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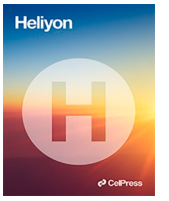

# The defects of the hippocampal ripples and theta rhythm in depression, and the effects of physical exercise on their amelioration

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ABSTRACT

Adverse environmental stress causes depressive symptoms with the impairments of memory formation, cognition, and motivation, however, their underlying neural bases have not been well understood, especially based on the observation of living animals. In the present study, therefore, the mice model of restraint-induced stress was examined electrophysiologically to investigate the alterations of hippocampal sharp wave ripples (SWRs) and theta rhythms. In addition, the therapeutic effects of physical exercise on the amelioration of those hippocampal impairments were examined in combination with a series of behavioral tests. The data demonstrated that chronic restraint stress caused the reductions of occurrence and amplitude of hippocampal SWRs and the decreases of occurrence, duration, and power of theta rhythms, while physical exercise significantly reverted them to the levels of healthy control. Furthermore, hippocampal adult neurogenesis and microglial activation, previously reported to be involved in the etiology of depression, were histologically examined in the mice. The results showed that the impairment of neurogenesis and alleviation of microglial activation were induced in the depressed mice. On the other hand, physical exercise considerably ameliorated those pathological conditions in the affected brain. Consistently, the data of behavioral tests in mice suggested that physical exercise ameliorated the symptomatic defects of motivation, memory formation, and cognition in the depressed mice. The impairments of hippocampal SWRs and theta rhythms in the affected hippocampus are linked with the symptomatic impairments of cognition and motivation, and the defect of memory formation, respectively, in depression. Taken together, this study demonstrated the implications of impairment of the hippocampal SWRs and theta rhythms in the etiology of depression and their usefulness as diagnostic markers of depression.

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## 1. Introduction

The neural and molecular machineries underlying depression still remain to be elucidated. One of the main reasons why the etiology of depression has not been comprehensively understood is the methodology adopted to analyze the affected brain with depression, where the postmortem tissues at fixed timepoints are genetically or histologically analyzed [1–3], however, the dysfunction of neural activity and its related behavioral abnormalities are not able to be precisely appreciated in patients or model animals of depression. In the previous investigations in the postmortem samples of the affected hippocampus with chronic stress-induced depression, some anatomical abnormalities such as the defects of adult neurogenesis and the activation of neuroimmune cells were demonstrated. Therefore, in the present study the mice model of restraint stress-induced depression was developed and subject to electrophysiological analyses to examine the hippocampal dysfunctions characteristic of depression. Here, the alterations of hippocampal sharp wave ripples (SWRs) and theta rhythm were investigated in the depressive mice. In addition, the effect of physical exercise on their alterations in combination with that on the depressive symptoms were analyzed. The involvement of hippocampal dysfunction has been reported previously based on histological and genetical analyses mainly in the brain tissue slices [4,5], however, whether the hippocampal activities such as SWRs and theta rhythm alter in the affected brain with depression still remains obscure. Furthermore, to date whether physical exercise reversely influences the hippocampal activities has not been appreciated. The present study firstly examined the alterations of hippocampal SWRs and theta rhythm electrophysiologically in the mice model of depression, and also the reverse effects of physical exercise on them.

Among the hippocampal activities associated with functions such as memory, cognition, and motivation, which were previously reported to be impaired in depression, SWRs and theta rhythm are included [6,7]. SWRs, patterns of spike sequences thought to be involved in memory consolidation, are local field potentials, which reflect transient excitatory drives and high-frequency oscillations, based on the hippocampal pyramidal cell-interneuron interactions [8,9]. SWRs take place while resting and sleeping, which implies that environmental stress reduces the generation of SWRs [10]. Therefore, the reduction of SWRs is considered to be implicated in the defects of hippocampal functions in depression, such as memory. On the other hand, the hippocampal theta rhythm occurs, based on the projection from the medial septum, which receives the neural inputs from the hypothalamus and the brain stem. The hippocampal theta rhythm has recently been reported to occur during rapid eye movement (REM) sleep and link with arousal [11], while other studies demonstrated that theta rhythm promoted adult hippocampal neurogenesis and functioned in navigation, learning and memory [12]. Adult hippocampal neurogenesis was demonstrated to be impaired in the depressive brain [13]. Therefore, the correlation of theta rhythm with the causative input from the hypothalamus, which plays a crucial role in motivation, evokes its involvement in the etiology of depression [14].

To date the hippocampal activities in the brain with depression have not been fully appreciated in *vivo* experiments, and pathological markers reflecting the hippocampal defects have not been identified yet. The present study focused on 2 neuronal scales, SWRs and theta rhythm, previously reported to be linked with the hippocampal pivotal functions [15]. Such functions include memory, cognition, and motivation, which are impaired in depression [16]. Therefore, it is hypothesized that in the affected brain with depression the hippocampal SWRs and theta rhythm are impaired, reflecting the dysfunctions of the cerebral cortex-hippocampus connection and adult hippocampal neurogenesis. In combination with the exploration of electrophysiological marker, in the present study the effect of physical exercise to reverse the alterations of SWRs and theta rhythm is examined, where not only their reverse effect but also the effect to ameliorate the depressive symptom such as behavioral defect or neuroinflammation is investigated psychologically or histologically. As the results of this study, the usefulness of hippocampal SWRs and theta rhythm for the diagnosis of depression is appreciated, and the development of therapeutic physical exercise to ameliorate the depressive symptom is expected.

## 2. Methods

### 2.1. Animals

45 healthy male C57BL/6 mice (8 week-old) were purchased from Japan SLC. Mice were housed in a group of up to five animals on a 12 h light/dark cycle at 22 °C with free access to food and water. The handling, use of animals, and experimental protocols were approved by the Institutional Animal Care and Use Committee of Nagoya City University. All experimental procedures were conducted according to ARRIVE guidelines. All methods were performed in accordance with the guidelines from American Veterinary Medical Association and our institution.

### 2.2. Chronic restraint stress and spontaneous exercise

Mice were randomly divided into 3 groups, 1) a group of healthy control mice (HC, n = 15), 2) a group of mice subject to chronic restraint stress (CRS, n = 15), 3) a group of mice subject to chronic restraint stress and physical exercise (ExCRS, n = 15), and were bred in each environment for 21 days. HC mice were housed in a 20 × 25 cm plastic cage. CRS mice were subject to chronic restraint stress, which was previously described [11–13]. Briefly, individual mouse was inserted into a 50 ml tube with small holes on its wall, plugged up with pieces of paper towel, and left for 4 h. For the rest hours, CRS mice were bred similarly with HC mice. On the other hand, ExCRS mice were subject to the same stress and housed in 25 × 30 cm plastic cage with running wheel (Fast-Trac Activity Wheel, Bio-Serv). ExCRS mice were freely accessible to the wheel during the hours without restraint. The same groups of 15 HC, CRS and ExCRS mice respectively were used in the following behavioral tests (2.3.1 through 2.3.3).

### 2.3. Behavioral tests

#### 2.3.1. Forced swim test

The test was performed according to previous studies [11,13,14,17–21]. The mice were forced to swim for 6 min in a cylindrical vessel with 30 cm height and 10 cm diameter, filled with water at 24 °C. In the test, the movement of the mice was captured with video camera, and the total hours of immobility, in which the mice floated with minimal movement, were quantitatively analyzed.

#### 2.3.2. Open field test

The test was conducted in a white closed box (40 x 40 × 40 cm). The test was performed according to previous studies [11,12,18,19,22,23]. Mice were gently placed in the center of the box and freely explored. All the sessions were recorded on video and captured on a PC for analysis. A 20 cm square in the center of the box floor was defined as the center region. The time period the animal spent in the center region, number of times it entered the center region, and the distance it moved were analyzed. At the end of the session, the box was thoroughly cleaned with ethanol and dried.

#### 2.3.3. Novel object recognition test

The novel object recognition test was performed to examine the hippocampus-dependent cognitive function, based on the tendency of animals to have interests in new objects and spend more time for exploration [19,24–26]. At the beginning, two identical objects were placed in the box, and a mouse was allowed to explore the box for 10 min (learning step). After 2 h, one of the two objects was replaced with a new color and shape object and a mouse was again allowed to explore it for 10 min (memory step). All the sessions were recorded on video, and the duration exploring the new object was measured as an evaluation index.

### 2.4. Electrophysiology

Local field potential (LFP) recording was performed as previously described [27,28]. Briefly, the mice were anesthetized with urethane (1.2–1.4 g/kg, U2500 Sigma-Aldrich) and fixed in a stereotaxic frame (Narishige). After removing the scalp, a hole was drilled above the dorsal hippocampus on either side (Bregma: mediolateral 2.0 mm, anteroposterior −2.0 mm). The dura was surgically removed, and a 16-channel linear silicon probe (inter-channel distance = 50 μm; Alx15-5 mim-50-177-A16; NeuroNexus) was slowly inserted to the hippocampal CA1 so that the middle channel was located in the stratum pyramidale. A mixture of white petrolatum and liquid paraffin was applied to the surface of the brain to prevent it from drying out. Wideband (0.1–9000 Hz) extracellular field potentials were continuously recorded with a sampling rate of 31 kHz (TDT). Rectal temperature was measured and a heat mat was used to maintain the body temperature at 37 °C. The numbers of mice used in a series of electrophysiological experiments are as following; HC mice, n = 10: CRS mice, n = 9: ExCRS mice, n = 11. The same groups of HC, CRS and ExCRS mice were used through the experiments. All these mice were used in the behavioral tests, described above.

### 2.5. LFP data analysis

LFP data analysis was performed, using MATLAB (MathWorks Inc.) as was reported previously [27,28]. To analyze the ripple event, LFP signals in the stratum pyramidale were first resampled to 20 kHz. LFP signals were band-pass filtered over the ripple frequency band (80–250 Hz) and the resulting signals were squared and smoothed with a 19.2 ms length humming window. In the initial screening, the ripple events were detected as a period, during which the smoothed signal exceeded the mean of 7 times SD at a ripple interval of 100 ms. In the second screening, a minimum value within ±35 ms from each detected point (ripple through) was assigned as the ripple timing, and a 200 ms ripple filtering waveform centered on the ripple timing was extracted and further analyzed. After automatic detection, visually obvious noises were manually removed from further analyses. Ripple duration was defined as the range surrounding the ripple timing, in which the amplitude of the waves continuously more than doubled the SD. The peak amplitude of ripples is defined as the maximum amplitude through the extracted ripple event and expressed in absolute value. The frequency of ripples during non-theta periods was examined. Ripples observed within 35 ms were considered as one ripple event, and the sum of ripple events was considered as unilaterally occurred ripple.

The original data of LFP was resampled to 1.25 kHz and the spectrogram was calculated to automatically detect theta period. The theta period was detected in the LFP recorded from the CA1 radial layer in the right hemisphere (150 μm below the stratum pyramidale). The theta period was detected in accordance with following criteria: 1) The ratio of the peak power of the theta band (3.5–7 Hz) to that of the delta band (2–3 Hz) exceeds 0.6.2) The period is more than 10 s. Furthermore, the power spectral density of the detected theta period was estimated by the Welch periodogram method. The theta, low gamma and high gamma powers were calculated by integrating the power spectral densities of 3–6, 40–55, and 65–90 Hz, respectively. Spectral power was calculated from the average of the data of animal experiments, which was obtained from the multiple recording sessions.

### 2.6. Histology and immunohistochemical analysis

The mice were anesthetized with urethane and transcardially perfused with 4 % paraformaldehyde in 0.1 M phosphate buffer (PB). The brain samples were cut out, post-fixed overnight at 4 °C, submerged in 30 % sucrose in 0.1 M PB, and then frozen at −80 °C. The 10 μm slices of the hippocampus and cerebral cortex were prepared by the cryostat (HM525 NX, Thermo Fisher Scientific). Immunohistochemical staining was performed as previously reported [29]. Briefly, the brain sections were permeabilized with 0.1 % Triton

X-100 in PB for 20 min, blocked with 5 % bovine serum albumin for 30 min, and incubated overnight with primary antibodies: anti-Sox2 (rabbit IgG, 1:250, ab97959, Abcam), anti-ΔFosB (rabbit IgG, 1:500, #2251, Cell Signaling Technology), anti-Iba1 (rabbit IgG, 1:500, 013–26471, Wako). As a secondary antibody, anti-rabbit IgG-Alexa Fluor 594 were used. After counterstaining with DAPI (Vector Laboratories), the tissue images were taken under fluorescent microscope (Olympus). The numbers of the cells expressing Sox2, ΔFosB, and Iba1 were quantified by randomly choosing 4 view fields (100 × 100 μm each) under the microscope and taking an average of the numbers of the cells. Morphological analysis of microglia was performed by skeleton analysis method. Briefly, 10 images of microglia were cropped from each image and converted to 8-bit grayscale images, binarized and skeletonized using ImageJ. Skeleton analysis of ImageJ plug-in was performed in the obtained images, and the number and the total lengths of the processes were automatically analyzed [30,31]. In the histological examinations, the same 3 mice randomly selected from each of the groups of HC, CRS and ExCRS mice, which were examined by behavioral tests and electrophysiological analyses, were used.

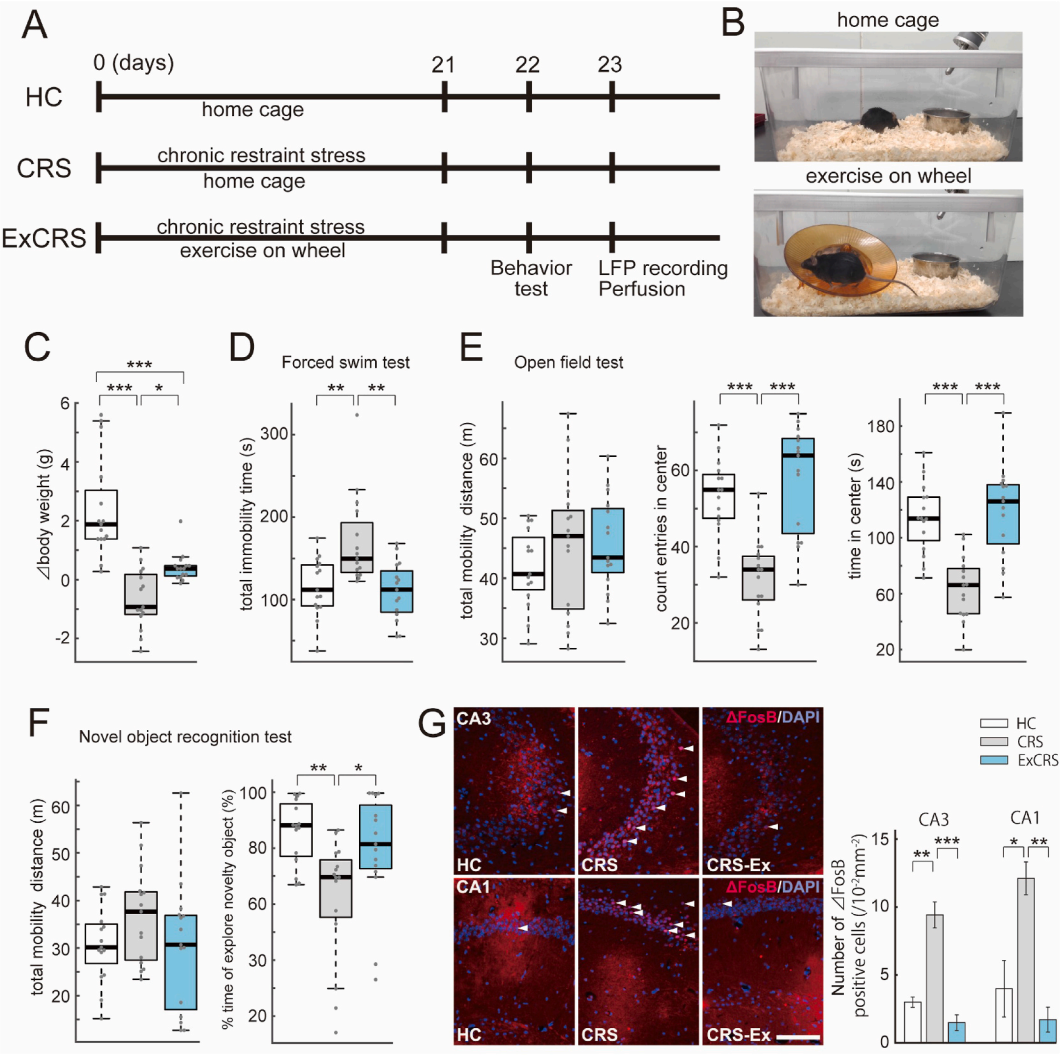


**Fig. 1.** Physical exercise ameliorates depressive symptoms in the restraint stress-induced depression model of mice.
**(A) Schematic of experimental procedures.** The mice were reared for 3 weeks in three conditions; 1) normal housing (HC: healthy control), 2) chronic restraint stress 4 h a day (CRS), and 3) chronic restraint stress 4 h a day and simultaneous physical exercise (ExCRS). **(B) The normal cage (upper) and the cage with running wheels for exercise (lower). (C) The change of body weight before and after the experiment in each group of mice. (D) Forced swim test.** The total time of immobility in 6 min was measured. **(E) Open field test in 10 min.** Left: total distance traveled. Center: Number of times the mice entered the center of the open field. Right: Total time the mice spent in the center of the open field. **(F) Novel object recognition test.** Left: Total distance the mice traveled in 10 min. Right: Percentage of time the mice spent to explore novelties in 10 min. **(G) Morphological analyses of the hippocampal activity.** Left: Representative images of immunohistological staining of ΔFosB positive cells in hippocampus CA3 and CA1 at day23. Right: Quantification of ΔFosB positive cells in CA3 and CA1. Scale bar: 100 μm. Data represent the mean ± SD. One-way ANOVA and the Tukey-HSD test (C–G). n = 15 mice/group (C–F) and n = 3 mice/group (G). *P < 0.05, **P < 0.01, ***P < 0.001.

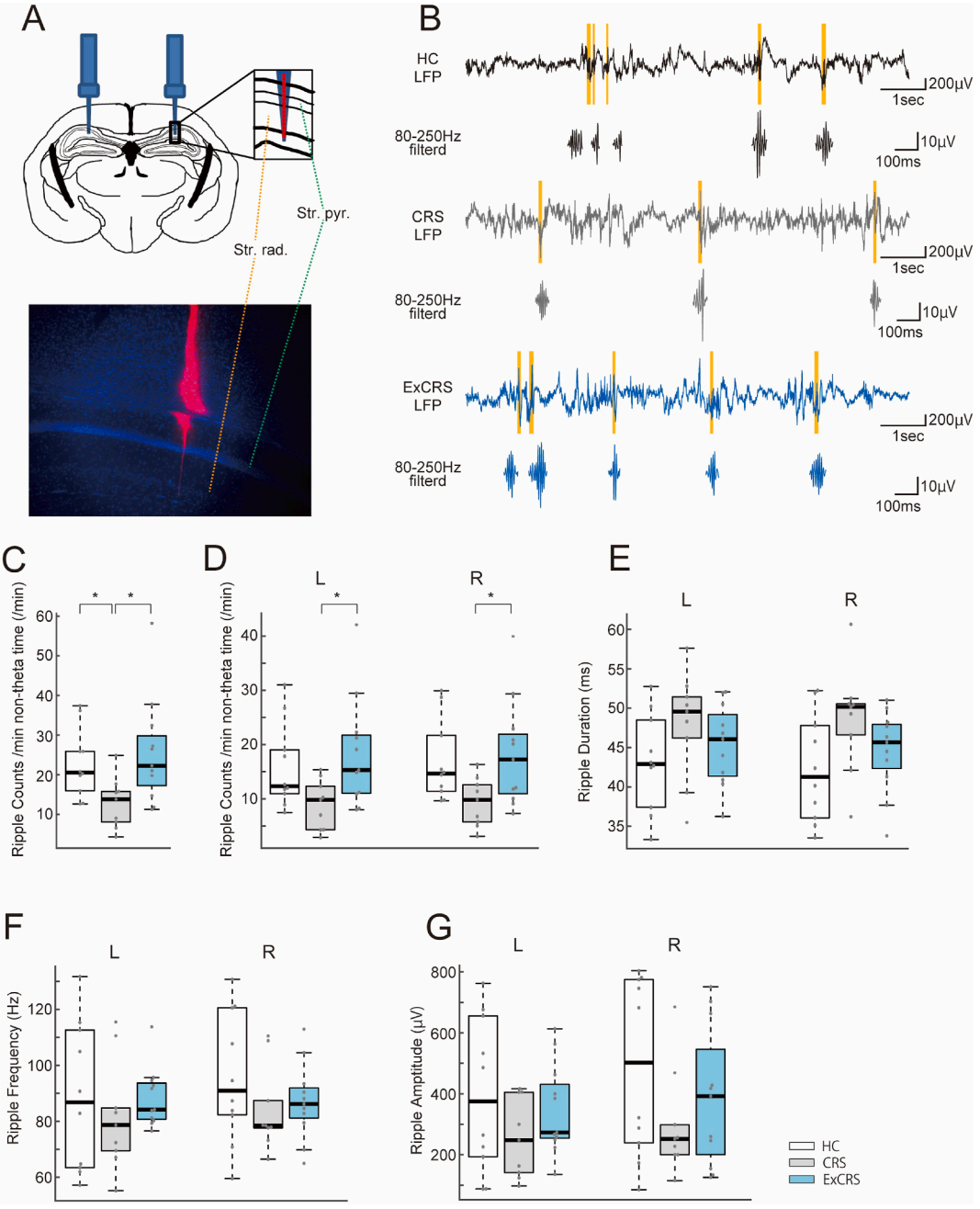


**Fig. 2.** Examinations of the influence of chronic stress-induced depression on the hippocampal ripples.
**(A) Schematics of LFP recording from the hippocampal CA1.** The lower panel shows an example of morphological verification of electrode location in the hippocampus. Str. Pyr.: Stratum pyramidale, Str. rad: stratum radiatum. **(B) Examples of LFP traces during non-theta periods in the CA1 stratum pyramidale.** The LFP were recorded from HC mice (top, black), CRS mice (middle, gray) and ExCRS mice (bottom, blue) in the left hemispheres. The ripples were highlighted in the LFP trace (yellow). Ripple waveforms extracted from the band-pass filtered traces were magnified and displayed below. **(C) Analysis of the number of ripples, occurring simultaneously in the both sides of the hippocampus.** Steel-Dwass test. **(D–G) Examinations of the influences of chronic stress on the ripples in the both hemispheres.** The numbers (D), the durations (E), the frequencies (F), and the amplitudes (G) of the ripples were examined in the left (L) and the right (R) hippocampi. One-way ANOVA and the Tukey-HSD test (D–G). n = 10 mice (HC), n = 9 mice (CRS), n = 11 mice (ExCRS) (C–G). *P < 0.05.

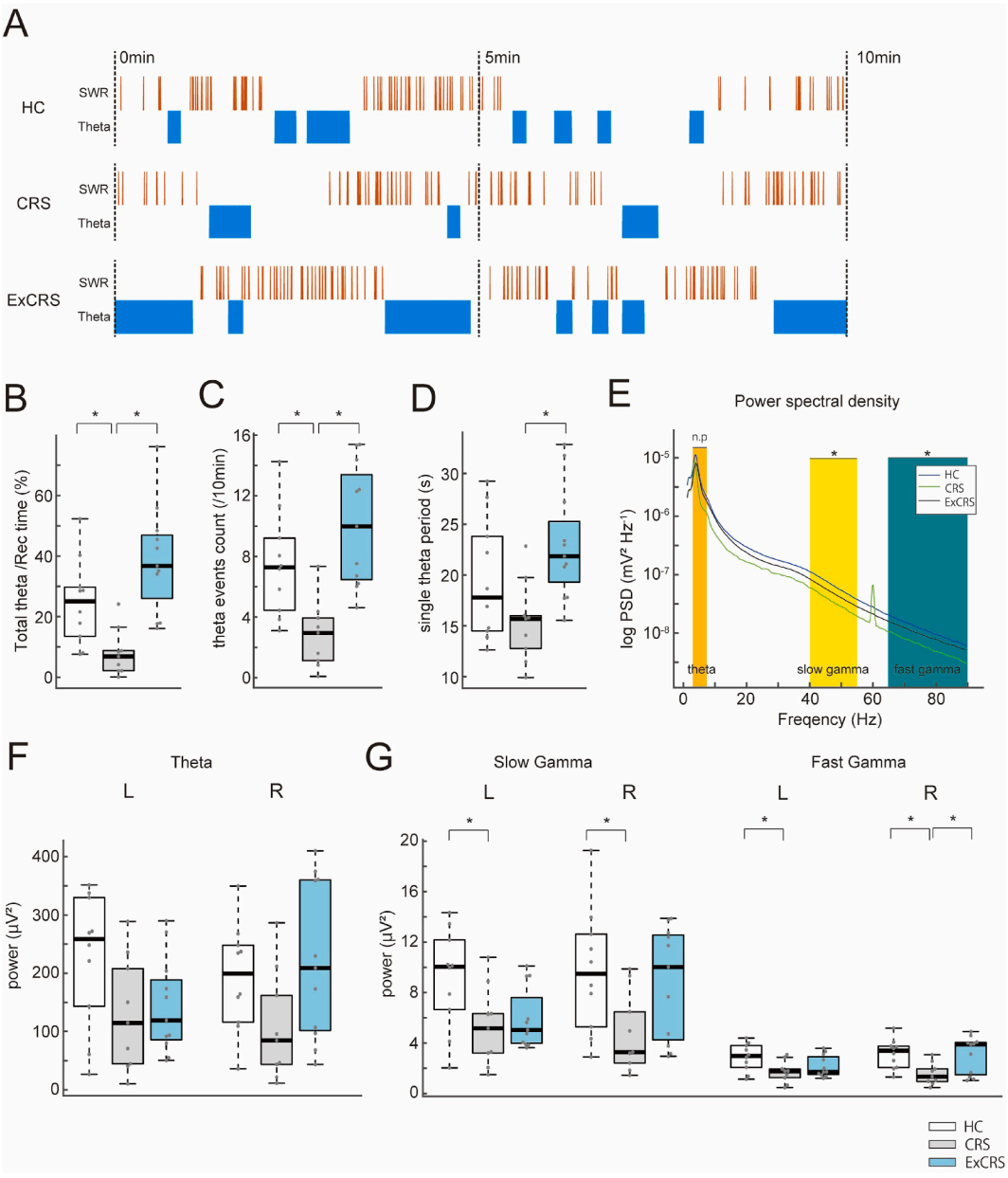


**Fig. 3.** Examinations of the defects of the theta and the theta-associated gamma oscillations in the CA1 stratum pyramidale in the depression model of mice.

**(A) Schemes of the typical sharp wave ripples (SWR) and theta rhythms.** The SWRs are shown in orange, and the theta rhythms are shown in blue. **(B–D) Analyses of the influence of chronic stress on the theta.** Statistics for spontaneously occurring theta periods are computed for (B) the proportion of theta periods in the total recording time, (C) the frequency of theta state, (D) the duration of single theta period. **(E) Power spectral densities of LFP in the CA1 stratum radiatum.** Shaded areas represent the frequency ranges for slow (40–55 Hz) and fast (65–90 Hz) gamma oscillations. **(F, G) Analyses of the influence of chronic stress on the theta and gamma powers.** (F) The theta power in HC, CRS, and ExCRS mice. (G) The slow and fast gamma power in the left (L) and right (R) hemispheres. One-way ANOVA and the Tukey-HSD test (B–G). n = 10 mice (HC), n = 9 mice (CRS), n = 11 mice (ExCRS) (B–G). *P < 0.05.

### 2.7. Statistics

Unless otherwise noted, comparisons of multiple populations were performed using a one-way ANOVA followed by the Tukey-HSD test (MATLAB 2019b). A p-value 0.05 was considered as significant.

## 3. Results

### 3.1. Development of restraint stress-induced depression model of mouse, and the effect of physical exercise on depressive symptoms

The mouse model of depression was developed by restraining a mouse in a cramped container for 4 h every day over a 3-week period (chronic restraint stress (CRS) mice), while the healthy control (HC mice) was reared in normal housing. In addition, the effect of physical exercise on restraint stress-induced depression was examined in the mice, which were subject to the restraint stress for 4 h every day and subsequent voluntary exercise over a 3-week period (exercise and chronic restraint stress (ExCRS) mice) (Fig. 1A and B). After rearing for 3 weeks, change of body weight and depressive behavior were analyzed in CRS, HC and ExCRS mice. The body weight significantly decreased in CRS mice compared to that in HC mice, and reverted considerably in ExCRS mice (HC-CRS, $p < 0.001$; HC-ExCRS, $p < 0.001$; CRS-ExCRS, $p = 0.048$) (Fig. 1C). The forced swimming test to estimate depressive behavior [17,20,21] demonstrated that the total immobility time for the period of 6 min significantly extended in CRS mice compared to that in HC mice, and shortened in ExCRS mice (HC-CRS, $p = 0.0032$; CRS-ExCRS, $p = 0.0012$) (Fig. 1D). The open field test showed that the number of times to enter to the center and the time period to spend in the center of the field significantly decreased in CRS mice compared to those in HC mice, while physical exercise reversed the alteration (entries; HC-CRS, $p < 0.001$; CRS-ExCRS, $p < 0.001$: time of stayed; HC-CRS, $p < 0.001$; CRS-ExCRS, $p < 0.001$) (Fig. 1E). The result demonstrated that physical exercise considerably attenuated anxiety in the depression model mice [22,23]. The novel object recognition test was performed to assess the hippocampal cognitive function [24–26], and the result showed that the ratio of the duration exploring novelty object to the total duration of exploration significantly decreased in CRS mice compared to that in HC mice, while that ratio reverted in ExCRS mice (HC-CRS, $p = 0.0037$; CRS-ExCRS, $p = 0.042$) (Fig. 1F). The data suggest that physical exercise ameliorates the hippocampal cognitive dysfunction in depression.

In addition to the stress-induced depressive behavior, the effect of restraint stress on the hippocampal neural activity and the attenuation of the effect by physical exercise were examined in the hippocampal tissues obtained from CRS, HC and ExCRS mice. The tissue samples were immunostained with anti-ΔFosB antibody. ΔFosB, a member of the FosB family of immediate early genes, has been reported to be upregulated, responding to environmental stress [32–34]. The number of ΔFosB expressing neurons in the CA1 and CA3 significantly increased in CRS mice compared to that in HC mice, while the increase of those neurons considerably reverted in ExCRS mice (CA3; HC-CRS, $p = 0.001$; CRS-ExCRS, $p < 0.001$: CA1; HC-CRS, $p = 0.019$; CRS-ExCRS, $p = 0.006$) (Fig. 1G). In comparison with HC mice, CRS mice did not show symptom of insomnia and disruption of circadian rhythm (data not shown). Taken together, the present findings demonstrate that physical exercise ameliorates the restraint stress-induced depressive behavior, cognitive decline and the hippocampal hyperactivity.

### 3.2. The hippocampal ripples are impaired in depression and retrieved by physical exercise

Local field potential (LFP) was recorded from the dorsal hippocampal CA1, using a 16-channel silicon probe under anesthesia with urethane (Fig. 2A). As was previously demonstrated, the temporary ripple oscillations appeared in the stratum pyramidale in parallel with the generation of the sharp waves in the stratum radiatum [35–37]. In the present study, the effects of stress-induced depression on the occurrence and magnitude of the hippocampal ripples and their attenuation by physical exercise were examined in the depressive mice. The ripples occurred several times in 10 s during the period of the large irregular activity in HC, CRS and ExCRS mice (Fig. 2B). The frequencies of the occurrence of ripples were 22.6, 12.7, and 25.5 in 1 min in HC, CRS, and ExCRS mice, and steel-dwass analysis demonstrated significant differences (HC-CRS, $p < 0.05$; CRS-ExCRS, $p < 0.05$) (Fig. 2C). Ripples occurred in most cases bilaterally, and in a few cases occurred unilaterally. Furthermore, the difference in frequencies of the hippocampal ripples in both sides of the brain was examined and the data showed that the frequency in either side was quite similar (Left; HC-CRS, $p = 0.17$; CRS-ExCRS, $p = 0.038$: Right; HC-CRS, $p = 0.114$; CRS-ExCRS, $p = 0.045$) (Fig. 2D). Then, the duration, frequency, and amplitude of the hippocampal ripples were analyzed in the extracted ripple waveforms. The duration, which the ripples continued, was longer in CRS mice than that in HC mice, while the extension of the duration was attenuated in ExCRS mice, compared to that in CRS mice (Left; HC-CRS, $p = 0.22$; CRS-ExCRS, $p = 0.62$: Right; HC-CRS, $p = 0.093$; CRS-ExCRS, $p = 0.334$) (Fig. 2E). There was no significant difference in the frequency of the ripples among HC, CRS, ExCRS mice (Left; HC-CRS, $p = 0.745$; CRS-ExCRS, $p = 0.737$: Right; HC-CRS, $p = 0.358$; CRS-ExCRS, $p = 0.942$) (Fig. 2F). The amplitude of the ripples in CRS mice was smaller than that in HC mice or ExCRS mice (Left; HC-CRS, $p = 0.244$; CRS-ExCRS, $p = 0.521$: Right; HC-CRS, $p = 0.213$; CRS-ExCRS, $p = 0.69$) (Fig. 2G).

### 3.3. Chronic stress impairs the hippocampal theta rhythm and physical exercise restores it

As previously reported [28,38], the hippocampal LFPs alternated between theta and non-theta patterns. The non-theta period, which consists of the large irregular activity and the small irregular activity, contained the ripples (Fig. 3A). The theta state was automatically detected by an algorithm based on the theta/delta power ratio of LFP in the stratum radiatum. The ratio of the theta period to the whole recorded period was 24.9, 8.2, and 38.8 (%) in HC, CRS, and ExCRS mice ($n = 15$ respectively), and significantly reduced in depression and reverted by physical exercise (HC-CRS, $p = 0.045$; HC-ExCRS, $p = 0.086$; CRS-ExCRS, $p < 0.001$) (Fig. 3B).

The frequency of the theta for 10 min also showed the similar tendency (HC-CRS, $p = 0.017$; HC-ExCRS, $p = 0.203$; CRS-ExCRS, $p < 0.001$) (Fig. 3C). The duration of the theta shortened in depression and considerably reverted by physical exercise (HC-CRS, $p = 0.237$; HC-ExCRS, $p = 0.290$; CRS-ExCRS, $p = 0.0095$) (Fig. 3D). Furthermore, the gamma oscillations, contained in the theta LFPs in the stratum radiatum, were examined. The powers of the slow gamma (40–55 Hz) and fast gamma (65–90 Hz) oscillations were calculated by spectral analysis (Fig. 3E). The spectral powers of the theta, slow gamma, and fast gamma among HC, CRS, and ExCRS mice were compared. The theta power was lower in CRS mice than that in HC mice, while reverted in ExCRS mice (Left; HC-CRS, $p = 0.102$; CRS-ExCRS, $p = 0.94$: Right; HC-CRS, $p = 0.234$; CRS-ExCRS, $p = 0.074$, Fig. 3F). Interestingly, the theta power reverted in the right hippocampus only. On the other hand, the slow and fast gamma powers were significantly lower in CRS mice than those in HC mice (fast gamma Left, $p = 0.040$; fast gamma Right, $p = 0.049$; slow gamma Left, $p = 0.035$; slow gamma Right, $p = 0.022$) (Fig. 3G). Of note is that in the right hippocampus the fast gamma dominantly reverted as the result of exercise in ExCRS, while that reverted less in the left hippocampus (fast gamma Left, $p = 0.888$; fast gamma Right, $p = 0.111$; slow gamma Left, $p = 0.544$; slow gamma Right, $p = 0.027$).

### 3.4. Physical exercise attenuates the defect of hippocampal adult neurogenesis

As was demonstrated in previous studies, the defect of hippocampal adult neurogenesis is involved in the etiology of depression [39–41]. In the present study the influence of physical exercise on hippocampal adult neurogenesis was examined in the depression model of mouse. The hippocampal tissues were obtained from the mice and their neural stem cells were immunostained with anti-Sox2 antibody. In CRS mice, the number of neural stem cells in the hippocampal dentate gyrus (DG) was considerably fewer than that in HC mice, while in ExCRS mice the number of neural stem cells restored (HC-CRS, $p = 0.205$; CRS-ExCRS, $p = 0.022$) (Fig. 4A and B).

### 3.5. Physical exercise suppresses stress-induced neuroinflammation in the hippocampus

Accumulated evidence demonstrated that the inflammation with microglial activation in the hippocampus is correlated with the dysfunction of hippocampal adult neurogenesis and implicated in the etiology of depression [42,43]. In the present study microglial activation, which accompanied the morphological change from ramified to ameboid shape and the change in length and number of processes [30,31], was examined in the brain tissue samples of the depression model mouse. The change of microglial shape was morphologically analyzed by immunohistochemical staining with anti-Iba1 antibody, and the number and total length of microglial processes were quantified by skeleton analysis of ImageJ plug-in. There was no significant difference among HC, CRS and ExCRS mice in the number of microglia in the hippocampal DG, CA1 and CA3 (Fig. 5A and C), while the number and total length of microglial processes in CRS mice were significantly less than those in HC mice in the hippocampal DG, CA3 and CA1 (number of processes: DG, $p = 0.005$; CA3, $p = 0.024$; CA1, $p = 0.009$. length: DG, $p = 0.019$; CA3, $p = 0.019$; CA1, $p = 0.026$). Further analyses revealed that the number and total length of microglial processes significantly increased in ExCRS mice, whose microglia took ramified shape, compared to those in CRS mice (number of processes; DG, $p = 0.001$; CA3, $p = 0.014$; CA1, $p = 0.006$: total length; DG, $p < 0.001$; CA3, $p = 0.004$; CA1, $p = 0.003$) (Fig. 5B, D and E).

## 4. Discussion

In the present study the alterations of the hippocampal activities in the affected brain with depression were analyzed electrophysiologically in living organisms, focusing on SWRs and theta rhythm. As the previous studies analyzed the postmortem brain tissue samples obtained from the patients and model animals of depression histologically or genetically, they had fundamental limitations, in which the pathological alterations of neural activities in the working brain could not be detected, and the development of therapeutic

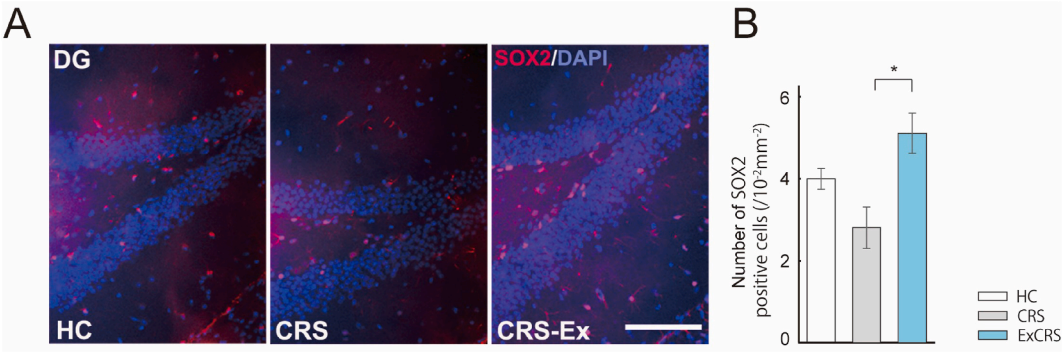


**Fig. 4.** Physical exercise ameliorates the defect of hippocampal adult neurogenesis in depression.
**(A) Representative images of Sox2-expressing neural stem cells in the hippocampal dentate gyrus (DG) at day 23.** Scale bar: 100 μm. **(B) The defect of adult neurogenesis in depression and its amelioration by physical exercise.** Data represent the mean ± SD. One-way ANOVA and the Tukey-HSD test. n = 3 mice/group. *P < 0.05.

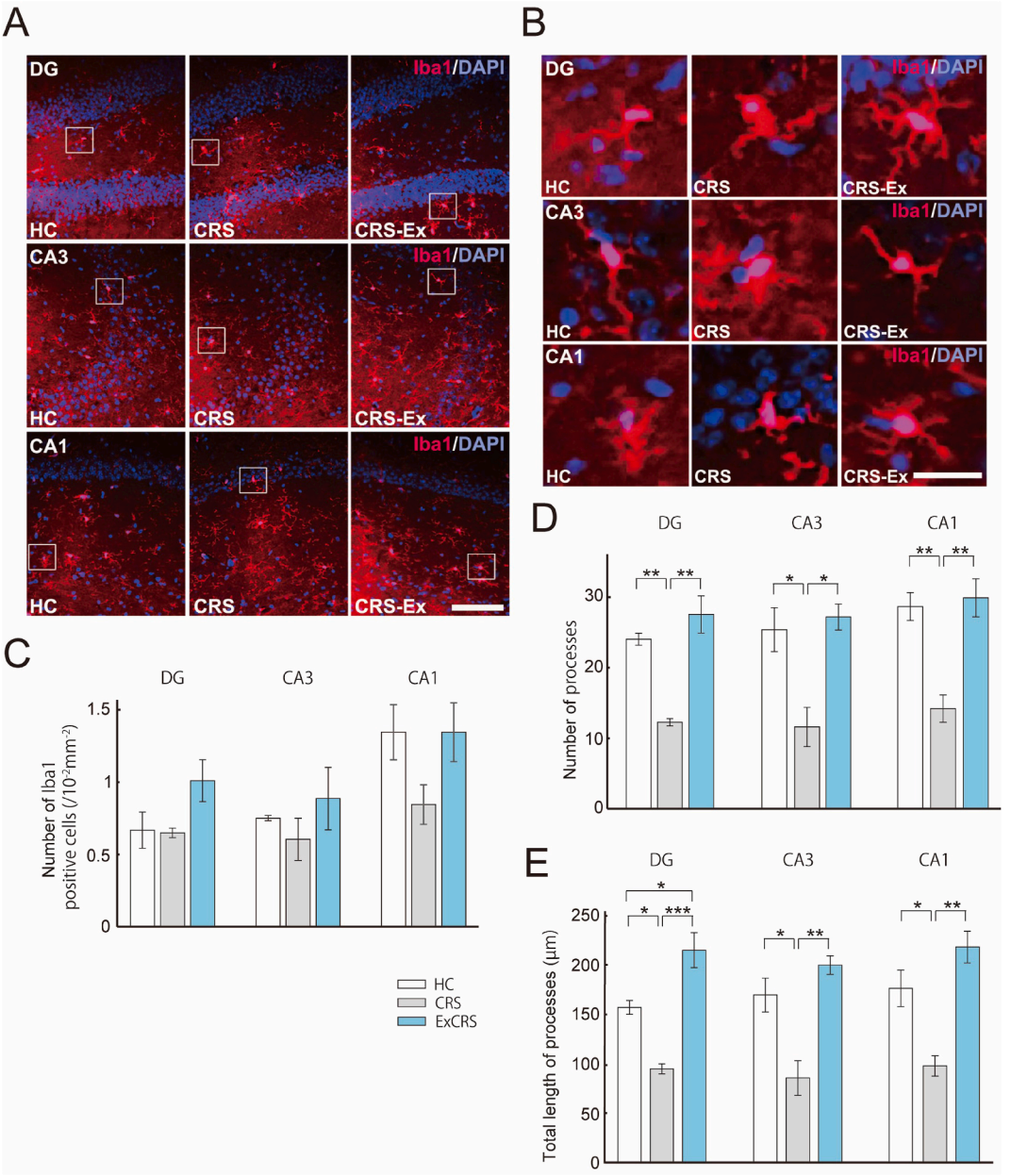


**Fig. 5.** The suppression of neuroinflammation in depression by physical exercise.
**(A) Representative images of Iba1-expressing microglia in the hippocampal DG, CA3 and CA1 in mice at day 23.** Scale bar: 100 μm, **(B) Magnified images of the boxed areas in (A).** Scale bar: 25 μm. **(C–E) Morphological analyses of the hippocampal microglia.** (C) The number of microglia, (D) the number of processes in a cell, (E) the total length of processes in a cell. DG; dentate gyrus. Data represent the mean ± SD. One-way ANOVA and the Tukey-HSD test (C–E). n = 3 mice/group (C–E). *P < 0.05, **P < 0.01, ***P < 0.001.

intervention, referring to the symptoms could not be expected. To overcome those limitations, the present study adopted real-time monitoring methods for traces of electrophysiological indexes, SWRs and theta rhythm, and in addition, the effects of physical exercise on their alterations were simultaneously examined *in vivo*. Accumulated evidence demonstrates that the cerebral cortex-hippocampus connections, which function in memory consolidation are impaired in depression [44,45], while other findings suggest that pathological condition of depression impairs adult neurogenesis in the hippocampus [46] and innervations from the amygdala and the medial septum to the hippocampus [47,48]. Therefore, the defect of SWRs implies the dysfunction of those innervations and result in that of memory consolidation subsequently. On the other hand, as theta rhythm links with the neural inputs from the amygdala and medial septum, its defect reflects the dysfunctions of those nuclei, and is coupled with the pathology of emotion and recognition. Based on the examination of depression-induced alterations of the hippocampal indexes, SWRs and theta rhythm, the

ameliorative effect of physical exercise on those alterations were investigated. Although previous studies reported that physical exercise ameliorated the affected functions of hippocampus in model animals and patients of depression, in which the alterations of pathological markers such as neural stem cells and inflammatory cytokines were histologically and genetically examined [49], its influences on SWRs and theta rhythm, or other electrophysiological markers, coupling with the hippocampal activities in living organisms, have not been precisely appreciated to date. Our data firstly demonstrated the alterations of SWRs and theta rhythm in the affected hippocampus with depression, and the effects of physical exercise on defects of hippocampal activities.

The restraint stress-induced depression model of mice was developed, and its depressive symptoms were estimated by a series of physical and behavioral examinations, in which weight loss (Fig. 1C), immobility (Fig. 1D), anxiety (Fig. 1E), cognitive disability (Fig. 1F) were observed. In addition to those psychiatric defects, the model mice demonstrated the increase of ΔFosB expressing hippocampal neurons (Fig. 1G), reflecting the hyperactivation of hippocampal projecting neurons, which was previously related to the neuropathology of depression [50]. These observations support the appropriateness of the mice as a model of depression. The present experimental data demonstrated that physical exercise diminished the effect of restraint stress and relieved the depressive symptoms. In spite of accumulated evidence, reporting the ameliorative effect on depression [51], the mechanism how physical exercise attenuates the symptoms of depression is still to be elucidated. Therefore, in the present study the neural bases underlying the influence of physical exercise on the amelioration of depressive symptoms were electrophysiologically investigated in terms of hippocampal SWRs and theta rhythm in living mice model of depression.

The present data suggested that hippocampal SWRs were affected in their numbers (Fig. 2C and D), duration (Fig. 2E), frequency (Fig. 2F), and amplitude (Fig. 2G) in depressive mice. SWRs are considered to reflect the intensity of cerebral cortex-hippocampus connections, functioning in memory consolidation, and recently suggested to link with the activity of hippocampus-amygdala connections, involved in contextual emotional memory [52]. The machinery underlying the defect of SWRs in depression, therefore, can be attributed to the suppression of those connections. Very recently, it was reported that the expression level of intrinsic calbindin in the ventral hippocampus (vHC) is crucial for determining stress susceptibility [53]. As the vHC innervates the amygdala and relates to emotional memory, it is possible that the defect of SWRs brings about depressive symptoms such as anxiety. The present data also demonstrated that physical exercise diminished the effects of restraint stress on tendencies of SWRs (Fig. 2C–G). Previous study implied that physical exercise enhanced GABAergic innervation of the medial septum to the hippocampus, and subsequently increased hippocampal SWRs [54]. Therefore, it is possible that restraint stress induces the dysfunction of medial septum and results in the defects of SWRs, while physical exercise restored the activity of medial septum. Despite our previous observation, in which the hippocampus on each side of the brain was demonstrated to asymmetrically process cortical inputs [55], SWRs in either side of the brain didn't generate differential pattens (Fig. 2D–G).

The present data demonstrated that restraint stress-induced depression impaired theta and gamma rhythms in the hippocampus, while physical exercise ameliorated their impairments (Fig. 3A–G). The previous studies showed that disruptions of medial septal neurons innervating the hippocampus resulted in loss of theta power, and impaired spatial learning [56] and learning in contextual fear conditioning [57]. Other study reported that hippocampal theta rhythm linked to the input from the hypothalamus and its dysfunction resulted in the defect of motivation [58]. These findings imply that the defects of hippocampal theta and gamma rhythms reflect the dysfunctions of the medial septum and hypothalamus in pathological conditions of depression. To date, neural bases underlying the reversion of theta and gamma rhythms by physical exercise has not been well understood. As recent studies reported that physical exercise induced the secretion of ghrelin and other feeding-regulatory peptides, which suppressed the hypothalamic inflammation [59], it is possible that the anti-inflammatory action of feeding-regulatory peptides is implicated in the reversion of theta and gamma rhythms.

It is established that the dysfunction of adult hippocampal neurogenesis occurs in depression [60]. As was shown previously, the defects of medial septal innervation to the hippocampus and impairment of theta rhythm reduced adult hippocampal neurogenesis [61,62]. Therefore, the neural mechanism underlying the present data, in which the neurogenesis impaired in depression (Fig. 4A and B), can be attributed to the dysfunction of the medial septum, and subsequent defect of hippocampal theta rhythm. The reverse effect of exercise on neurogenesis in the affected hippocampus might be explained by the recovery of hippocampal theta rhythm.

In relation to the defect of adult hippocampal neurogenesis in depression, neuroinflammation accompanied with the activation of microglia is well described before [63], however, the pathophysiology of its occurrence is not well understood. The possible explanation how hippocampal microglia is activated might be attributed to the aberrant septal innervation to the hippocampus, in which GABAergic inhibitory input, linked to hippocampal theta rhythm is impaired, altered the gene expression profiles of microglia [64]. The present data demonstrated the microglial histological transition of morphology from ramified to ameboid in depression, and exercise reversed it. Further investigations are required to reveal the influence of depression on microglial gene expression patterns in the affected hippocampus.

The present study demonstrated for the first time electrophysiologically *in vivo* that chronic stress-induced depression impaired the hippocampal activities, SWRs and theta rhythm, and in addition showed that physical exercise reversed the alterations of SWRs and theta rhythm, accompanying the amelioration of behavioral symptoms. As the neural bases underlying the generation of hippocampal SWRs and theta rhythm overlap in the septal innervation to the hippocampus and the depressive symptoms such like impairment of hippocampal adult neurogenesis and hippocampal microglial activation can be attributed to the dysfunction of the septum, it is suggested that the septum and its innervation to the hippocampus are involved in the pathophysiology of chronic stress-induced depression, and comprehensive understanding how chronic stress induces dysfunction of the septum might open the new avenue for the development of therapeutic technologies of depression.

### 4.1. Limitations of the study

Following below are the limitations of the present study. In all the experiments, in which local field potential recording was performed, the mice were anesthetized with urethane anesthesia. As anesthesia is known to interfere with both synaptic transmission and brain rhythms, further examinations to reveal the alterations of SWRs and theta rhythm in depression in anesthesia-free awake mice are needed. In addition, in the present study voluntary wheel running was used as a method of physical exercise, in which mice could voluntarily access the wheel, however other ways of exercise such like treadmill apparatus, where mice are forced to run, should be considered to examine the differential ameliorative effect of forced exercise on depressive symptom. Furthermore, the limitations derived from the restricted numbers of analyzed mice ($n = 3$) and subsequent results of statistical analyses exist in some populations of mice subjected to histological examinations of the brain tissue samples, such as those in the evaluation of the dysfunction of hippocampal adult neurogenesis (Fig. 4B).

## Additional information

No additional information is available for this paper.

## Data availability statement

All the obtained sets of data and the information of experimental materials are thoroughly described in the article, and the further detailed information of experimental data and materials can be provided based on the request to the authors.

## CRediT authorship contribution statement

**Shinnosuke Koketsu:** Investigation, Writing – original draft. **Kohki Matsubara:** Investigation, Writing – original draft. **Yoshino Ueki:** Conceptualization, Data curation, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Yoshiaki Shinohara:** Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Writing – original draft. **Koichi Inoue:** Data curation, Supervision. **Satona Murakami:** Conceptualization, Data curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Takatoshi Ueki:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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