40	0.98	
	Sham–Bilateral	6.61	<0.001	*
Day 7	Sham–Right	0.20	0.99	
	Sham–Left	0.20	0.99	
	Sham–Bilateral	6.61	<0.001	*

Data analyses were performed by the simple main effect test, followed by the post hoc Tukey method. \* indicates  $p < 0.05$ .

The two-way ANOVA showed a significant effect for the accuracy on Days 1–7 (all  $n = 10$ , Trials 1–5, main effect Condition  $F_{(3, 252)} = 26.47$ ,  $p < 0.001$ ; main effect Day  $F_{(6, 252)} = 45.56$ ,  $p < 0.001$ ; interaction Condition–Day  $F_{(18, 252)} = 1.38$ ,  $p = 0.14$ ). The simple main effect test showed a significant effect on Days 2–7 (Day 1  $F_{(3, 252)} = 0.63$ ,  $p = 0.59$ ; Day 2  $F_{(3, 252)} = 2.23$ ,  $p = 0.085$ ; Day 3  $F_{(3, 252)} = 4.15$ ,  $p = 0.0068$ ; Day 4  $F_{(3, 252)} = 2.37$ ,  $p = 0.071$ ; Day 5  $F_{(3, 252)} = 9.94$ ,  $p < 0.001$ ; Day 6  $F_{(3, 252)} = 9.67$ ,  $p < 0.001$ ; Day 7  $F_{(3, 252)} = 5.77$ ,  $p < 0.001$ ). The post hoc comparison revealed significantly lower accuracy in the bilateral lesion group on Days 5 to 7. There was no significant difference in the right and left lesion groups compared to the sham group (Figure 4a). The statistics and  $p$  values for these tests are summarized in Table 2.

The two-way ANOVA showed a significant effect for the accuracy on Days 1–7 (all  $n = 10$ , Trials 6–10, main effect Condition  $F_{(3, 252)} = 60.78$ ,  $p < 0.001$ ; main effect Day  $F_{(6, 252)} = 42.20$ ,  $p < 0.001$ ; interaction Condition–Day  $F_{(18, 252)} = 3.16$ ,  $p < 0.001$ ). The simple main effect test showed a significant effect on Days 2–7 (Day 1  $F_{(3, 252)} = 2.20$ ,  $p = 0.088$ ; Day 2  $F_{(3, 252)} = 4.77$ ,  $p = 0.0030$ ; Day 3  $F_{(3, 252)} = 11.72$ ,  $p < 0.001$ ; Day 4  $F_{(3, 252)} = 13.01$ ,  $p < 0.001$ ; Day 5  $F_{(3, 252)} = 4.99$ ,  $p = 0.0022$ ; Day 6  $F_{(3, 252)} = 11.08$ ,  $p < 0.001$ ; Day 7  $F_{(3, 252)} = 13.39$ ,  $p < 0.001$ ). The post hoc comparison revealed significantly higher accuracy in the right lesion group compared to the sham group on Days 2 and 3, and significantly lower accuracy in the bilateral lesion group on Days 4 to 7. There was no significant difference in the left lesion group compared to the sham group (Figure 4b). The statistics and  $p$  values for these tests are summarized in Table 3.



**Figure 4.** The results of the plus-maze test. (a) Percentage accuracy (the rate of selection of the correct arm during 5 trials) on Days 1–7; 5 trials in the first half of 10 trials. (b) Percentage accuracy on Days 1–7; 5 trials in the second half of 10 trials. Yellow, red, blue, and green bars represent the sham group ( $n = 10$ ), the right lesion group ( $n = 10$ ), the left lesion group ( $n = 10$ ), and the bilateral lesion group ( $n = 10$ ), respectively. All measures are shown as means  $\pm$  SEM and \* indicates  $p < 0.05$ .

**Table 2.** Results of multiple comparisons for the accuracy (the rate of selection of the correct arm during 5 trials) on Days 1–7 (Trials 1–5).

		Statistics	$p$ -Value	$p < 0.05$
Day 1	Sham–Right	0.23	0.99	
	Sham–Left	0.45	0.97	
	Sham–Bilateral	0.90	0.81	
Day 2	Sham–Right	1.35	0.53	
	Sham–Left	0.68	0.91	
	Sham–Bilateral	1.13	0.67	
Day 3	Sham–Right	1.58	0.39	
	Sham–Left	0.90	0.81	
	Sham–Bilateral	1.80	0.28	
Day 4	Sham–Right	0.68	0.91	
	Sham–Left	0.23	0.99	
	Sham–Bilateral	1.80	0.28	
Day 5	Sham–Right	1.80	0.28	
	Sham–Left	0.68	0.91	
	Sham–Bilateral	3.38	0.0047	*
Day 6	Sham–Right	0.90	0.81	
	Sham–Left	1.58	0.39	
	Sham–Bilateral	3.38	0.0046	*
Day 7	Sham–Right	0.45	0.97	
	Sham–Left	0.23	0.99	
	Sham–Bilateral	3.60	0.0021	*

Data analyses were performed by the simple main effect test, followed by the post hoc Tukey method. \* indicates  $p < 0.05$ .



**Table 3.** Results of multiple comparisons for the accuracy (the rate of selection of the correct arm during 5 trials) on Days 1–7 (Trials 6–10).

		Statistics	<i>p</i> -Value	<i>p</i> < 0.05
Day 1	Sham–Right	2.27	0.11	
	Sham–Left	0.28	0.99	
	Sham–Bilateral	1.42	0.49	
Day 2	Sham–Right	3.12	0.011	*
	Sham–Left	0.85	0.83	
	Sham–Bilateral	0.28	0.99	
Day 3	Sham–Right	3.69	0.0015	*
	Sham–Left	1.70	0.32	
	Sham–Bilateral	1.99	0.19	
Day 4	Sham–Right	0.00	1.00	
	Sham–Left	1.42	0.49	
	Sham–Bilateral	5.40	<0.001	*
Day 5	Sham–Right	0.28	0.99	
	Sham–Left	0.57	0.94	
	Sham–Bilateral	3.41	0.0042	*
Day 6	Sham–Right	0.28	0.99	
	Sham–Left	1.42	0.49	
	Sham–Bilateral	5.11	<0.001	*
Day 7	Sham–Right	0.85	0.83	
	Sham–Left	0.00	1.00	
	Sham–Bilateral	4.83	<0.001	*

Data analyses were performed by the simple main effect test, followed by the post hoc Tukey method. \* indicates  $p < 0.05$ .

#### 4. Discussion

The aim of this study was to investigate whether left or right unilateral hippocampal damage can lead to the development of savant-like exceptional learning and memory abilities.

The PMT, which requires spatial learning memory, was used as the behavioral test in this study because there are many reports of findings in savant syndrome related to spatial memory.

In the PMT, turning behavior is required in selecting one correct arm from four arms arranged at 90-degree intervals. In this process, it was necessary to avoid the appearance of bias in the direction of turning. In fact, it is known that some brain regions involved in locomotion—such as the striatum, for example—show biases in the direction of turning and rotation due to left–right functional differences [66,67]. It has also been reported that turning behavior in rats is modulated by early life stress [68]. Therefore, before starting this test, we first checked whether the unilateral hippocampal lesions affected the turning direction. We did not detect any left–right bias at the population level in all the lesion groups compared to the control group, and the score of each group was about 50% vs. 50% for left and right (Figure 2c). Therefore, the results indicate that there was no left–right bias in the direction of turning in the condition of the rats used in this experiment.

Next, in the PMT, the bilateral lesion group had significantly lower learning performance for 7 days and significantly lower rate of time spent in the correct arm on Day 8 compared to the control group (Figure 3b,c). The histological results show that all groups were accurately damaged in the hippocampal structure (Figure 1b). These results provide evidence that the behavioral test used in this study was hippocampal-dependent, indicating that bilateral hippocampal damage impairs spatial learning. For unilateral hippocampal damage, there was no significant difference in the left lesion group, while there was a significant enhancement in the right lesion group (Figure 3b,c). This is a surprising result in the following points: (1) “left” hippocampal damage did not reduce learning performance; (2) unilateral hippocampal damage “enhanced” performance in the PMT,

contrary to general intuition; and (3) left hemispheric damage has been reported to enhance memory in several human savants, but in the present results, this was caused by “right” hemispheric damage.

Regarding (1), it is a controversial result considering that the results of a similar behavioral test by Shipton et al. [58,59] showed that optogenetic inhibition of the left CA3 resulted in lower performance. (It should be noted, however, that there is some difference in the mechanism between the suppression of neural activity by optogenetics and the lesions we used here.) In addition, our previous study showed that left hippocampal lesion impaired long-term memory. On the other hand, however, there is another report that normal spatial learning can be executed as long as the unilateral hippocampus and the ipsilateral medial prefrontal cortex are intact [69,70]; that is, the differences in these results may be due to differences in the types of behavioral tests, the difficulty of the tests, and the number of trials. Regarding (2), it is surprising that enhancement after unilateral damage similar to that in humans was observed in rodents. Importantly, however, the results of a similar behavioral study conducted by El-gaby and colleagues [59], in which the mouse right CA3 was suppressed, showed surprisingly higher values than in the control group (see Figure 4c in the paper [59]). Although the extent to which our results follow the same neural basis as the savant mechanism will require further investigation, it is important to note that at least one commonality was found: unilateral damage in the temporal lobe caused enhanced learning and memory. In addition, our previous study [63] showed that interaction between the left and right hemispheres is not necessary to perform the PMT, based on the results of cutting the commissural fibers. Therefore, there is no simple interhemispheric inhibition between the left and right hippocampi, but rather a more complex mechanism that is thought to be working in the left hippocampus to enhance its potential for spatial learning. Regarding (3), the results were not what we had initially expected. Because accidental damage or artificial inhibition of the left hemisphere has been reported in many cases of savant syndrome, we initially expected that damage to the left hippocampus would contribute to memory enhancement in rats. However, the results were reversed, suggesting that the functions of the left and right hippocampus may be opposite in humans and rats. In our previous study [55], damage to the right hippocampus caused a loss of short-term memory, not long-term memory. Because the PMT used in this study requires long-term memory, it is possible that the damage to the right hippocampus weakened unnecessary short-term memory and allowed the left hippocampus to concentrate on long-term memory. In other words, as in the “Oshikuramanju hypothesis” proposed by Kawamura and colleagues [3,4], some function of the short-term memory system in the right hippocampus and some function of the long-term memory system in the left hippocampus might normally have antagonistic effects on each other. It may be possible to consider that, as in the case of our experiments, artificial damage to the right hippocampus reduces the power of short-term memory functions and, conversely, increases the power of long-term memory functions. However, organisms are supposed to be ecologically adaptive under normal conditions, and excessive long-term memory will cause the brain to stock up on all the information from the environment, which will unnecessarily eat up memory capacity. Therefore, this enhanced learning function should be called an abnormality, and it may even inhibit the normal execution of essential behaviors (such as short-term memory).

In order to examine the results in more detail, we analyzed whether there were any changes in learning within one session (10 trials). We found no significant difference between the right and left lesion groups in the first five trials, whereas we detected a significant enhancement in the performance of the right lesion group on Days 2 and 3 in the second set of five trials (Figure 4a,b). Therefore, it is suggested that the learning was particularly efficient in the latter five trials, which may indicate that the correct responses in the first five trials were immediately consolidated and stored in long-term memory within the session (the delay per trial was 5 min, and there was a total delay of about 1 h between the first and second half-trials, indicating that this was due to long-term memory rather

than short-term memory). However, there is not enough evidence to state exactly which process (memorization, fixation, or recall) is the reason for the enhancement, and future studies will need to address this issue in more detail. In addition, our previous study [55] showed that right hippocampal lesion impaired short-term memory, including working memory, but in the present behavioral study, we cannot completely rule out that the right hippocampal lesion induced enhancement of working memory by a different mechanism. This is because the increase in accuracy in the latter five trials on Days 2–3 might be due to the enhancement of PMT-specific working memory within the session. Also, we cannot exclude several other possibilities, such as the possibility that the results are not purely due to learning and memory, or that they are dependent on, for example, spatial recognition, or perhaps, although much less likely, the effects of stress and anxiety [54,71–76], which are often reported to differ between left and right.

In the present study, we revealed that savant-like learning enhancement is caused by damage to the right hippocampus in rats. The use of such a rodent model of savantism is expected to make a significant contribution to the elucidation of the neurological mechanisms of savants, because the experimental approach in humans is difficult due to the small number of savants and the inability to perform invasive manipulations. In addition to memory, future research would be expected to provide remarkable insights into other functions, such as music and calculation, and whether the same phenomenon can be observed in other brain regions, such as the left frontal lobe.

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