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ORIGINAL PAPER

# Decreased Neuron Number and Synaptic Plasticity in *SIRT3*-Knockout Mice with Poor Remote Memory

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**Abstract** The sirtuin family of proteins consists of nicotinamide adenine dinucleotide-dependent deacetylases that are involved in the response to calorie restriction and various physiological phenomena, such as aging and cognition. One of these proteins, sirtuin 3 (SIRT3), is localized in the mitochondria and protects the cell against oxidative or metabolic stress. Sirtuin protein deficiencies have been shown to accelerate neurodegeneration in neurotoxic conditions. The mechanisms underlying the involvement of SIRT3 in cognition remain unclear. Interestingly, SIRT1, another member of the sirtuin family, has been reported to modulate synaptic plasticity and memory formation. To learn more about these proteins, we examined the behavior and cognitive functions of *Sirt3*-knockout mice. The mice exhibited poor remote memory. Consistent with this, long-term potentiation was impaired in the *Sirt3*-knockout mice, and they exhibited decreased neuronal number in the anterior cingulate cortex, which seemed to contribute to their memory deficiencies.

**Keywords** Sirtuin · Neurodegeneration · Remote memory · Synaptic plasticity

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## Introduction

Sirtuin, which is also known as the silent information regulator 2 (Sir2), is a class of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases that regulate the lifespan of budding yeasts [1–3]. There are 7 mammalian sirtuin proteins (SIRT1 to SIRT7), which have various molecular substrates and subcellular localizations. Sirtuin proteins are involved in dynamic biological functions, such as apoptosis, stress responses, cell survival, differentiation, and tumor suppression [1, 4]. SIRT1-deficient mice show impaired learning memory and long-term potentiation (LTP), which suggests that sirtuin proteins play a role in neurocognitive functions [5]. However, whether other SIRT proteins are involved in learning and memory is not yet known.

Among the sirtuin proteins, SIRT3, which is localized in mitochondria, regulates mitochondrial dynamics and protects cells against oxidative and metabolic stresses [6, 7]. For example, neurons of mice with knockout of the *Sirt3* gene ($Sirt3^{-/-}$), which encodes the SIRT3 protein, display reduced resistance to 3-nitropropionic acid, hydrogen peroxide, glutamate, and *N*-methyl-D-aspartate. In addition, SIRT3 prevents axonal degeneration in the central nervous system [7, 8]. Whether SIRT3 is involved in neurocognitive behaviors is not yet clear. The expression of SIRT3 is altered in mouse models of Alzheimer's disease (AD) [9, 10]. In line with this, patients with AD frequently show mitochondrial dysfunction and metabolic stress responses [11, 12]. Because AD is a prominent neurodegenerative disease involving impaired memory and SIRT3 is involved in neurodegeneration, we predicted that $Sirt3^{-/-}$ mice would show impairments in both memory and synaptic plasticity. Interestingly, although the recent memory functions of the $Sirt3^{-/-}$ mice were comparable with their wild-type littermates ($Sirt3^{+/+}$), the remote memory functions of the $Sirt3^{-/-}$ mice were

significantly impaired. Consistent with this finding, LTP in the anterior cingulate cortex (ACC), which has been implicated in the regulation of remote memory, was decreased in the *Sirt3*$^{-/-}$ mice. Finally, we found that the number of neurons in the ACC of the *Sirt3*$^{-/-}$ mice was reduced, which might have contributed to the findings of the impairments in remote memory and LTP.

## Materials and Methods

### Animals

The *Sirt3*$^{-/-}$ line was procured from Dr. Hyun Seok Kim of Ewha Womans University and bred at Seoul National University. Adult (8–20 months old) male *Sirt3*$^{-/-}$ mice and their wild-type littermates were used in the behavior (ages 8–15 months old), electrophysiological (ages 10–17 months old), and immunohistochemical (ages 18–20 months old) experiments. All mice were housed under a 12-h light/dark cycle with food and water provided ad libitum. The behavioral experiment was performed during the light phase of the cycle. All procedures, which were conducted according to the policies and regulations for the care and use of laboratory animals, were approved by the Institutional Animal Care and Use Committee of Seoul National University.

### Behavior

*Open-Field Test (OFT)*

The mice were first allowed to acclimate to the test room by keeping them in the front of the test room for 30 min. They were then placed in a square opaque white box (40 × 40 × 40 cm). Their movements in the box were tracked with a tracking program (EthoVision 9.0, Noldus Information Technology bv, Wageningen, The Netherlands) for 30 min under dim light. The center of the box was defined as the middle area that occupied half of the total area. The experimenters were blinded to genotype.

*Elevated Zero Maze Test (EZM)*

The mice were first allowed to acclimate to the test room by keeping them in the front of the test room for 30 min. They were then placed in the center of one of the closed arms of the maze. Their movements were tracked for 5 min with the tracking program (EthoVision 9.0) under bright lights. The maze was round (inner diameter: 50 cm, outer diameter: 60 cm) and made of white Plexiglass. The two closed arms (each arm occupied one quarter of the area) had 20-cm walls on both sides. If a mouse fell onto the floor, the mouse was excluded from the analysis. The experimenters were blinded to genotype.

*Object Location Memory Test (OLM)*

The mice were first allowed to acclimate to the test room by keeping them in the front of the test room for 30 min, and they were handled for 3 min for 4 consecutive days. After the handling, the mice were habituated to the experimental chamber that did not contain any objects for 15 min daily for 2 days. One day after the habituation, the mice were placed in the chamber, which now contained two identical objects (small glass bottles with paper cones on top), for 10 min. The following day, the location of one of the objects was changed, and the mice were allowed to explore each object for 5 min. The time spent exploring each object was measured, and the discrimination index was calculated as 100 × (exploration time of the moved object)/(total exploration time of the two objects).

*Morris Water Maze (MWM) Test*

The mice were handled for 3 min for 4 consecutive days before the training. During the training, the mice were placed in a white opaque tank (diameter 140 cm, height 100 cm) that was filled with water (22–23 °C) in a room with multiple spatial cues. The tank was divided into 4 virtual quadrants (TQ: target quadrant, OQ: opposite quadrant, AQ1: adjacent quadrant 1, AQ2: adjacent quadrant 2), and a 10-cm-diameter platform that was placed 1 cm below the water surface at the center of TQ. On training days, the mice were randomly released at the edge of the maze facing the inner wall of the tank and then trained to swim to the platform within 60 s. If the mice did not reach the platform within 60 s, they were guided to the platform. When the mice successfully reached the platform and stayed on the platform for more than 1 s, the mice were removed from the maze. The mice were trained with four trials per day with an intertrial interval of 1 min. The training lasted 5 days. 24 h after the final training trial, a probe test (recent) was performed under the same conditions as those used in the training trials except the platform was absent and the mice were tracked for 60 s with the tracking program (EthoVision 9.0). Four weeks after the recent probe test, the remote probe test was performed under the same conditions as those used in the recent probe test. The experimenters were blinded to genotype.

### ACC Field Potential Recordings with Multielectrode Arrays

For multielectrode recordings in the ACC, 300-μm-thick coronal brain slices were obtained behind the corpus

callosum with a vibratome (Leica Mikrosysteme Vertrieb GmbH, Wetzlar, Germany). The animals were first anesthetized with isoflurane, and the brains were then removed and sliced. The brain slices were incubated in oxygenated artificial cerebrospinal fluid (124 mM NaCl, 2.5 mM KCl, 1 mM $NaH_2PO_4$, 25 mM $NaHCO_3$, 10 mM glucose, 2.5 mM $CaCl_2$, and 1 mM $MgSO_4$) at room temperature (25 °C) for at least 1 h before the experiment. A MED64 recording system (Alpha MED Scientific Inc., Osaka, Japan) was used as previously described [13]. A slice was placed on the MED64 probe (MED-P515A; 8 × 8 array; interpolar distance, 150 µm), and artificial cerebrospinal fluid was perfused at 2–3 mL/min at 28–30 °C. A channel in the deep layer was selected for electrical stimulation, and one pulse per min was applied throughout the experiment. For the LTP experiment, a 20-min baseline recording was made. Theta-burst stimulations were then applied three times with 10-min intervals and recorded for 3 h. MED64 Mobius software (Alpha MED Scientific Inc.) was used for the data acquisition and analysis, and the data were averaged every 4 min for plotting. The field excitatory postsynaptic potential (fEPSP) slope of the last 8 min of data was normalized by the average value of the 20-min baseline.

### Neuronal Nuclei (NeuN) Staining and Cell Counting

The mice were anesthetized and transcardially perfused with 4% paraformaldehyde in phosphate-buffered saline (PBS). The brains were fixed in 4% paraformaldehyde overnight at 4 °C and then dehydrated in 30% sucrose in PBS at 4 °C for 1 day. Forty-micrometer-thick coronal brain slices were prepared with cryosectioning, and the slices were stored in 50% glycerol in PBS at − 20 °C. The slices were stained with anti-NeuN antibody (Cat# MAB377; 1:1,000; EMD Millipore Corporation, Billerica, MA, USA) and 4′,6-diamidino-2-phenylindole. The slices containing the ACC were imaged with confocal laser scanning microscopy (LSM 700-1; Carl Zeiss AG, Oberkochen, Germany), and all of the NeuN-positive cells in the ACC area were manually counted by two genotype-blinded experimenters. The average of the experimenters' counts of the NeuN-positive cells was used in the data analysis.

### Data Analysis

All data are presented as mean ± standard error of the mean. The statistical analyses were performed with unpaired *t*-tests and two-way analysis of variance (ANOVA) with SigmaPlot software (version 11.0; Systat Software, Inc., San Jose, CA, USA). The two-way ANOVAs were followed with Bonferroni posthoc tests. *P* values less than 0.05 ($*P < 0.05$) were considered statistically significant.

## Results

### Impaired Remote Memory and Normal Recent Memory in *Sirt3*$^{-/-}$ Mice in the MWM Test

Locomotor activity and anxiety are important aspects of mouse behavior, and they sometimes distort the results of other behavioral tests. Therefore, we examined the locomotor activity and anxiety of the *Sirt3*$^{-/-}$ mice with the OFT. The total distance moved in the open field and the cumulative time in the center of the field were similar in the *Sirt3*$^{-/-}$ and *Sirt3*$^{+/+}$ mice (*Sirt3* +/+: n = 9; *Sirt3* $^{-}$/$^{-}$: n = 6, two-way two-way repeated measures ANOVA of distance moved, unpaired *t*-test of time in the center, $P > 0.05$, Fig. 1a). Similarly, the cumulative time of the mice in the open area of the elevated zero maze in the *Sirt3*$^{-/-}$ mice did not significantly differ from that of the *Sirt3*$^{+/+}$ mice (*Sirt3* +/+: n = 9; *Sirt3* −/−: n = 6, unpaired *t*-test of time in the center, $P > 0.05$, Fig. 1b). Given that the locomotion and anxiety of the *Sirt3*$^{-/-}$ mice were normal, we then examined how the memory of the *Sirt3*$^{-/-}$ mice was affected. First, we tested object placement memory, which did not differ between the two groups (*Sirt3*$^{+/+}$, n = 9; *Sirt3*$^{-/-}$; n = 6, unpaired *t*-test, $P > 0.05$, Fig. 1c).

After the object placement memory test, we performed the MWM, which is another spatial memory test. We handled the *Sirt3*$^{+/+}$ and *Sirt3*$^{-/-}$ mice for 4 days and then trained them to find a platform in the water maze for 5 days (Fig. 2a). During the training, the learning curve did not differ significantly between the two groups (*Sirt3*$^{+/+}$ n = 11; *Sirt3*$^{-/-}$, n = 10, two-way repeated measures ANOVA, $P > 0.05$, Fig. 2b). After the training, we tested the memory of the mice at two time points: 1 day after the training (recent memory) and 4 weeks after the training (remote memory) (Fig. 2a). In the recent test, the *Sirt3*−/− mice stayed in the TQ where the platform was located, found the platform as well as the *Sirt3*$^{+/+}$ mice, and their proximity and platform crossing abilities were similar to those of the *Sirt3*$^{+/+}$ mice (*Sirt3*$^{+/+}$: n = 11; *Sirt3*$^{-/-}$: n = 10, unpaired *t*-test, $P > 0.05$, Fig. 2c). Interestingly, in the remote test, the *Sirt3*$^{-/-}$ mice stayed in the TQ significantly less than the *Sirt3*$^{+/+}$ mice (*Sirt3*$^{+/+}$: n = 11; *Sirt3*$^{-/-}$: n = 10, unpaired *t*-test, $*P < 0.05$, Fig. 2d, left). In addition, the mean distance from the platform of the *Sirt3*$^{-/-}$ mice tended to be longer than that of the *Sirt3*$^{+/+}$ mice, and, consistently, platform crossings tended to lower in the *Sirt3*$^{-/-}$ mice than in the *Sirt3*$^{+/+}$ mice. However, these differences were not statistically significant (*Sirt3*$^{+/+}$:

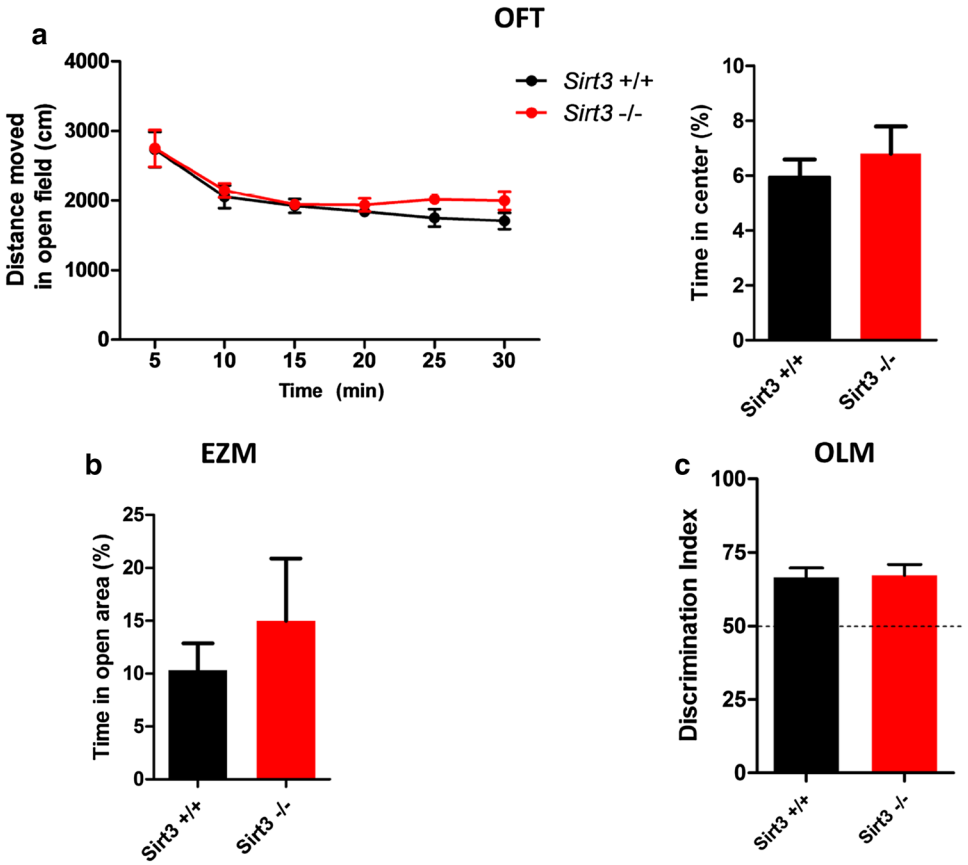


**Fig. 1** Normal locomotion, anxiety, and object location memory in the *Sirt3*$^{-/-}$. **a** Distance moved in the open field test (OFT) during each 5-min interval for 30 min (left) and the cumulative time in the center over 30 min (right) (*Sirt3*$^{+/+}$: n = 9; *Sirt3*$^{-/-}$: n = 6, two-way repeated measures ANOVA for distance moved, unpaired *t*-test for time in center, $P > 0.05$ for both). **b** Cumulative time in the open area of elevated zero maze (EZM) (*Sirt3*$^{+/+}$: n = 9; *Sirt3*$^{-/-}$: n = 6, unpaired *t*-test, $P > 0.05$). **c** Exploration of the object placed in a novel location in the object location test (OLM) (*Sirt3*$^{+/+}$: n = 9; *Sirt3*$^{-/-}$: n = 6, unpaired *t*-test, $P > 0.05$)

n = 11; *Sirt3*$^{-/-}$: n = 10, unpaired *t*-test, $P > 0.05$, Fig. 2d, center and right).

### Decreased Synaptic Plasticity and Neuronal Number in the ACC of the *Sirt3*$^{-/-}$ Mice

Based on the findings of the remote memory impairments of the *Sirt3*$^{-/-}$ mice, we examined physiological features that we suspected contributed to these behavioral impairments. Remote memory is processed with dynamic and brain-wide networks, and the neuronal activity and synaptic plasticity in the ACC are related to remote memory [14–16]. Thus, we investigated the electrophysiological phenotypes of the *Sirt3*$^{-/-}$ mice in the ACC. We recorded the fEPSPs of pyramidal neurons in the ACC by enhancing the input stimulation intensities. The input–output relationship of the *Sirt3*$^{-/-}$ mice was normal (*Sirt3*$^{+/+}$: n = 16; *Sirt3*$^{-/-}$: n = 14; two-way repeated measures ANOVA, $P > 0.05$, Fig. 3a). Next, we investigated LTP in the ACC of the *Sirt3*$^{-/-}$ mice. LTP is a type of synaptic plasticity that lasts for several hours. LTP was reduced in the *Sirt3*$^{-/-}$ mice compared with the (*Sirt3* $^{+/+}$: n = 7; *Sirt3* $^{-/-}$: n = 8, unpaired *t*-test, $^{*}P < 0.05$, Fig. 3b).

To further investigate the causes of the LTP impairment in the *Sirt3*$^{-/-}$ mice, we stained the ACC of the *Sirt3*$^{-/-}$ and *Sirt3*$^{+/+}$ mice with NeuN, a molecular marker for neurons. We hypothesized that the neuronal survival ratio would be reduced in the ACC because SIRT3 proteins regulate cellular death through mitochondrial mechanisms [7, 9]. We found that the number of NeuN-positive cells was reduced in the ACC of the *Sirt3*$^{-/-}$ mice compared with the *Sirt3*$^{+/+}$ mice (*Sirt3* $^{+/+}$: n = 2; *Sirt3* $^{-/-}$: n = 3, unpaired *t*-test, $^{*}P < 0.05$, Fig. 4a, b).

## Discussion

In the present study, we explored the behavioral phenotypes of *Sirt3*-depleted mice because the *Sirt3* gene encodes the SIRT3 protein. Although the mice showed normal locomotion, anxiety, and recent memory, their remote memory was impaired. Consistently, the LTP in the ACC was also impaired. We found that the number of neurons in the ACC was reduced, and this neuronal number change might have caused the impairments in synaptic plasticity and remote memory [17, 18].

Besides the ACC, other brain areas might also be affected by the loss of SIRT3. Because they are also involved in remote memory, the prefrontal cortex and dorsal hippocampus are possible target regions to examine. Interestingly,

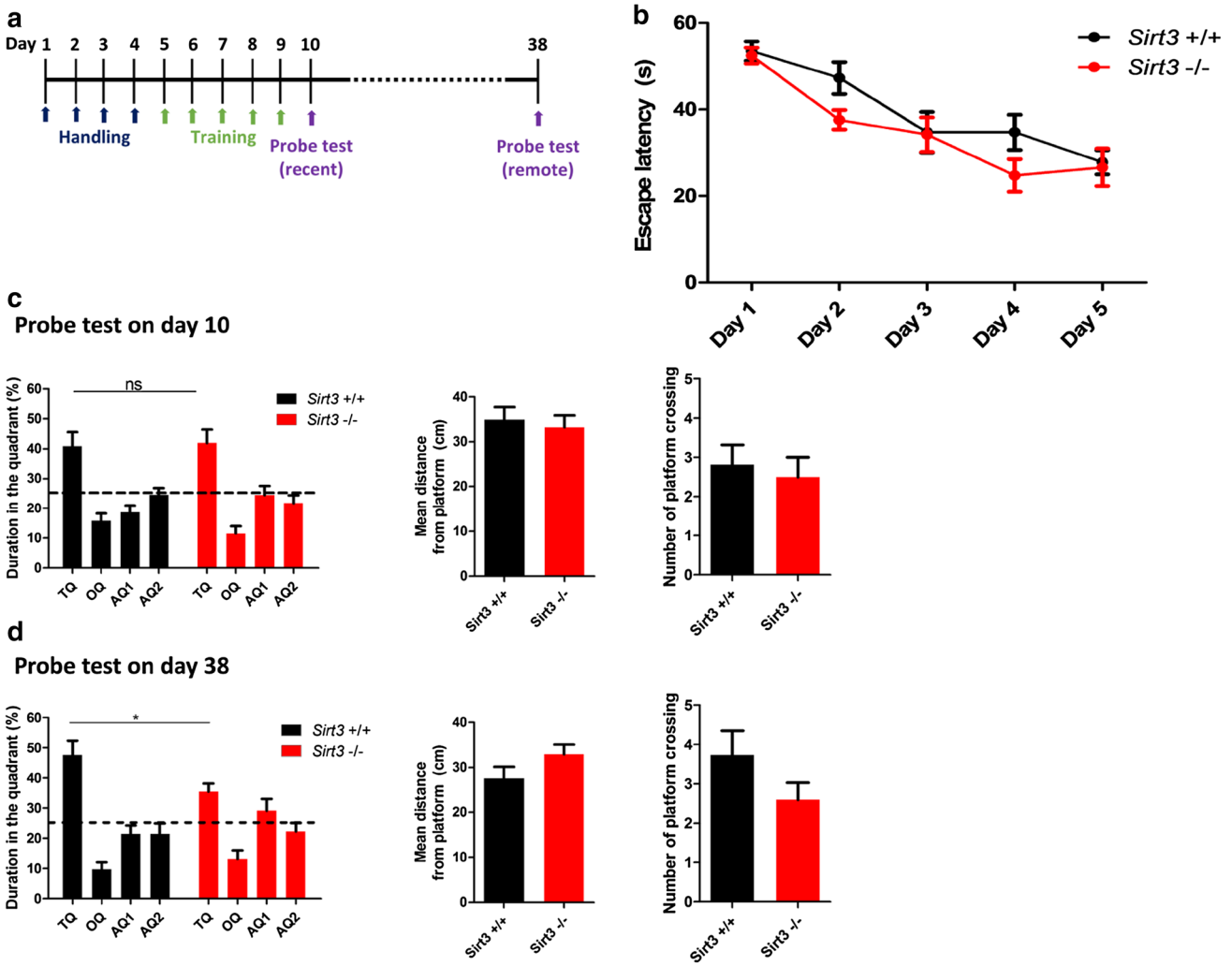


**Fig. 2** *Sirt3*$^{-/-}$ mice have impaired remote memory and normal recent memory. **a** Schematic of the Morris water maze experiment testing recent and remote memory. **b** Learning curves for the 5 days of training and the time required to find the platform (*Sirt3*$^{+/+}$: n = 11; *Sirt3*$^{-/-}$: n = 10, two-way repeated measures analysis of variance ANOVA, $P > 0.05$). **c** Results of the probe test performed on day 10. The time spent in each quadrant (left), mean distance from the platform (center), and number of platform crossings during the probe test are shown. The times in the target quadrant (TQ) did not significantly differ between the *Sirt3*$^{+/+}$ and *Sirt3*$^{-/-}$ mice (*Sirt3*$^{+/+}$: n = 11; *Sirt3*$^{-/-}$: n = 10, unpaired *t*-test, $P > 0.05$). *OQ* opposite quadrant, *AQ1* adjacent quadrant 1, *AQ2* adjacent quadrant 2. **d** Results of the probe test performed on day 38. The time spent in each quadrant (left), mean distance from the platform (center), and number of platform crossings during the probe test are shown. The time in the TQ was significantly reduced in the *Sirt3*$^{-/-}$ mice compared with the *Sirt3*$^{+/+}$ mice (*Sirt3*$^{+/+}$: n = 11; *Sirt3*$^{-/-}$: n = 10, unpaired *t*-test, $^{*}P < 0.05$)

despite the normal locomotion of the knockout mice in the OFT, the number of neurons in the secondary motor cortex of the *Sirt3*$^{-/-}$ mice appeared reduced. Thus, these neurons might affect other motor behaviors and/or motor learning, which is tested in the Rotarod test. In addition, behaviors other than remote memory might also be affected by a SIRT3 deficiency. For instance, increased oxidative stress in the ACC is associated with schizophrenia and bipolar disorder [19].

SIRT3 directly contributes to neuroprotection through several molecular pathways. The protein activates manganese superoxide dismutase (MnSOD) by deacetylating it. Because MnSOD converts superoxide to hydrogen peroxide, activation of MnSOD would reduce reactive oxygen species [7, 20]. In addition, SIRT3 promotes NAD-phosphate (NADPH) production, which acts as an antioxidant, by activating isocitrate dehydrogenase [20]. However, it is unclear which of these molecular mechanisms are involved in the decrease in neuronal number in the SIRT3-deficient mice.

In addition to SIRT3, other SIRT family proteins have been reported to regulate neurodegeneration [1, 21]. For example, SIRT1 and SIRT2 contribute to neuroprotection against oxidative stress by activating the forkhead box, subgroup O, which is a transcription factor that regulates

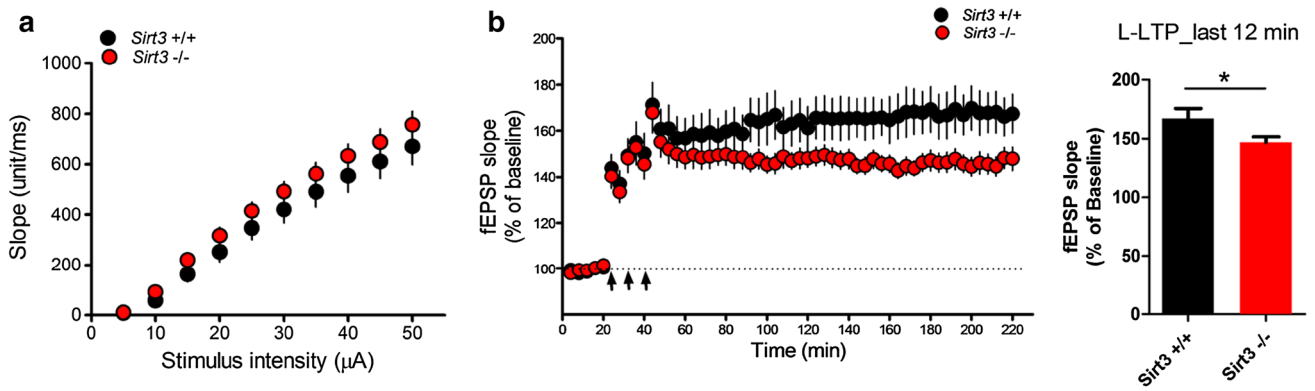


**Fig. 3** Impaired long-term potentiation (LTP) in the anterior cingulate cortex (ACC) of the *Sirt3*$^{-/-}$ mice. **a** The input–output (I/O) relationships in the ACC were similar in the *Sirt3*$^{+/+}$ and *Sirt3*$^{-/-}$ mice (*Sirt3*$^{+/+}$: n = 16; *Sirt3*$^{-/-}$: n = 14, two-way repeated measures analysis of variance ANOVA, $P > 0.05$). **b** LTP recordings in the ACC for 220 min (left) and the average slope of field excitatory postsynaptic potential (fEPSP) in the last 12 min (right). The fEPSP slope in the last 12 min was significantly reduced in the *Sirt3*$^{-/-}$ mice compared with the *Sirt3*$^{+/+}$ mice (*Sirt3*$^{+/+}$: n = 8; *Sirt3*$^{-/-}$: n = 7, unpaired *t*-test, $^{*}P < 0.05$). The black arrows indicate a theta burst stimulation (TBS) for LTP induction

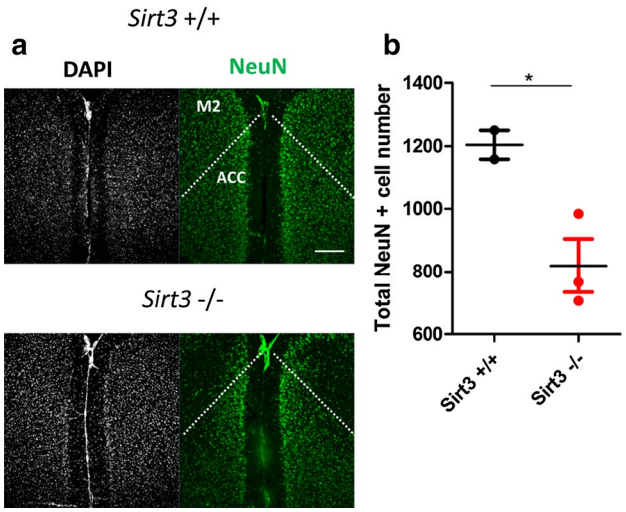


**Fig. 4** Neuronal number was reduced in the anterior cingulate cortex (ACC) of *Sirt3*$^{-/-}$ mice. **a** Photomicrograph of neuronal nuclei (NeuN) staining of the ACC of *Sirt3*$^{+/+}$ and *Sirt3*$^{-/-}$ mice. *M2* secondary motor cortex, *ACC* anterior cingulate cortex. Scale bar 100 μm. **b** Quantification of the number of NeuN-positive cells in the ACC. The number of NeuN-positive cells was reduced in the ACC of *Sirt3*$^{-/-}$ mice compared with *Sirt3*$^{+/+}$ mice (*Sirt3*$^{+/+}$: n = 2; *Sirt3*$^{-/-}$: n = 3, unpaired *t*-test, $^{*}P < 0.05$)

oxidative-stress-dependent gene expression [22, 23]. In addition, SIRT6 was recently reported to prevent DNA damage that is induced by Aβ42, which is a major component of Aβ plaques in patients with AD, even though SIRT6 has relatively low deacetylase activity [24]. Because the incidences of neurodegenerative diseases, such as AD, Parkinson's disease, and Huntington's disease are tightly correlated to age, the SIRT family of proteins is an attractive molecular target in the treatment of diseases involved in both aging and neuroprotection. Indeed, SIRT3 has been shown to attenuate neurodegeneration in mouse models of Parkinson's disease and Huntington's disease [7, 25]. Considering the involvement of SIRT3 in neurodegenerative diseases, upregulating the expression of SIRT3 might help prevent age-related neurodegenerative diseases.

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**Compliance with Ethical Standards**

**Conflict of interest** The authors declare that they have no competing interests.

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