RESEARCH ARTICLE

Effect of the High-Intensity Interval Training on BDNF Level in Ischemic Stroke Rat Model on the Recovery of Motor Function

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Abstract

BACKGROUND: Stroke is one of the major causes of disability in the world. High-intensity interval training (HIIT) is known as a novel treatment to promote stroke recovery. However, the results differ in their effects on irisin, which is a regulator of brain-delivered neurotrophic factor (BDNF). Therefore, this study was conducted to investigate the effect of HIIT on BDNF and irisin levels in a rat model of ischemic stroke with middle cerebral artery occlusion (MCAO) induction on recovery motor function.

METHODS: Rats were categorized into 4 groups: sham, MCAO, MCAO+moderate-intensity interval training (MIIT), and MCAO+HIIT. MCAO induction was performed to create the ischemic stroke rats model. The motor function was assessed through rotarod and footprint tests. Blood samples were obtained 6 days before MCAO and 14 days after MCAO to examine BDNF and irisin levels with enzyme-linked immunosorbent assay (ELISA). Brain tissue samples were collected 14 days after MCAO for histopathological examination of cortical tissue with hematoxylin-eosin (HE) staining.

RESULTS: Rats in the MCAO+HIIT group exhibited an enhanced ability to walk on the rotarod (p=0.016). The stride-length hind paw right in the MCAO+HIIT group demonstrated a noteworthy increase in comparison to baseline value (p=0.036), and the stride-length fore paw right showed a significant increase in both the MCAO+HIIT (p=0.036) and MCAO groups (p=0.034). BDNF significantly improved in the MCAO+MIIT (p=0.043) and MCAO+HIIT groups (p=0.018). The irisin level only showed a significant enhancement in the MCAO+HIIT group (p=0.018).

CONCLUSION: HIIT increased motor function, while BDNF level increased with HIIT and MIIT intervention. This preclinical research is useful for supporting the recovery of stroke patients by HIIT intervention.

KEYWORDS: BDNF, HIIT, MIIT, irisin, ischemic stroke, MCAO

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Introduction

Strokes, which are a prominent contributor to disability worldwide, have a significant impact on individuals, their families, and healthcare systems.(1) It is estimated that half of stroke patients suffer from hemiplegia, and 30% of these individuals require assistance with walking.(2) The presence of motor neurological impairments commonly gives rise to walking difficulties post-stroke.(3) However, it is essential to note that spontaneous recovery from ischemic stroke is limited, often resulting in the loss of both motor and sensory functions, to address these challenges, rehabilitative training has emerged as the most widely accepted approach to improve long-term outcomes.(4) Moreover, high-intensity interval training (HIIT) specifically tailored for locomotion has shown promise as an innovative therapeutic intervention for stroke recovery.(5)

HIIT is a type of physical activity that involves brief periods of vigorous aerobic exercise followed by short periods of low-intensity or recovery exercises.(6) The practice of HIIT has been observed to positively influence the malleability of the hippocampus, a brain region associated with the processes of learning and memory.(7) Moreover, HIIT has been found to have beneficial effects on the regeneration of muscles and physical function.(8) HIIT has a greater impact on VO_2 max, neuromuscular components, and the vascular system compared to low-intensity interval training (LIIT).(9) HIIT and moderate intensity continuous exercise (MICE) interventions have enhanced neurocognitive performance and peripheral brain-delivered neurotrophic factor (BDNF) levels. However, they differ in their effects on irisin (6), a myokine released by skeletal muscles that play a protective role in the central and peripheral nervous systems and the regulation of BDNF.(10)

Post-stroke rehabilitation entails the process of reacquiring motor abilities through the mechanism of neuroplasticity.(11) BDNF has emerged as a substantial promoter of neuroplasticity in the context of motor acquisition and recuperation following a stroke.(12) Neuroplasticity is the foundation for reinstating motor functionality and functional capacity after a stroke.(13) Optimal neuroplasticity transpires within the initial 0-6 months post-stroke.(14)

The polypeptide hormone irisin was synthesized through the cleavage of fibronectin type III domain containing 5 (FNDC5) which is produced and expressed in skeletal muscle tissue.(15) Irisin exerts its effects on adipose tissue by stimulating the transformation of white adipose tissue into brown adipose tissue.(16) In instances of ischemic stroke, physical activity has the potential to enhance the circulation of irisin.(17) In the aftermath of cerebral ischemia, physical exercise, particularly using activating irisin, could potentially decrease mortality rates and enhance cognitive function.(18) A study has demonstrated that irisin can impede the damage inflicted upon neurons by ischemia.(19) The utilization of irisin presents the possibility of effectively treating ischemic stroke.(20)

The middle cerebral artery occlusion (MCAO) model is the most representative model for studying human ischemic stroke *in vivo*. This model is employed in more than 40% of trials. The use of intraluminal sutures to induce the blockage of the middle cerebral artery (MCA) in rats is a well-known and standardized animal model.(21)

Limited research investigating the subject of irisin and BDNF on ischemic stroke, both from a clinical perspective and *in vivo* conditions. There has not been enough research done to investigate the benefits of HIIT in the recovery of motor function following a stroke that is linked to neurotrophins and myokines. Consequently, this study was conducted to investigate the impact of HIIT on the levels of BDNF and irisin, as well as the enhancement of motor function in rats subjected to the MCAO model.

Methods

Animals Model and Treatment

Twenty-eight male Wistar rats weighing 250-400 g, procured from PT Biofarma (Bandung, Indonesia), were housed in cages with a light/dark cycle of 12 hours and given *ad libitum* access to food, water, and lithium. The rats were randomly allocated into 4 distinct groups with 7 rats in each group; namely 1) the sham group, which was not ischemia-induced and did not receive any exercise; 2) the MCAO group, which was ischemia-induced but did not receive any exercise; 3) the MCAO+MIIT group, which was ischemia-induced and received moderate-intensity interval training (MIIT); and 4) the MCAO+HIIT group, which was ischemia-induced and received HIIT.

Blood samples were collected 6 days before the surgical procedure through the suborbital route and 14 days after the occurrence of MCAO. Treadmill and rotarod training were conducted 5 days to 1 day before MCAO. Rotarod and footprint examinations were performed 1 day before MCAO and on day-1, -7, and -13 following

MCAO. The research design was graphically depicted in Figure 1. The protocol of this study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo Central General Hospital (No. KET-762/UN2.F1/ETIK/PPM.00.02/2022).

MCAO Procedure

In our investigation, the MCAO procedure adhered to previous scholarly inquiry.(22) Briefly, all rats were administered with sedatives consisting 80mg/kg ketamine and 10mg/kg xylazine, through intraperitoneal injection and were then positioned supine. The cervical skin was incised, followed by the ligation of the left common carotid artery (CCA), external carotid artery (ECA), and internal carotid artery (ICA). A small incision was subsequently made in the ICA. A nylon suture 4.0 tip was rendered blunt by applying heat from an incandescent lamp.

The nylon suture 4.0 was then introduced into the origin of the MCA through an incision in the ICA. The nylon suture 4.0 positioned within the MCA was maintained for a duration of 90 minutes. Subsequently, the nylon suture 4.0 was slowly withdrawn. Rats in the sham group underwent all surgical procedures without occlusion of the MCA. The consciousness and body temperature levels were monitored before, during, and after the occlusion period.

Training and Incremental Exercise Tests on the Treadmill

Training and maximum speed tests followed previous research (23) and were modified and adapted to the rats condition. All rats were accustomed to running on a treadmill to determine the running speed according to the rats' ability and to limit stress while running on the treadmill. The training sessions, lasting 5 minutes each, were conducted daily for 5 consecutive days at a low-velocity range of 39-59 revolutions per minute (rpm). Specifically, on the initial and 2nd days, the training was executed at a pace of 39 rpm; the 3rd and 4th days entailed training at 49 rpm, while the 5th day encompassed training at a rate of 59 rpm.

Velocity examinations were conducted on the day following MCAO to determine the dose of HIIT and MIIT interventions. The assessment involved an initial warm-up period of 5 minutes, during which the speed was set at 39 rpm. Subsequently, a 20-second rest period ensued, followed by the continuation of the treadmill at a speed of 49 rpm for a duration of 3 minutes. Another 20-second resting interval ensued before progressing to the subsequent speed level. The highest speed attained during the previous stage was the maximum speed (S_{max}).

HIIT and MIIT

The HIIT intervention employed in this study was based on previous research conducted by others.(23) However, it was essential to note that the duration of the exercise period was relatively short, spanning only a duration of 2 weeks. The intervention itself consisted of 5 sessions per week over the course of these 2 weeks. Both HIIT and MIIT interventions involved utilizing maximum speed during the exercise sessions. Specifically, the MCAO+HIIT group exercised at 80% S_{max} in the first week of treadmill intensity. In contrast, this intensity was increased to 90% of S_{max} in the 2nd week.

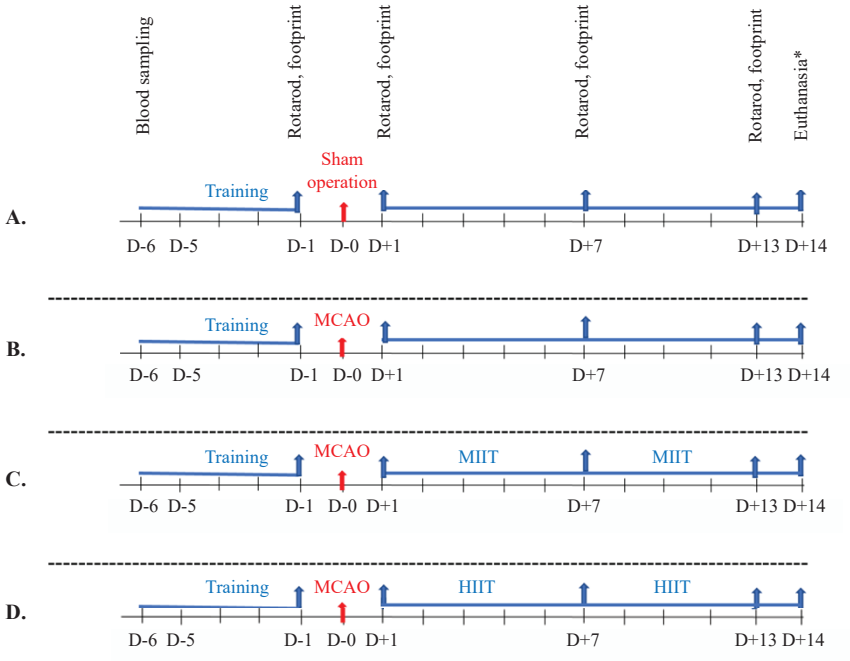

Figure 1. Schematic illustration of the *in vivo* experimental study. A: Sham group; B: MCAO group; C: MCAO+MIIT group; D: MCAO+HIIT group. HIIT and MIIT intervention were conducted with treadmill apparatus. *After the euthanasia, blood, brain, and muscle tissue sampling were conducted.

On the other hand, the MCAO+MIIT group exercised at an intensity of 50% of S_{max} during the 1st week and then increased to 60% of S_{max} during the 2nd week. The remaining speed for the MCAO+HIIT and MCAO+MIIT groups remained consistent at 30% S_{max}. The HIIT and MIIT interventions comprised four sets of four-minute exercise intervals, followed by four sets of three-minute rest periods. Thus, the total duration for each HIIT and MIIT intervention session was 28 minutes. Further details regarding the speed at which each rat exercised can be found in Table 1.

Rotarod Test

The motor coordination and balance of the forelimbs and hindlimbs were assessed using the rotarod test conducted with the Apparatus Rotarod from the Department of Physiology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia. The rats were subjected to the accelerating rotor mode, wherein the acceleration varied from 4 to 40 rpm for a duration of 300 seconds. An impartial investigator, unaware of the experimental groups, observed and noted the duration for which the animal remained on the rod. The statistical analysis produced the ultimate score, representing the average duration a rat maintained its balance on the rod throughout three trials.(24)

Footprint Test

The test procedure for assessing footprints refers to the previously employed methodologies.(25) Before the commencement of the experiment, the rats underwent a training process wherein they were familiarized with traversing the SFI Alley, a designated walkway in the Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia. The prepared sheet of paper was situated within the confines of the SFI Alley, and subsequently, the paws of the rats were coated with ink of four distinct hues. Once this preparatory step had been completed, the rats were promptly placed at the proximal extremity of the alley and were permitted to traverse towards the distal end. It is important to note that the rats needed to maintain a unidirectional trajectory throughout the walking phase, if it returns to its direction then the test is repeated. Upon the experiment's conclusion, the rats were carefully reintroduced to their respective cages.

The paper, which had documented the footprints of the rats, was subjected to a drying process while the SFI Alley was thoroughly cleaned. The test was repeated when the obtained results were deemed inconclusive. Ultimately, evaluating the stride lengths of the forepaws and hind paws constituted the outcome measurements. The stride length of the right hind paw (SLHR) was obtained by measuring the stride distance of the right hind foot and the stride length of the fore paw right (SLFR) was obtained by measuring the distance of the right front foot.(26)

Neurological Assessment

Before being nylon suture pulled again, as a parameter of MCAO's success, each rat was subjected to a meticulous assessment of neurological deficit using the Bederson scoring system, which ranges from 0 to 5.(23) In current study, the Bederson parameters employed were as delineated below: A score of 0 signifies the absence of any observable impairment, a score of 1 indicates flexion of the forelimb, a score of 2 denotes flexion of the forelimb coupled with diminished resistance to lateral force, a score of 3 signifies the occurrence of circling, a score of 4 indicates the presence of circling together with spinning around the cranial-caudal axis, and lastly, a score of 5 signifies the absence of any spontaneous movement.

Triphenyl Tetrazolium Chloride (TTC) staining

After a period of 24 hours following MCAO, a single rat was sacrificed for experimental purposes. Before the sacrifice, the rat was administered a sedating mixture consisting of ketamine and xylazine with a lethal dose via intraperitoneal injection. To determine the extent of brain infarction, the staining technique involving the utilization of 2, 3, and TTC staining was employed. The brain tissue was promptly extracted and then sectioned into slices that were 2 mm thick. These slices were subsequently immersed in a 2% TTC solution at a temperature of 37.8°C for a duration of 15

Table 1. Maximum speed, intervention speed, and rest speed on MCAO+MIIT and MCAO+HIIT groups.

Session	Group	Maximum Speed*	Speed of intervention*	Rest Speed*
Week 1	MCAO+MIIT	88±9	44±4	27±3
	MCAO+HIIT	79±10	63±8	24±3
Week 2	MCAO+MIIT	88±9	52±5	27±3
	MCAO+HIIT	79±10	71±9	24±3

*unit in rpm.

minutes, all within a dark environment. The digital scanning of these slices was performed using a smartphone. It is important to note that infarcted tissue appears white, while normal tissue is characterized by its red coloration.(27)

Enzyme-linked Immunosorbent Assay (ELISA)

Blood samples were obtained 6 days before MCAO through retroorbital collection and 14 days after MCAO through cardiac sampling. An approximate volume of 3mL of blood was acquired. Subsequently, the blood underwent centrifugation at a force of 3500 x g for a duration of 15 minutes, resulting in the extraction of approximately 1.2 mL of serum. The BDNF level measurement was accomplished using the Rat BDNF ELISA Kit (Cat No. MBS824814, My BioSource, San Diego, CA, USA). In contrast, the determination of the irisin level was carried out by Rat ELISA Kit (Cat No. MBS2601445, My BioSource), according to the manufacturer's stipulations. Then, approximately 100 µL from each sample was transferred into a 96-well ELISA plate, and the ultimate absorbance within each well was measured at 450 nm utilizing a plate reader.(28)

Haematoxylin and Eosin (HE) Staining

After 14 days following MCAO, all rats were euthanized. After the euthanization process, cerebral tissues were preserved through fixation utilizing a 4% solution of paraformaldehyde. The tissues were embedded in paraffin and subsequently sectioned into 4 µm pieces with a microtome (LEICA RM2125 RTS, Leica Camera, Wetzlar, Germany). These sections were subsequently stained with HE. Subsequently, the sections were subjected to examination via microscopy to ascertain and evaluate any potential histopathological alterations occurring within the frontalis lobes of the cortex of the rats. Using ImageJ software (National Institutes of Health, Bethesda, MD, USA), the number of surviving neurons in the cerebral cortex was counted and then divided by the area to obtain the density of the neuron.(29)

Results

MCAO Induced Ischemia in Rats

The successful creation of an experimental animal model for ischemic stroke through the use of MCAO was confirmed by a neurological examination revealing a deficit, as indicated by a Bederson score ranging from 0 to 5, conducted 1 hour after the occlusion procedure. TTC staining performed 24 hours after the occlusion further validated the model's efficacy. The results of the Bederson test showed an average score of 3 among the MCAO, MCAO+MIIT, and MCAO+HIIT groups (Figure 2).

Effect of HIIT in Restoring Motor Performance

The application of the rotarod was subjected to a non-parametric Friedman test analysis, revealing a significant difference in the MCAO+HIIT group (p=0.016) compared to the MCAO+MIIT, MCAO, and sham groups (Figure 3A). Wilcoxon signed-rank involving Bonferroni correction showed that the rats walking time on the rod on D+13 was higher than D+1 (p=0.018) on the MCAO+HIIT group.

The non-parametric Friedman Test was employed to analyze the SLHR data. The results indicated a significant difference on D-1, D+1, D+7 and D+13 in the MCAO+HIIT group (p=0.036) and in the MCAO group as well (p=0.034), but no difference in MCAO+MIIT and sham groups. However, the MCAO group exhibited a decline in data from D-1 to D+13 (Figure 3B). Wilcoxon signed-rank involving Bonferroni correction showed SLHR on the MCAO+HIIT group on D+13 was higher than D+1 (p=0.018). While the MCAO group showed SLHR on D+13 was lower than D+7 (p=0.028) and on D+13 was lower than D+1 (p=0.018). One-way ANOVA of SLHR on D+7 between groups showed a difference significant (p=0.038). LSD *post hoc* showed MCAO+MIIT *vs.* MCAO showed a significant difference (p=0.010) and MCAO+MIIT *vs.* sham also showed a significant difference (p=0.025).

The non-parametric Friedman Test was conducted for SLFR using the D-1, D+1, D+7, and D+13 data. The results revealed a significant difference in D-1, D+1, D+7, and D+13 in the MCAO+HIIT group (p=0.036) and the MCAO group as well (p=0.034) but no difference in the MCAO+MIIT and sham groups (Figure 3C). Wilcoxon

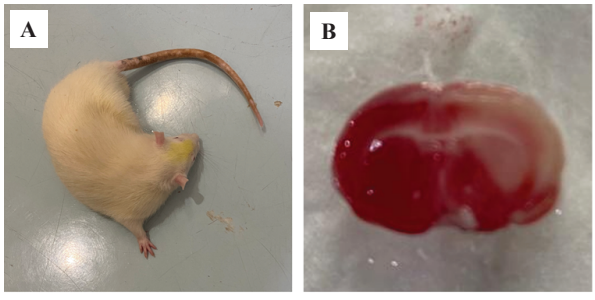

Figure 2. Results of neurological assessment and TTC staining. A: Clinical features and results of Bederson examination value of 3. B: TTC staining results in cerebral artery occlusion stroke models after 24 hours of occlusion, with white indicating the area of infarction.

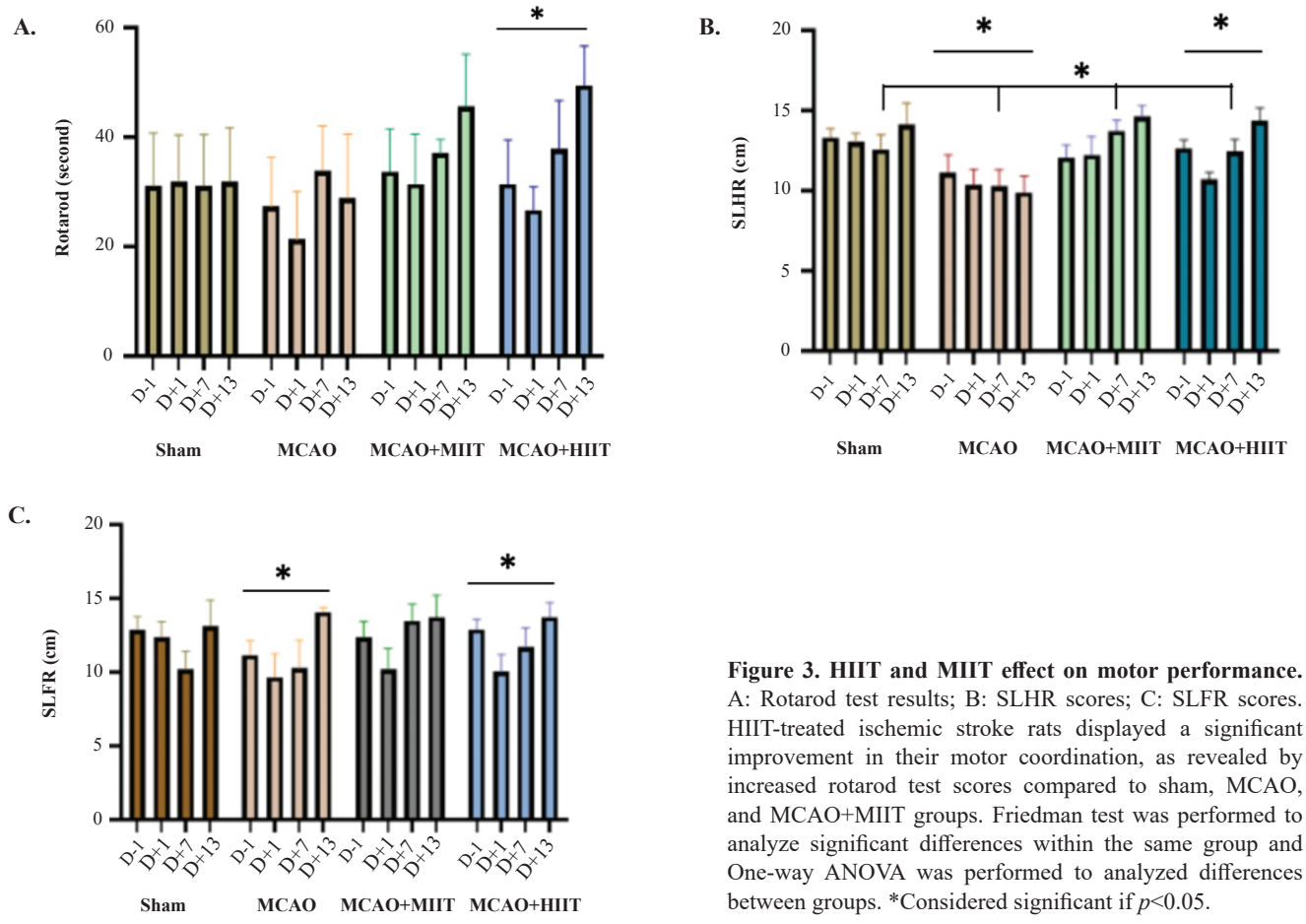

Figure 3. HIIT and MIIT effect on motor performance. A: Rotarod test results; B: SLHR scores; C: SLFR scores. HIIT-treated ischemic stroke rats displayed a significant improvement in their motor coordination, as revealed by increased rotarod test scores compared to sham, MCAO, and MCAO+MIIT groups. Friedman test was performed to analyze significant differences within the same group and One-way ANOVA was performed to analyzed differences between groups. *Considered significant if $p<0.05$.

signed-rank involving Bonferroni correction showed SLFR on the MCAO group on D+13 was higher than D+1 ($p=0.018$) and on D+13 was higher than D-1 ($p=0.028$). While the MCAO+HIIT group showed SLFR on D+7 was higher than D+1 ($p=0.027$).

Effects of HIIT on BDNF and Irisin Levels

Wilcoxon's non-parametric related-samples test assessed the BDNF level in the pre-and post-data. The analysis revealed a noteworthy disparity in the MCAO+HIIT group ($p=0.018$), and the MCAO+MIIT group ($p=0.043$), and no difference in the MCAO and sham groups. There was a substantial dissimilarity between the group that received high-intensity and moderate interventions and the MCAO and sham groups (Figure 4A).

Meanwhile for the irisin level, Wilcoxon's non-parametric related-samples test on pre- and post-data showed a significant difference between pre and post in the MCAO+HIIT group ($p=0.018$) but no difference in MCAO+MIIT, MCAO, and sham groups. However, the irisin level for the MCAO group was already elevated in pre-data (Figure 4B).

Correlation between BDNF and Irisin Levels

The correlation test was performed by Pearson correlation test on D-6 and D+14 data at BDNF and irisin serum levels. The D-6 data of BDNF and irisin serum levels obtained $p<0.050$ ($p=0.027$) with a moderate correlation level ($\rho=0.417$). The D+14 data on BDNF and irisin levels obtained $p>0.050$, which stated no relationship between BDNF and irisin levels.

Effects of HIIT on Neurons in the Cerebral Cortex

The representative photomicrographs of the cerebral cortex's neurons are shown in Figure 5A. Neurons showed an orderly and compact arrangement in the cortex area in the sham group. In the MCAO group, loss, shrinkage, and loose neurons were observed in the cerebral cortex. In contrast, the MCAO+HIIT group performed almost the same as the sham group in the cerebral cortex region. The number of intact neurons decreased significantly in the cerebral cortex areas in the MCAO and MCAO+MIIT groups. Meanwhile, the number of intact neurons in the MCAO+HIIT group was higher compared to the MCAO and MCAO+MIIT groups ($p<0.001$) (Figure 5B).

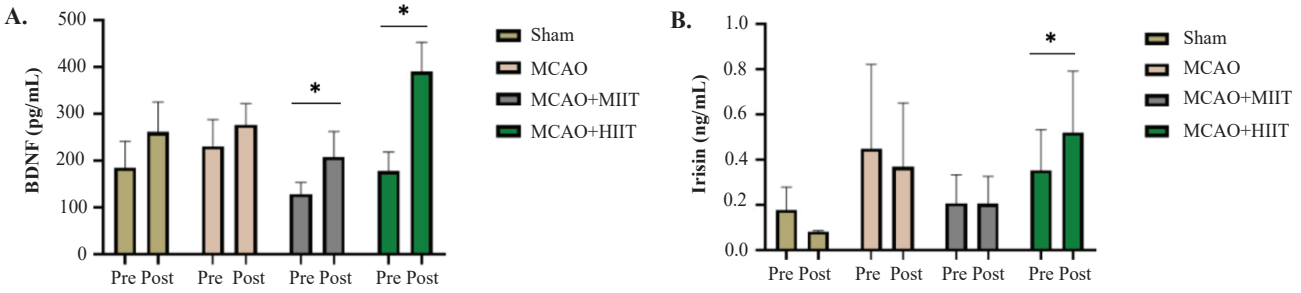

Figure 4. Effect of HIIT on BDNF and irisin levels. A: HIIT-treated ischemic stroke rats significantly improved BDNF levels in the MCAO+HIIT and MCAO+MIIT groups; B: The irisin level improved in the MCAO+HIIT group and was already elevated in pre-data on the MCAO group. Tested with related-samples Wilcoxon. *Considered significant if $p<0.05$.

Discussion

The current study investigated the effect of HIIT on BDNF and irisin levels in a rat model of ischemic stroke with MCAO induction on recovery motor function. The results showed the ability of rats to walk on rotarods increased in the MCAO+HIIT group. The SLHR of the rats in the MCAO+HIIT group showed a significant increase and no difference in the other groups, and the SLFR showed a significant increase in the MCAO+HIIT and MCAO groups. At the BDNF level, our results showed significant improvement in the MCAO+HIIT and MCAO+MIIT groups and no difference in the MCAO and sham groups. The irisin level in the MCAO+HIIT group significantly improved and no difference in the MCAO+MIIT, MCAO, and sham groups.

We utilized the rotarod examination to evaluate post-stroke motor proficiency and equilibrium. The duration of time that rodents were able to ambulate on the rotarod was documented. Our study states that HIIT improves motor coordination with the rotarod test (Figure 3A) The outcomes of the examination and analysis of the rotarod coincided with earlier research, which demonstrated the time it took for the rat to maintain stability while traversing the rods.(30) We did not investigate the latency and distance

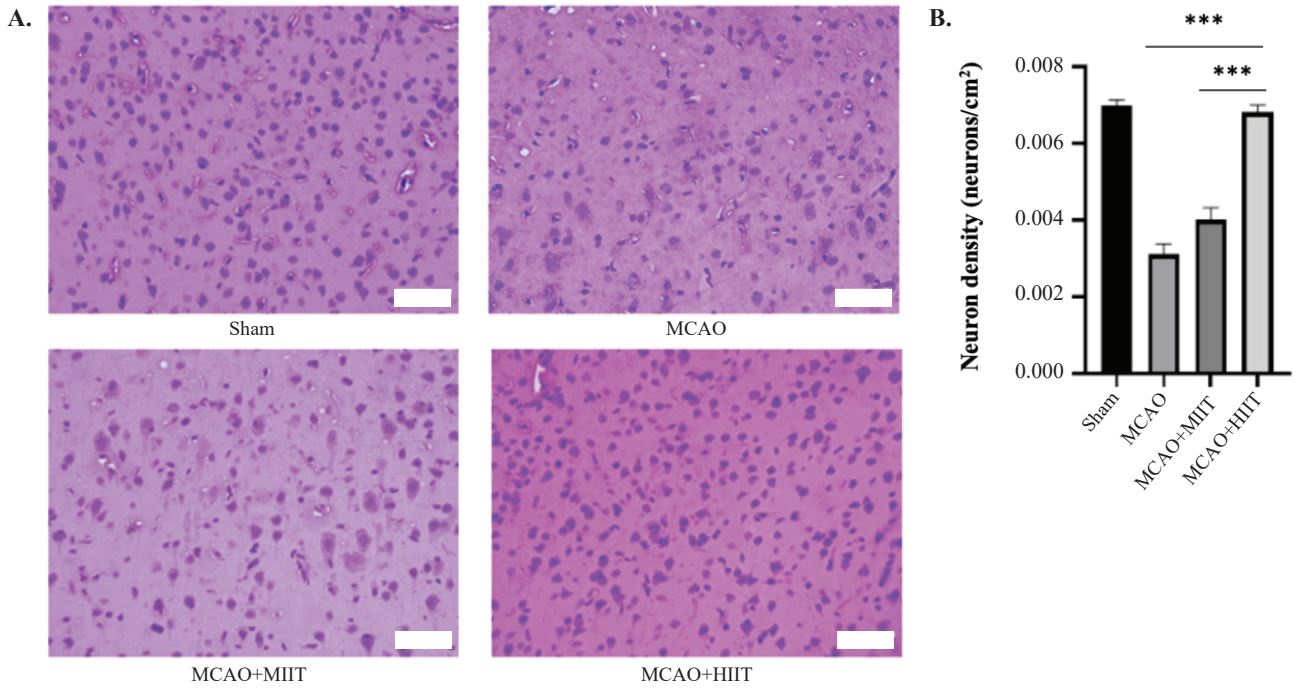

Figure 5. HIIT reduces brain tissue damage and neuronal deformation. A: Cell morphology in the cerebral cortex of rats in each group by hematoxylin and eosin staining (white bar: 10 µm); B: Quantification analysis of the density of neurons in the cortex. Tested with one-way ANOVA and Bonferroni *post hoc*. ***$p<0.001$ (considered significant if $p<0.05$).

in our findings because not all specimens could run on rods rotating at 5 rotations per minute for a duration of 60 seconds before the examination. This contradicts a previous investigation that asserted that latency (measured in seconds) and distance (measured in meters) to the initiation of the fall were assessed until the rat seized the contraption or descended from the rod to analyze rotarod examination outcomes.(31) Based on earlier studies, HIIT augmented rotarod examinations after the intervention, implying that the intervention can enhance the motor abilities of individuals with ischemic stroke.(8)

The assessment of stride length also serves as a parameter for evaluating post-stroke ambulatory capability.(26) Our study states that HIIT can increase the stride length of the hind paws right from the rats (Figure 3B) As a consequence of our investigation, HIIT significantly increased stride length in the hind limbs, as opposed to the forelimbs. Clinical research findings suggest combining HIIT with standard care improves walking distance, equilibrium, and executive function.(32) Our study showed that SLFR there was no difference between the MCAO and MCAO+HIIT groups, the MCAO group also saw an increase in front leg stride length. This is in line with previous research which stated that the length of the front leg stride increased on the 6th day after MCAO.(26)

In this study, both the HIIT and MIIT groups demonstrated elevated levels of BDNF (Figure 4A) This aligns with previous investigations that exhibited a significant increase in BDNF levels during the phase of rehabilitative treatment and lower BDNF levels in untreated individuals.(33) In a clinical study, HIIT raised VO_2 max and BDNF levels in patients with chronic stroke. High-intensity exercise training substantially enhanced aerobic fitness. This physiological adaptation bolstered regional cerebral blood flow and oxygen utilization in the brain, resulting in improved executive and motor function.(34) In other clinical studies, moderate-intensity exercise raised serum BDNF levels in individuals who are overweight.(35) Exercise can heighten the BDNF levels. Moderate treadmill activity before an ischemic stroke yields favorable effects, such as diminishing brain cell mortality in the acute stage and ameliorating sensorimotor function in the chronic stage through the augmentation of angiogenesis and neurogenesis.(36) Long after a stroke occurs, high BDNF plays a crucial role in regeneration and repair by preserving neuronal and plasticity.(37) Rehabilitative treatment impacts BDNF, although changes in BDNF are not consistently linked to enhanced motor performance. Without active rehabilitative treatment, BDNF levels frequently decline.(33)

The current study found that HIIT may increase irisin levels in rats with ischemic stroke in the MCAO+HIIT group and no impact in the other group (Figure 4B). This is based on previous research, which stated that after the HIIT intervention, notable increases in irisin levels were observed, and irisin may have an effective effect on working memory's neuropsychological functioning.(6) The results of current study showed that MIIT did not improve irisin level. This is contradictive with the other study that state irisin can improve with moderate intensity exercise in obese case.(38) Irisin played a significant role in safeguarding the brain against the detrimental effects of exercise in cerebral ischemia and effectively prevented neuronal damage in the MCAO model.(39) Irisin can regulate the Notch signaling system, reducing susceptibility to ischemic stroke.(19)

In conjunction with BDNF, irisin mitigates the risk of stroke by bolstering apoptosis and BDNF protein levels in an experimental stroke model.(40) This study shows a relationship between BDNF and irisin levels in the initial data. However, the relationship between BDNF and irisin levels were not explored further in this study since there was no relationship between BDNF and irisin levels after HIIT or MIIT interventions. More in-depth exploration about irisin as a prognostic marker in recovery after stroke was also did not performed. Hence, further study regarding this matter might be necessary.

Conclusion

In conclusion, HIIT had a positive impact on BDNF level and motor function with rotarod test in experimental models of MCAO. Despite MIIT's favorable effect on BDNF levels, it is still inferior to HIIT. Thus interval training involving both high and moderate intensities can be beneficial. This indicates that individuals who have experienced a stroke must engage in physical activity or perform exercises; refraining from activity is not recommended.

Acknowledgments

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Authors Contribution

SY, SH, and NI conceptualized and designed the study. SY, SH, AAJ and NI performed the synthesis and analysis. SY, RS, and FM carried out the experiments and data collection. Data were analyzed and interpreted by SY, SH, AAJ, and NI. SY drafted the manuscript with feedback from all authors. RS supervised the project. The final manuscript was approved by all authors.

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