As the aging of society, the number of surgical procedures among the elderly and the incidence of POCD is significant increasing [7, 8]. POCD has gained much attention from the public. In the light of existing studies, several hypotheses may explain the pathogenesis of POCD, like neuroinflammatory, nerve cell apoptosis, oxidative stress and epigenetic changes, but the underlying mechanisms are still unclear. Among them, neuroinflammation seems to play a central role [9–11]. Moreover, related studies have shown that stellate ganglion block (SGB) can reduce inflammation and improve cognitive impairment [12, 13].

SGB, which has been used since the beginning of the last century, is a common and safe clinical block technique [14, 15]. The technique temporarily reduces overactivity of the sympathetic nervous system and block its function of the innervation area (the head, neck, upper thorax and arms) by injecting local anesthetic in and around the stellate ganglion (located at the base of the neck) [16, 17]. With the development of modern medicine, some scientists have found that
SGB can regulate multisystemic functions in the body and is a treatment not only of the painful disorders, but also of other non-painful disorders such as autoimmune and neurological disorders [18, 19]. The findings from previous clinical studies suggested that SGB may be an effective intervention for POCD [20, 21]. This is most likely related to the reduce of inflammatory responses and the function of the SIRT1 signaling pathway [19, 21, 22]. In addition, growing evidence supports an important role for SIRT1 in the regulation of cognitive function and inflammatory response in the central nervous system [23].

Silent information regulator 1 (SIRT1) is a NAD+-dependent deacetylase [24]. SIRT1 regulates the function of many transcription factors and cofactors through deacetylation, and participates in the regulation of different biological processes, including inflammation, apoptosis, and metabolism [25]. SIRT1 is widely distributed in the neurons of brain, with high levels in the hippocampus and cerebral cortex, and low levels in the white matter [26, 27]. The hippocampus is a brain area that is known to be important for learning and memory and is highly susceptible to inflammation [28, 29]. Previous studies suggest that SIRT1 expression is essential for hippocampus-dependent memory formation [30]. This has been demonstrated in vitro and in various animal models [31].

Recently, evidence has demonstrated that white matter lesion (WML) is independent predictors and risk factors for developing dementia and POCD in the older [32, 33]. Previous research suggested that there are early widespread white matter microstructure abnormalities in POCD patients [34]. The severity of WMLs correlates with the extent of cognitive impairment [35, 36]. Lambert et al. have observed that white matter hyperintensity (WMH) is the earliest and consistent magnetic resonance imaging (MRI) change prior to the ischemic and cognitive symptoms onset [37]. Nonetheless, the exact pathophysiologic mechanisms through which white matter impair cognitive functions are unclear. Accordingly, this study aims to shed light on the underlying mechanisms that SGB improves postoperative cognitive dysfunction through SIRT1 in aged rats and investigates its association with the reduction of white matter damage using a variety of in vivo approaches.

**Materials and methods**

### Animals

A total of 128 healthy male Sprague-Dawley (SD) rats (weighing 300–350 g, 20-month-old) were used in this study. Animals were provided by Nanchang University Laboratory Animal Science (Nanchang, China) (license No.SYXXK 2021-0004). The rats were housed in a standard condition under a 12-hour light/dark cycle at constant temperature (22 ± 1 °C) and relative humidity (50 ± 10%). All animals were allowed free access to forage and activity. The animals were acclimated for at least 1 week before the start of the experiments. All procedures were conducted in accordance with the Regulations for the Administration of Affairs Concerning Experimental Animals in China. This study was approved by the Animal Ethics Committee of Nanchang University.

### Animal Experimental Design

The rats were randomly assigned to four groups (n = 32/group) using the random number table: group C, group S, group SGB and group EX. The rats in group C received a sham operation to act as a control. The rats in group S were exposed to splenectomy. The rats in group SGB underwent splenectomy and transection cervical sympathetic trunk (TCST). The rats in group EX were pretreated with EX527 before splenectomy and transection cervical sympathetic trunk. EX527 was a SIRT1 inhibitor and dissolved in 99% sterile saline/1% DMSO. The rats in group EX were pretreated with EX527 (5 mg/kg) by intraperitoneal injection five minutes before surgery, while the remaining rats were injected with equivalent amounts of saline containing 1% DMSO.

### POCD Model

In the present study, POCD model in aging rats was prepared by splenectomy, referring to the method of Bi Y et al. [38]. The rats were fasted for 12 h before surgery. The rats were deeply anesthetized with 2% sodium pentobarbital (40 mg/kg) and placed in the supine position on the surgery table. Under aseptic conditions, the abdominal wall was shaved and disinfected. A median abdominal incision (2-3 cm) was made to expose the spleen, which was then separated from the surrounding tissue. We ligated splenic vessels securely, removed the spleen and sutured the wound. Subsequently, the wound was infiltrated with 1% lidocaine for analgesia and 5% cefoperazone (50 mg/kg, intraperitoneal injection) was applied to prevent infection. After surgery, 1 ml of saline was given subcutaneously for volume repletion. The
control group (group C) was subject to the same treatment under identical conditions except for removal of the spleen.

**SGB Model**

SGB model in aging rats was made by transection of the cervical sympathetic trunk based on previous studies [39]. All groups need to do the following procedures on the basis of POCD model. After skin sterilization, a median incision (1.5-2 cm) was made on the neck. The subcutaneous tissues, fascia and muscles were bluntly detached to expose the right common carotid artery. However, the rats in the group SGB and EX need to do the additional surgical operations described below. Under a surgical microscope, the bifurcation of the right common carotid artery was exposed and the superior cervical ganglia on the dorsal side of it was found. Subsequently, the right cervical sympathetic trunk at 3-mm from the superior cervical ganglia was transected and ligated. The measures of analgesia, anti-infection and volume expansion were the same as above. The appearance of Horner syndrome (ptosis, miosis, and enophthalmos) was the measure of successful SGB model.

**Morris Water maze test**

The Morris water maze (MWM) test, established by Richard G. Morris, is widely used to evaluate the cognitive function [40, 41]. All parameters during the trials were recorded by a computerized video tracking system. The MWM comprised two portions: a circular pool and a submerged platform. The circular pool (160 cm diameter, 60 cm high) was filled with water (21–22 °C) and the water was made opaque with non-toxic and odorless white paint. The pool was divided into four quadrants, the target quadrant (the one containing the platform), and three non-target quadrants (adjacent
and opposite quadrant). The platform, 12 cm in diameter, was hidden 1 cm below the water surface. The MWM test consists of a training phase and a testing phase. The water maze test involved two phases: spatial training and probe test. On the first experimental phase, the rats without treatment were given the training of the spatial training for four consecutive days (4 trails per day with a 30s rest between each). They were randomly released in the water starting from one of four quadrants to locate the hidden platform in 120s. If at the 120s mark, the platform was not found, the rats were guided to the platform, kept on it for 30s and then the latency was recorded as 120s. For all groups, surgery was performed at the end of the first stage. One day later, the second experimental session was carried out. On the second experimental session, the spatial probe tests were performed at 1, 3, 7 and 8 days after treatment to examine spatial learning and memory. At 1, 3, 7 and 8 days after operation, eight rats per group were randomly and blindly selected respectively and each of these was allowed a free 120s swim after removing platform. The escape latency and the swimming trajectory during the probe trials were recorded separately at post-operative days 1, 3 and 7. The number of target platform crossing was recorded in post-operative day 8.

Preparation of Serum and Brain Tissue Samples

Following the MWM test on 1, 3, and 7 days, blood (2ml) were collected via tail vein bleeds from the rats (eight rats in each group) and centrifugated at 4,000 rpm for 10 min. Next, the supernatants were taken and preserved at -20 °C as serum samples. Brain tissue samples were made according to the following procedures. After that, the rats were euthanized by injecting chloral hydrate and removed the cerebral cortex. The segment of the intact hippocampus and white matter was isolated rapidly. The segment of intact hippocampus and white matter, especially corpus callosum, was stored respectively in liquid nitrogen as the hippocampal sample and the white matter sample for further use. Subsequently, we randomly chose three white matter samples from each group for the paraffin sample preparation. The paraffin samples of white matter were made as follows. The white matter samples were fixed in 4% paraformaldehyde for 24 h, washed, dehydrated, embedded in paraffin and evenly sectioned to 5 μm following standard procedure.

Enzyme-linked Immunosorbent Assay

According to manufacturer’s instructions, the supernatant of serum and white matter samples were assayed for the concentrations of TNF-α (P01375, Elabscience, China), IL-6 (P08505, Elabscience, China) and IL-10 (P18893, Elabscience, China) using Enzyme-linked immunosorbent assay (ELISA) kits.

Kluver-Barrera Staining

The demyelination, the major pathological change of white matter lesion, was observed and recorded by Kluver-Barrera staining and correlative light microscopic analysis. The previous paraffin sections (n= 3/group) were stained with Kluver-Barrera staining using NovaUltra Luxol Fast Blue Stain Kit (Abcam ab150675, USA), according to the manufacturer’s instructions.

Measurement of Expression of SIRT1 and NF-κB

Western blotting was used to determine the SIRT1 and NF-κB protein expression levels of the hippocampus and white matter. Based on the previous method of our research group [42], the above hippocampal and white matter samples were placed in EP tubes and were lysed by a radio-immunoprecipitation assay (RIPA) buffer (Boster, China) containing 1 mM phenylmethylsulfonyl fluoride (PMSF, Boster, China). The supernatant (soluble lysate) was collected after centrifugation and the protein concentration was determined using BCA assay. An equal amount of protein was separated by 8% SDS-PAGE, transferred to a polyvinylidene difluoride (PVDF) membrane, blocked with 5% non-fat milk and incubated with primary antibodies overnight. The following day, blots were incubated with the secondary antibodies for one hour at room temperature. Finally, blots were detected and recorded by a Bio-Rad Gel imaging system. The grey value of each band was analyzed by Image J (RRID: SCR_003070) and normalized to the grey value of β-actin. At least three independent experiments have been carried out. Antibodies used for western blotting analysis are listed below: Primary antibodies used in the study included rabbit monoclonal anti-SIRT1 (1:1000, Abcam Cat# ab104833, RRID: AB_10710679), rabbit monoclonal anti-NF-κB p65 (1:1000, ab222494, Abcam), rat monoclonal anti-β-actin (1:1000, Abcam Cat# ab11003, RRID: AB_297660); Secondary antibodies: goat anti-rabbit immunoglobulin G-horseradish peroxidase (IgG-HRP) (1:1000, Abcam Cat# ab6703, RRID: AB_956015).

Measurement of NF-κB Activity

NF-κB activity was analyzed using electromobility shift assays (EMSA). According to the manufacturer’s instructions, the previous hippocampal and white matter samples were separately taken and used for detection of NF-κB activity.
activity by EMSA kit (ab6558, Abcam). The EMSA gel obtained by electrophoresis were compressed by a direct compression technique with X-ray film. Autoradiography was performed at -70 °C. After 8–12 h, we used auto developing X ray film machine to develop a film. Afterwards, the results were developed on X-ray film, scanned and recorded. Quantitation and analysis of NF-κB activities was carried out by densitometry (Bandleader 3.0 software, Magnitec Ltd. Israel), and the background density was normalized by band density.

Statistical Analyses

All of the data are presented as means ± S.E.M. All data were first analyzed for normal distribution. Then, differences between two groups were compared using the Student’s t test. Differences among multiple groups were assessed using two-way ANOVA followed by Tukey Kramer multiple comparisons test. Data were analyzed with GraphPad Prism (GraphPad Software, RRID: SCR_002798). Image analysis was performed with Image J software (RRID: SCR_003070) and Bandleader 3.0 software (Magnitec Ltd. Israel). Values of p < 0.05 were considered statistically significant.

Results

The Postoperative Cognitive Dysfunction is Associated with White Matter Lesions and Inflammatory Responses

In this study, we established animal model of POCD by splenectomy, and assessed changes in inflammatory cytokines on post-operative days 1, 3 and 7 and cognitive function on post-operative days 1, 3, 7 and 8 (Fig. 1). Spatial learning and cognitive flexibility were tested by the Morris water maze test (MWM). On post-operative days 1, 3, and 7, both group C and group S could reach the hidden platform (Fig. 2a). However, the rats in group S exhibited more disordered routes, longer escape latency and lesser number of platform crossings when compared to group C (Fig. 2a, c, d). The Student’s t tests for number of platform crossing revealed significant differences (Fig. 2c; t = 9.303, p < 0.0001). The two-way ANOVA for escape latency revealed significant differences (Fig. 2d; T1: F = 194.702, p < 0.01; T2: F = 119.514, p < 0.01; T3: F = 72.000, p < 0.01). The results of probe test reflect hippocampal-dependent learning and memory. These data suggest cognitive function is impaired in aged rats of POCD.

The pathological changes of white matter in old rat were observed by Kluver-Barrera staining under light microscope. Kluver-Barrera staining of the white matter showed that the myelin sheaths were regular and uniform without evident vacuolization in group C (Fig. 2b). However, the white matter revealed aberrant myelination with vacuolar-like defects in group S, which represented white matter injury (Fig. 2b). These data indicated that white matter lesions are present in postoperative cognitive dysfunction.

ELISA was applied to compare TNF-α, IL-6, and IL-10 level in the serum and white matter between group C and S. Two-way ANOVA showed a significant difference in the serum TNF-α (T1: F = 676.672, p < 0.01; T2: F = 665.381, p < 0.01; T3: F = 470.658, p < 0.01), IL-6 (T1: F = 587.156, p < 0.01; T2: F = 511.479, p < 0.01; T3: F = 459.071, p < 0.01), and IL-10 (T1: F = 112.531, p < 0.01; T2: F = 113.484, p < 0.01; T3: F = 65.281, p < 0.01) level between group C and S. Two-way ANOVA also showed a significant difference in the TNF-α (T1: F = 42.711, p < 0.01; T2: F = 39.200, p < 0.01; T3: F = 28.900, p < 0.01), IL-6 (T1: F = 199.712, p < 0.01; T2: F = 184.500, p < 0.01; T3: F = 90.944, p < 0.01), and IL-10 (T1: F = 120.059, p < 0.01; T2: F = 73.333, p < 0.01; T3: F = 34.055, p < 0.01) level in the white matter between group C and S. At days 1, 3 and 7 after surgery, the concentrations of TNF-α, IL-6, and IL-10 in the serum and white matter were significantly increased in group S compared to group C, which demonstrated inflammatory response in vivo were activated during POCD (Fig. 2e-j). These results suggest the postoperative cognitive dysfunction is associated with white matter lesions and inflammatory responses, including peripheral and central inflammation.

Decreased SIRT1 expression and activated NF-κB signaling in the hippocampus and white matter induces postoperative cognitive dysfunction

Western blotting was used to detect the SIRT1 and NF-κB protein expression levels of the hippocampus and corpus callosum on post-operative days 1, 3 and 7. Compared with group C at the same time points, decreased expression of SIRT1 and increased expression of NF-κB in group S were observed, regardless of in the hippocampus and corpus callosum (Fig. 3a). These suggest SIRT1 activity was inhibited and NF-κB signaling was activated in the aged POCD model.

To provide further evidence of the alteration of SIRT1 and NF-κB in the hippocampus and corpus callosum, we performed two determinations. The NF-κB activity was determined with EMSA, while the relative SIRT1 protein expression was analyzed with densitometric analysis of western blotting. Two-way ANOVA showed a significant difference in SIRT1 expression (T1: F = 114.499, p < 0.01; T2: F = 113.673, p < 0.01; T3: F = 84.380, p < 0.01), and NF-κB activity (T1: F = 123.124, p < 0.01; T2: F = 72.692, p < 0.01;
our results suggest that the inhibition of SIRT1 and activation of NF-κB in both the hippocampus and white matter induces POCD.

**SGB Attenuates Inflammatory Responses by Upregulating SIRT1 and Inhibiting NF-κB Signaling**

To determine whether SGB has a potential role in POCD, we established animal model of SGB by transection of the cervical sympathetic trunk (Fig. 1). We have previously...
of the hippocampus decreased in all other groups, but that of group SGB was higher than that of group S and EX; with the exception of group C, the NF-κB activity (T1: $F = 39.609$, $p < 0.01$; T2: $F = 27.394$, $p < 0.01$; T3: $F = 22.008$, $p < 0.01$) of the hippocampus increased in all other groups, but that of group SGB was lower than that of group S and EX (Fig. 4a).

This finding was also supported by EMSA and densitometry analysis (Fig. 4b, c). Similar changes also occurred in the expression of SIRT1 and NF-κB at the white matter demonstrated that decreased SIRT1 expression in the hippocampus and white matter causes postoperative cognitive dysfunction, however it’s unclear whether SIRT1 can help SGB improve cognitive function. Therefore, we designed group EX (rats were pretreated with EX527, a SIRT1 inhibitor, before surgery) for comparison purposes (Fig. 1).

On days 1, 3 and 7 after treatment, blot images of western blotting analyses showed that, with the exception of group C, the relative SIRT1 expression (T1: $F = 46.267$, $p < 0.01$; T2: $F = 42.354$, $p < 0.01$; T3: $F = 29.609$, $p < 0.01$) of the hippocampus decreased in all other groups, but that of group SGB was higher than that of group S and EX; with the exception of group C, the NF-κB activity (T1: $F = 39.609$, $p < 0.01$; T2: $F = 27.394$, $p < 0.01$; T3: $F = 22.008$, $p < 0.01$) of the hippocampus increased in all other groups, but that of group SGB was lower than that of group S and EX (Fig. 4a). This finding was also supported by EMSA and densitometry analysis (Fig. 4b, c).
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Fig. 4 SGB modulates inflammatory responses in aged rats of the POCD model by upregulating SIRT1 and inhibiting NF-κB signaling in the hippocampus. (a) Representative western blotting bands of SIRT1 and NF-κB protein expression in the hippocampus. (b) Semi-quantitative analysis of SIRT1 protein expression in the hippocampus during post-operative days 1, 3 and 7 by densitometry. (c) Quantification of NF-κB activity in the hippocampus during post-operative days 1, 3 and 7. NF-κB activity was determined by electromobility shift assays. (d-f) The concentration of serum TNF-α, IL-6, and IL-10 during post-operative days 1, 3 and 7. (g-i) The concentration of TNF-α, IL-6, and IL-10 in white matter during post-operative days 1, 3 and 7. All data are mean ± S.E.M., N = 8/group. Two-way ANOVA and Tukey Kramer multiple comparisons test was used to analyze the significance among groups. *P < 0.05 vs. group C, +P < 0.05 vs. group S, #P < 0.05 vs. group SGB. T1 represent post-operative day 1, T2 represent post-operative day 3 and T3 represent post-operative day 7.
SGB Activates SIRT1 to Repair White Matter Damage in Postoperative Cognitive Dysfunction

To investigate the effect of SGB on white matter in POCD and a possible functional role of SIRT1, histopathology changes in white matter were first observed using Klüver-Barrera staining. The demyelination was used to assess the brain white matter damage. Compared with group C, various degrees of injury in white matter (i.e., myelin vacuolization) can be observed in the other three groups. However, that in group SGB was significantly improved compared with group S and EX (Fig. 5a). These findings imply that SGB can improve white matter damage in postoperative cognitive dysfunction.

Next, the expression of SIRT1 in white matter was assessed by western blotting. Representative samples of group S and EX revealed a markedly weakened decreased SIRT1 expression in white matter in comparison with group C; SIRT1 expression in group SGB was weaker than that of group C but much stronger than that of group S and EX (Fig. 5b). The tendency of SIRT1 expression in white matter was further confirmed by western blotting, EMSA and densitometry analysis (Fig. 5c; T1: F = 33.619, p < 0.01; T2: F = 27.624, p < 0.01; T3: F = 19.891, p < 0.01). Meanwhile, the NF-κB expression in white matter exhibited an opposite trend to that of SIRT1 (Fig. 5d; T1: F = 34.274, p < 0.01; T2: F = 32.379, p < 0.01; T3: F = 20.290, p < 0.01). These findings imply that SGB can reverse white matter damage in POCD by activating SIRT1.

SGB Ameliorates Postoperative Cognitive Dysfunction Through Activating SIRT1

To explore the effect of SGB on postoperative cognitive dysfunction, we selected to conduct a behavioral assessment on days 1, 3, 7 and 8 after surgery. The representative trajectories in spatial probe tests of MWM is shown above (Fig. 6a). The two-way ANOVA for escape latency (T1:
Discussion

In this study, we identified SIRT1 as a key molecular determinant of SGB’s effects on white matter lesion repair and hippocampus-dependent memory using a combination of molecular biology, cellular morphology, ethology, and light microscopy. The splenectomy, which was used for POCD model building, decreased SIRT1 expression in the hippocampus and white matter. The reduced SIRT1 levels could further trigger or exacerbate neuroinflammation, caused white matter damage and eventually lead to cognitive impairments in old rats. It’s worth noting that EX527, a SIRT1 inhibitor, caused increased neuroinflammation, aggravated white matter injury, and worsened cognitive impairment. SGB could ease SIRT1-mediated neuroinflammation, correct white matter injury, and diminish cognitive impairments in old rat. These results imply that SIRT1-mediated white matter damage repair may play a key role...
in the mechanism that SGB improved POCD in aged rats (Fig. 7).

POCD is a universal central nervous system complications defined by a cognitive disturbance after surgery [43]. Since POCD was originally reported in 1955, it has been a hotspot subject in anesthesiology and neurology [44]. POCD may produce many adverse outcomes, including worse recovery, lower quality of life, heavier economic burden and higher mortality [3–6]. Therefore, POCD has gained widespread attention from the public. Multiple studies were used for exploring POCD pathogenesis [45] and establishing the means of diagnosis and treatment. The etiology of POCD is multifactorial. Previous studies have indicated that it involved a complex interaction between patient, environmental, and iatrogenic factors, and the main is advancing age [46]. Many research has demonstrated that patients over 65 years of age who have undergone operation or critical illness are at a higher risk for it [47–49]. Thus, we adapted 20-month-old male rats for establishing animal model. POCD present in 25.8% of patients at seven days after surgery and 9.9% at three months; in some cases, it may persist in the long run [50]. So, we selected the samples on postoperative day 1, 3, 7 and 8 for detecting molecular, histologic and cognitive function changes. Many studies have revealed that several potential mechanisms, including hippocampal neuroapoptosis with the correlations in SIRT1, central autophagy, oxidative stress and neuroinflammation, would induce cerebral neuron damage and may underlie the

Fig. 7 The pathophysiological mechanism that decreased SIRT1 induced white matter lesion in POCD and SGB reversed POCD using SIRT1-mediated white matter damage repair. WML represent white matter lesion.
pathogenesis of POCD [51–53]. Although the exact pathophysiological mechanisms underlying POCD remain to be clarified, neuroinflammation and blood-brain barrier damage has been confirmed as the major factors [9, 52, 54]. Habbas et al. (2015) have found that increased levels of the cytokines tumor necrosis factor alpha (TNF-α) and Interleukin-6 (IL-6) have been linked to the emergence of cognitive impairments following inflammation in the central nervous system [55, 56]. In the present study, to confirm that inflammatory responses were affecting POCD in animal model, we examined inflammatory factors in aged rats. We found that peripheral and central concentrations of the inflammatory chemokines, including fibrinogens and complement components, including fibrinogens and complement components, may cause endothelial injury and increased blood-brain barrier permeability, resulting in neuroinflammation and cognitive dysfunction (Fig. 2).

Cerebral white matter is the place where nerve fibers and neuroglial cells gather inside the brain, and the white color of the subcortical tissue comes from myelinated nerve fibers. Generally, cognitive abilities are determined by the integrity of white matter structures [57–59]. With the development of advanced imaging and detection techniques, WML is well-visualized. The major pathological change of WML is demyelination whose early feature is myelin vacuolization; the imaging manifestation of WML is WMH, which is hyperintense signals on T2-weighted MRI in the subcortical white matter. In recent years, a large number of research have shown that white matter injury contributes to postoperative cognitive dysfunction [60–62], which is associated with blood-brain barrier [63]. The WMH was detected by MRI in over 50% of the elderly [64–66]. The mechanism, white matter injury causes POCD, is focused on oxidative stress, inflammation and excitotoxicity [67, 68]. Nevertheless, the specific mechanism remains elusive. WML has been associated with cerebral hypoperfusion or blood-brain barrier disruption. Because white matter components (e.g., oligodendrocytes) are highly sensitive to ischemia-induced oxidative stress and excitotoxicity [64]. Our research validated that the overexpression of peripheral and central inflammatory chemicals and WML is involved in POCD (Fig. 2). Studies showed that blood-brain barrier compromise may explain the correlation between the peripheral inflammation and the neuroinflammation [69]. Inflammation could also impair neuronal function by demyelination [70, 71]. Therefore, one possibility is that overproduction of peripheral inflammatory cytokines after surgery leads to blood-brain barrier damage. When the blood-brain barrier is disrupted, inflammatory cells and other serum substances including fibrinogens and complement components are transferred into the central nervous system, where they release a range of cytokines. These may eventually result in the white matter demyelination and axonal damage, and induce the white matter lesion.

SIRT1 is a NAD+-dependent deacetylase. NF-κB is an important transcription factor and is a downstream regulatory protein of SIRT1 [72]. NF-κB, a heterodimer formed by p65 (RelA) and p50 (NF-kB1), can induce pro-inflammatory factors and form the hippocampus-dependent memory [73–75]. Therefore, SIRT1 can inhibits NF-κB activity by deacetylating its subunit RelA/p65, remits inflammation responses and decreases neurons lesions [76]. Increasing evidence supports SIRT1 plays a significant role in the cognitive dysfunction and inflammatory reaction [23, 77]. The hippocampus is a brain area that plays a vital role in learning and memory. Meanwhile, the hippocampus highly express proinflammatory cytokine receptors, specifically receptors for TNF-α and IL-6, and more vulnerable to the deleterious effects of pro-inflammatory molecules, which have been proved in various animal models [31]. Thus, earlier research of cognitive function mainly focused on hippocampus [78, 79], with less attention to other tissues. However, as research progresses, we found white matter injury can cause POCD, SIRT1-mediated hippocampal neuroapoptosis may causes POCD, and both are correlated with inflammation. So, is POCD caused by white matter damage related to inflammatory and the function of SIRT1? Where do these changes in SIRT1 occur? To further confirm this idea, we evaluated white matter injury by Kluter-Barrera staining, tested the expression of SIRT1 and NF-κB in hippocampus and white matter by western blot, and detected the cognitive functions by water maze. Our findings indicated that SIRT1 was expressed in white matter and hippocampus and downregulated SIRT1 expression enhanced NF-κB signaling. These could induce inflammation, cause white matter injury, and eventually lead to cognitive dysfunction (Figs. 2 and 3). These agree with earlier research.

Related research have shown that SGB can improve POCD [12, 21]. The pathophysiologic mechanisms were linked to the reduce in inflammatory responses and the function of the SIRT1 signaling pathway [19, 22]. Recent advances in neuroprotection research have identified that white matter is an underlying therapeutic target for neuroprotection [80]. Myelin sheath and oligodendrocyte are considered as the key treatment target of white matter lesion repair [81–83]. In order to further elaborate the impact of SGB on white matter lesion in POCD and its relationship with SIRT1, we established SGB model in aging rats by transection of the cervical sympathetic trunk based on previous studies, and set group EX that rats were pre-treated with EX527 (a SIRT1 inhibitor) as a comparison. Next, we observed the expression of SIRT1 and NF-κB by western blot, white matter lesion by Kluver-Barrera staining and
cognitive function by water maze in different experimental groups at days 1, 3, 7 and 8 after treatment. Our results showed that SGB stimulated the secretion of anti-inflammatory (IL-10) and pro-inflammatory (IL-6, TNF-α) chemicals at the same time and anti-inflammatory was higher than pro-inflammatory chemicals, in accordance with the results of inflammatory molecules levels in serum and white matter (Fig. 4d-i). The rats exhibited an anti-inflammatory state. Our results have also demonstrated SGB activated SIRT1 expression, inhibited the pro-inflammatory NF-κB signaling pathway and the rats exhibited an anti-inflammatory state. That reduced white matter injury and improve cognitive deficits in aged rats (Figs. 4, 5 and 6). After Ex527 treatment, the SIRT1 expression was inhibited, NF-κB signaling was activated, pro-inflammatory response was elicited, white matter injury was obversed, and cognitive dysfunction occured (Figs. 4, 5 and 6). That is the same as related studies and our observation. Based on these results, one possible is that SGB exerts anti-inflammatory effects by activating SIRT1 and inhibiting NF-kB, and hence repaired WML and improved POCD. Therefore, these findings proved that SGB have the capacity to repair white matter injuries and neuroprotective for POCD. The capacity may be SIRT1-dependent. The utility of SIRT1 in SGB repairing WML and POCD provides a new direction for future diagnosis and treatment of POCD in the aged population.

There are several limitations to this study. First of all, in addition to morphology and molecular biology, more methods should be used for the assessment of white matter injury. Secondly, although our research has a potential clinical application, we should more conservative when extrapolating the findings to humans because our current study was mainly carried out in rat. Finally, the effects of cerebral perfusion on neuroinflammation and cognitive dysfunction were not considered in this study, which is worthy of further study.

**Conclusion**

In conclusion, we provide strong evidence to prove that postoperative cognitive dysfunction is associated with white matter injury, and reveal that stellate ganglion block can improve postoperative cognitive impairment by repairing white matter lesion by activating SIRT1. Among them, neuroinflammation are a key hallmark of neurodegenerative diseases, including POCD. SIRT1 acts as a link between white matter damages and cognitive impairments after surgery. Our study sheds new light on the pathophysiology of POCD and clarifies that SIRT1 and white matter could be a new therapeutic target in neurodegenerative illnesses.

**Abbreviations**

- DMSO: Dimethyl sulfoxide
- ELISA: Enzyme-linked immunosorbent assay
- EMSA: Electromobility shift assays
- IgG-HRP: Immunoglobulin G-horseradish peroxidase
- IL-6: Interleukin-6
- IL-10: Interleukin-10
- MRI: Magnetic resonance imaging
- MWM: Morris water maze test
- NF-κB: Nuclear factor- kappa B
- POCD: Postoperative cognitive dysfunction
- PMSF: Phenylmethylsulfonyl fluoride
- PVDF: Polyvinylidene difluoride
- RIPA: Radio-immunoprecipitation assay
- SD rats: Sprague-Dawley rats
- SGB: Stellate ganglion block
- SIRT1: Silent information regulator 1
- TNF-α: Tumor necrosis factor-alpha
- WMH: White matter hyperintensity
- WML: White matter lesion

**Contributions:** Study conception and design and animal study: Jun Zhang, Yang Liu, Hejian Li; data acquisition and analysis: Qin Liu, Yanyui Hu, Shuchun Yu; manuscript draft: Jun Zhang; manuscript revision: Yong Chen. All authors read and agreed to the final manuscript of the manuscript.

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**Data Availability** All relevant data are available in the main text or from the authors.

**Declarations**

**Competing Interests** All authors declare that they have no competing interests.

**Consent to Participate and Publish.** Not applicable.

**Ethical Approval** Our study was approved by the Animal Ethics Committee of Nanchang University.

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