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THE EFFECT OF MODERATE INTENSITY INTERVAL TRAINING (MIIT) ON SHORT-TERM MEMORY FUNCTION, THE RATIO OF NEURONS AND NEOCORTICAL GLIA CELLS, AND THE NUMBER OF HIPPOCAMPUS PYKNOSIS GRANULE CELLS IN RATS WITH A HIGH-CALORY DIET

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KEYWORDS

Glia, granule cells, hippocampus, MIIT, neurons, and short-term memory.

ABSTRACT

Consumption of a high-calorie diet correlates with increased metabolic disturbances that lead to various organ disorders, including neurodegenerative disease. Women are more susceptible to metabolic disorders due to a high-calorie diet, so they have higher risk factors for neuroinflammation. This study was conducted to explain the effect of Moderate Intensity Interval Training (MIIT) on short-term memory, neocortex glia neuron ratio, and hippocampal pyknotic granule cells in female Wistar rats (Rattus norvegicus) with a high-calorie diet. The Wistar rats used were two months old. The study was conducted for four weeks, preceded by the acclimatization of experimental animals. MIIT intervention in the form of swimming is done every 5 minutes with a rest period of 2.5 minutes with two repetitions. Measurement of short-term memory using Y-maze instrument. Results: Before treatment, the highest average body weight was in groups C, B, and A (p=0.006). After treatment, the highest average body weight was found in groups B, C, and A (p=0.569). The test results of short-term memory measurement using the alternation indicator showed no significant difference between groups in the pre-alternation test (p=0.481). There was a significant difference between groups for the neuron-glia ratio (p=0.370) and the hippocampus of the pyknosis granule cells (p=0.078). In conclusion, there is a significant difference between groups A, B, and C towards the MIIT intervention.

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INTRODUCTION

Nutrition is one of Indonesia's most significant contributing factors to health problems (Ramlah, 2021). Consuming food that meets the nutritional adequacy rate (RDA) can reduce the risk of non-communicable diseases such as hypertension, diabetes mellitus, cancer, stroke, and others (Downer et al., 2020). In 2018, the average calorie consumption of Indonesian people was 2,147.09 Kcal/day, while in 2022, it was 2,079.09 Kcal/day. The level of consumption of ready-made food and drinks in Indonesia in 2022 will reach 99.19% percent. This figure is much higher than in 2018, namely 24.61% (Kumara & IWGAE, 2022). Even though Indonesian people's calorie consumption in 2022 tends to decline, changes in food consumption patterns are visible in the largest group, namely from the grain group to ready-made foods and drinks (Kumara & IWGAE, 2022). According to 2018 Riskesdas data, 47.8% of people consumed sweet foods six times per week, and 61.3% consumed sweet drinks more than once daily (Sari & Adelina, 2020). Consuming excessive amounts of processed foods and drinks with sugar can harm the body and increase metabolic disease risk (Lawrence & Baker, 2019). A high-calorie diet is associated with increased risk factors for dementia

due to impaired regulation of reactive oxygen species (ROS) and glucose toxicity, which results in neuroinflammation and impaired cognitive function (Pikir, 2015). Currently, an estimated 55 million people with dementia worldwide, with 10 million new cases every year. Dementia is the number seven killer among other diseases and the most significant cause of instability among geriatric patients. Dementia has social, psychological, and economic impacts on sufferers, families, caregivers, and the wider community (Weston et al., 2021). Around 60-70% of dementia cases are dominated by Alzheimer's. Studies suggest that gender differences play a role in the pathogenesis of Alzheimer's disease, which is caused by the presence of risk factors such as cardiometabolic, depression, circadian and hormonal cycles, which are higher in women compared to men (Nebel et al., 2018).

Regular activities such as brisk walking or swimming can help reduce the risk of developing Alzheimer's disease, especially in women with higher risk factors. Therefore, exercise not only provides physical benefits but can also have a positive impact in reducing the social, psychological, and economic consequences associated with dementia, not only for patients but also for families, caregivers, and the wider community (Wang & Ashokan, 2021). Studies show that Moderate Intensity Interval Training (MIIT) improves fitness in patients with cardiovascular and metabolic diseases by improving blood sugar control and reducing chronic inflammation. Research also states that moderate-intensity exercise better influences cardiometabolic function in obese patients than high-intensity exercise (Putri, 2021). Improvements in the antioxidant status of the hippocampus were observed in mice with MIIT intervention and improved memory function, especially Brain-Derived Neurotrophic Factor (BDNF) (Shafiei et al., 2022). Other research states that moderate-intensity exercise performed on Parkinson's patients can reduce neuroinflammatory processes, especially Tumor necrosis factor alpha (TNF-α) (Zoladz et al., 2014).

Short-term memory (STM) is the capacity to store a certain amount of information in a short period, generally a few seconds (van Goethem et al., 2018). STM forms working memory, namely temporary sensory input, into stable memory that can be manipulated and recalled after a delay (Ricker et al., 2018). Sensory input received by the eyes will be transmitted to the parietal and occipital lobes of the brain (Lazarou et al., 2022). Furthermore, the invocation of STM requires connections with the prefrontal lobe and hippocampus areas (Friedman & Robbins, 2022). STM disorders are observed in the early stages of neurodegenerative diseases, followed by impairments in problem-solving, judgment, executive function, lack of motivation, and disorganization. Language disorders and visuospatial abilities can follow these symptoms (Herman, 2016).

The nervous system consists of neurons and glia, essential for maintaining physiological functions. Neurons are cells that carry out receiving, sending, and modulating impulses, translated as a response to external stimuli. Glia are supporting cells of the nervous system that are as important as neurons (Matias et al., 2019). Glial cells can maintain the condition of the extracellular environment of neurons, remodeling, nutrient storage, repair, and defense to maintain brain homeostasis (Verkhratsky et al., 2019). Research says there is a correlation between brain density and the ratio of neuron-glia, namely that the greater the brain density, the higher the ratio. This is because the number of glial cells is much greater than neurons to support the physiological functions of neurons (Herculano-Houzel, 2014). Depletion of astrocytes is found in the brains of people living with Alzheimer's, so it will also reduce the ratio of neuron-glia. Astrocyte sheathing is increased in

Parkinson's disease with a greater surface area of astrocyte processes (B. Zhou et al., 2019). Research states a significant difference in the ratio of neuron-glia in the laminar compartment of the human optic nerve, making it more susceptible to ischemia than other species (Chan et al., 2020).

The hippocampus is a component of the limbic system, located deep in the brain's parietal lobe (Haładaj, 2020). Histologically, the hippocampus is divided into several subregions: the cornu ammonia (CA), CA1, CA2, and CA3. The CA3 subregion borders CA4, part of the dentate gyrus (DG). Cells found in the hippocampus are neurons, astrocytes, oligodendrocytes, microglia, and granule cells (Adler et al., 2018). These cell components can change due to certain diseases. There is increased autophagy, phagocytosis, and proteostasis in the microglia of Alzheimer's patients (Smith et al., 2022). Research reveals an accumulation of Tau protein in dentate gyrus astrocytes, which causes neuronal dysfunction in people with Alzheimer's (Richetin et al., 2020). The processes of apoptosis and necrosis have also been found to play a role in the pathogenesis of Alzheimer's, especially in the hippocampus (Telegina et al., 2019). Moreover, recent studies found that granule cells are responsible for neurogenesis to maintain brain plasticity (Y. Zhou et al., 2022). As dementia progresses, changes in granule cell morphology in the dentate gyrus are found (Marquez-Valadez et al., 2022).

Based on the explanation above, a high-calorie diet can cause metabolic disorders, which affect the incidence of other diseases, such as neurodegenerative diseases, which are a global burden disease. On the other hand, MIIT is currently an alternative in the world of health for exercise therapy, which targets subjects with obesity and a sedentary lifestyle because it is considered safer (Finer, 2021).

However, studies analyzing the effects of MIIT in subjects with a high-calorie diet on changes in brain morphology and function still need to be made more explicit. Therefore, researching the effect of Moderate Intensity Interval Training (MIIT) on Short Term Memory (STM), the ratio of neocortical glial neurons, and hippocampal pyknotic granule cells in rat subjects on a high-calorie diet is essential to provide a solution to the above problems (Schworer et al., 2022).

This research is expected to promote regular exercise, especially MIIT, as part of a healthy lifestyle, particularly for individuals at risk of cognitive decline or those following a high-calorie diet, and it could open opportunities for non-pharmacological interventions for memory-related issues.

This study aimed to analyze the effect of Moderate Intensity Interval Training (MIIT) on short-term memory, the ratio of neocortical glial neurons, and hippocampal pyknotic granule cells in subjects on a high-calorie diet. To explain the comparison of short-term memory in rat subjects on a high-calorie diet (McNeilly et al., 2016). To compare the ratio of neocortical glia neurons in rat subjects on a high-calorie diet. To compare the number of hippocampal pyknotic granule cells in rat subjects on a high-calorie diet.

METHOD

The research design uses experimental research with a post-test control design model. The research subjects used female white rats (Rattus Copernicus) that had undergone acclimatization. Each rat underwent a vaginal swab before testing the Y maze to obtain the same estrus phase. Then, the mice will be randomized and grouped into three groups, and testing will be carried out for four weeks. The sample size in the study was measured using the Federer formula. The sample was

increased to 15 animals per group in the research process. When taking the video, three samples could not be read due to technical errors, so exclusion was done. Namely, B2 left rear, B2 without markings, and D3 head so that the total number taking part in this study was 33 mice. The sampling technique in this research uses probability sampling with simple random sampling. The research was carried out at the Laboratory of the Biochemistry Experimental Animal Unit of the Faculty of Medicine, Universitas Airlangga and the research time was carried out from September to October 2021. The study was conducted within 9 weeks.

RESULTS AND DISCUSSION

Group Characteristics

The total number of samples calculated based on the Ferderer formula was 9 per group, so a minimum of 27 mice were needed. Researchers then gave 15 mice to each group so that the total number of mice participating in this study was 45. As time passed, seven animals died, namely A2 front right, A3 rear left, B1 front right, B3 without markings, D2 front right, D2 back, and D3 rear left. Then, two mice were dropped out through the outliers process, namely in groups 31 (D2 head) and 35 (D3 without markings). When taking the video, three samples could not be read due to technical errors, so exclusion was carried out; namely B2 left rear, B2 without markings, and D3 head, so the total number taking part in this study was 33 mice.

Before treatment, the highest average body weight was in groups C, B, and A (p=0.027). After treatment, the highest mean body weight was found in groups B, C, and A (p=0.569). There was no difference between groups A, B, and C in body weight after treatment. The average results for each body weight between groups are listed in Table 1.

Table 1 Body Weight Characteristics

Variable	Group			Markp
	A (N=13)	B (N=11)	C (N=9)	
Average Body WeightBeginning (Mean±SD) (grams)	138.92±17.134	140.27±14.332	158.33±19.052	0.027
Average Final Body Weight (Mean±SD)(grams)	148.84±15.328	156.18±22.855	151.22±7.902	0.569

The analysis results found that the data was normally distributed or there were no differences in variance in the three variables analyzed using the Shapiro-Wilk homogeneity test (p>0.05). Further analysis was carried out using One-Way Anova, and there were no differences between groups in the three variables (p>0.05) in Table 2.

Table 2 Analysis Descriptive

Variable	Group			p
	A	B	C	
pre-Alternation (%) (Rerata±SD)	38.29± 20.012	32.41±13.191	40.19±6.552	0.481
post-Alternation (%) (Rerata±SD)	38.40±11.835	34.98±9.290	35.20±7.023	0.646
Granul Piknosis(Rerata±SD)	134.77±17.608	151.82±20.188	151.56±23.410	0.078
Ratio NeuronsGlia (Mean±SD)	0.44±.0632	0.39±0.101	0.41±0.073	0.370

Comparison of Mean Short-term Memory Counts between Groups

Short-term memory measurement uses an indicator, namely spontaneous alternation (SA). The test results showed no significant difference between groups in the pre-alternation test (p=0.481) (table 2). After treatment, there was no difference between groups in post-alternative (p=0.646) (table 2).

Comparison of Mean Neocortical Glia Neuron Count Ratio between Groups

The highest average results for measuring the ratio of neurons to glia were obtained in groups C, A, and B (table 2). There was no significant difference between groups (p=0.370) (table 2).

Comparison of Hippocampal Pycnosis Granule Cells between Groups

The mean pyknotic granule cells were found in groups C, B, and A based on the measurement results. There was no significant difference between groups (p=0.078) (table 2).

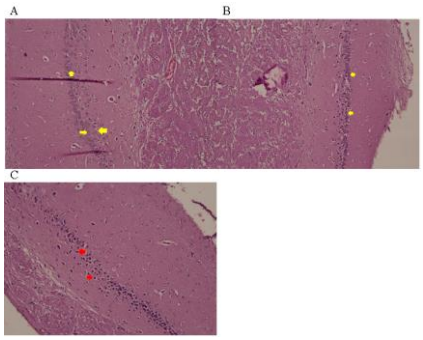

Figure 1. A: CA1 (A) Negative Control, yellow arrows show dense granule cells with open face type nuclei; B: CA1 Intervention (B), yellow arrows show granule cell features; C: CA1 Positive control (C), red arrow shows pyknotic granule cells with missing cytoplasm and very dense nuclei.

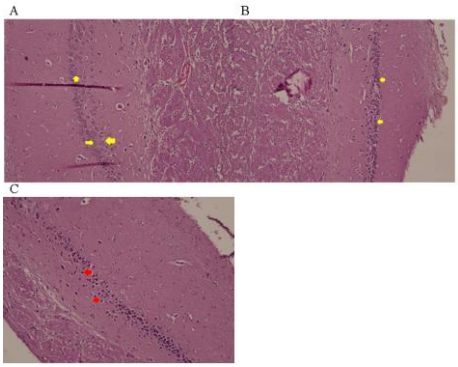

Figure 2. A: Neocortex of group A (negative control); B: Neocortex of the positive control group (B); C: Neocortex of the intervention group (D). Blue arrows: neurons; Green Arrows: astrocytes; Purple arrows: oligodendrocytes.

The study results showed that the two variables, spontaneous alternation, and pyknosis granule cells, did not have a significant difference; however, the variable ratio of neuron-glia showed a significant difference in the positive control and intervention groups. Before the research procedure, the intervention group had the highest average body weight. In contrast, the positive control group had the highest body weight after the procedure (Yin et al., 2013).

The high-calorie diet intake given to the intervention and control groups was positively related to the regulation of body metabolism by insulin, resulting in weight gain (Stice & Burger, 2019). Hyperglycemia conditions stimulate pancreatic beta cells to produce insulin, thereby triggering glucose uptake by the liver, muscles, and adipose tissue. Insulin prevents muscle glycogenolysis, adipose lipolysis, and liver gluconeogenesis (Shakoor et al., 2021). A study states that women have lower muscle mass, more adipose tissue, and higher Free Fatty Acid (FFA) levels than men. This indicates that women are more susceptible to insulin resistance (Mauvais-Jarvis, 2018). High androgen levels in men increase insulin sensitivity, but women show the opposite effect (Navarro et al., 2015). Researchers found a positive correlation between insulin regulation and the metabolic pathways of pyruvate, purine, cysteine, glycolysis, and gluconeogenesis in accelerating neuronal degeneration in Alzheimer's disease. These factors are known to be higher in women than in men, so women are at higher risk of neuroinflammation. (Maffioli et al., 2022) .

Research finds that hyperglycemia conditions decrease cognitive function (Dyer et al., 2021). (Šuput Omladič et al., 2020) stated that a decrease in spatial working memory function was observed in acute hyperglycemia conditions. Mice induced with long-term hyperglycemia show reduced integration of new hippocampal neurons, which affects the neurogenic capacity of the hippocampus, resulting in decreased synaptic plasticity and impaired short-term memory (Ferreiro et al., 2020). The mechanism of this reduction in cognitive function is not yet clearly known; however (Leão et al., 2020) found that there is involvement of glucose transporters (GLUT-1) and (GLUT3) in the neurodegeneration process in people living with Alzheimer's. In addition, hyperglycemia activates HSPO70 and HO-1, stress-induced proteins. Hence, ROS production increases through the stress-induced glucotoxicity pathway mediated by microglia (Hsieh et al., 2019). Research (Bonds et al., 2020) using mice revealed that chronic hyperglycemia reduces neurogenesis in the hippocampus, resulting in cognitive impairment.

Quantifying cells and ratios in the nervous system is an approach to understanding the cellular composition, development, and evolution of the brain to reveal the pathophysiology of neurological and psychiatric disorders (Von Bartheld et al., 2016). The ratio of neuron-glia does not correlate with an increase in brain size. Research suggests this relationship varies between species (Herculano-Houzel et al., 2015). Conversely, a decrease in the ratio of neurons to glia is associated with a decrease in neuron density and an increase in neuron size. Studies have found that the larger the size of neurons, the more glial cells they need for metabolic needs so that neurons can carry out their physiological functions (Herculano-Houzel, 2014) (Edler et al., 2020) found that there is a decrease in the ratio of neurons to glia with aging. In addition, (Stevens et al., 2023) stated that a reduced number of astrocytes results in increased contact between neurons, resulting in hyperactivation of neurons and impaired working memory in mice and is thought to play a role in the pathophysiology of Attention Deficit Hyperactivity Disorder (ADHD). Changes in the ratio of neurons to glia are also influenced by metabolism (Henn et al., 2022). Studies suggest that high-calorie diets reduce the neuron-glia ratio due to neuroinflammatory processes resulting from loss of oligodendrocytes, disruption of glucose homeostasis by astrocytes, and aberrations of microglial phagocytosis (Cope et al., 2018) ; (García-Cáceres et al., 2016) ; (Langley et al., 2020). In addition, research (Anggraeni et al., 2017) found that

mice induced by a high-calorie diet had decreased neuroglia due to increased superoxide production, which bridges the activation of Advanced Glycogen End-products (AGE).

Granule cells are the most abundant cell type found in the dentate gyrus of the hippocampus (Li et al., 2017). The dentate gyrus is essential in the learning process and memory formation. Granule cells have unmyelinated axons called mossy fibers. These specialized structures function as projectors of impulses conducted through collateral structures and mainly terminate in polymorphic layers in GABAnergic interneurons. Young granule cells have increased plasticity and have a long-term potentiation (LTP) induction threshold (Weston et al., 2021). (Razi et al., 2015) In mice induced by a high-calorie diet, granule cell density was reduced in the intervention group compared with the control group. Research (Gupta et al., 2022) found increased apoptosis markers, namely Bcl-2, Bcl-xl, Bax, and caspase 3, in mice exposed to a long-term high-calorie diet.

The direct influence of moderate-intensity interval training (MIIT) on the ratio of glial neurons and granule cells has yet to be widely studied. However, the correlation between exercise and cognitive ability has been widely studied. A study by (Chang et al., 2015) found that Moderate Intensity Interval Training (MIIT) for 20 minutes can improve cognitive abilities. Research (Kim et al., 2019) states that moderate-intensity exercise increases neurogenic factors so that they have a positive correlation with neurogenesis, memory, and learning. Apart from that, exercise also increases neuron proliferation in the dentate gyrus and prevents apoptosis. Moderate-intensity exercise also regulates the immune system, including microglia, and protects against neuroinflammation (Hashioka et al., 2021); (Xie et al., 2019). Another study suggested that moderate-intensity exercise affected the increase in neuroglia in the mouse cortex (Serra et al., 2019); (Verkhratsky et al., 2019).

Female rats whose memory was measured when estradiol levels were high or during the proestrus phase showed decreased spatial memory compared to measurements taken during the estrus phase with low estradiol levels (Duarte-Guterman et al., 2015). Measuring the Y maze was carried out during the estrus phase to avoid bias due to hormonal fluctuations in the rat's estrus cycle.

According to research, one of the factors that can cause research results to be less meaningful is the length of treatment on the subjects studied (Davidson et al., 2013). Research suggests that mice induced by a high-calorie diet can improve working memory as measured using the Y maze (Yoshizaki et al., 2020). Another study stated that mice induced on a sugar solution diet for a short period did not show significant short-term memory impairment (Pikir, 2015). Based on studies, a high-calorie diet is carried out to see changes in brain morphology and behavior for an average of 14 weeks (Arnold et al., 2014) ; (Davidson et al., 2013). On the other hand, this research was conducted for four weeks and included a short period. This causes the buildup of ROS and AGEs not to reach the saturation point so that changes in brain morphology cannot be observed with a simple microscope.

Young rats tend to have higher curiosity and lower risk factors for metabolic syndrome than adult rats, which can affect cognitive abilities (Wikgren et al., 2021). This study used an adult female Rattus norvegicus, which can influence the results of measuring spontaneous alternation, making it less meaningful.

Fat oxidation and blood glucose are The primary energy sources used during moderate-intensity exercise (Collins et al., 2022). Research shows moderate-intensity exercise has more excellent insulin sensitivity effects than high-intensity exercise. Research related to Moderate-Intensity Interval

Training (MIIT) is mainly carried out using cycling. At the same time, few studies have discussed aquatic MIIT (Jiménez-Pavón & Lavie, 2017). The research found that the effects of moderate-intensity exercise and high-intensity aquatic exercise were considered equally effective in improving hemodynamic, vascular quality, and blood glucose regulation in subjects with a sedentary lifestyle (Tang et al., 2022). Body weight measurement in the MIIT intervention group showed lower results than the control group. This shows that MIIT positively correlates with body weight regulation by reducing blood leptin levels.

Female mice have a higher threshold value of corticosterone, a stress hormone, than males. Acute stressors do not increase the level of this hormone. However, chronic exposure to stress increases corticosterone, which impacts hippocampal granule cell apoptosis (Hurin'in, 2023). Even though the experimental animals had undergone prior acclimatization, it does not rule out the possibility that the research intervention caused chronic stress in the subjects. Previous research found that mild stress over a long period changes mice's physiological and behavioral stress responses (Cavigelli et al., 2018).

Based on the research results, it was found that the highest mean for post-alternation was in group A. Groups B and C had almost the same mean neuron-glia ratio. The highest mean of pyknosis granule cells was also in group B. There was a shift in the results in alternation from initially the highest mean in group C to group A. Alternation describes cognitive abilities, namely short-term memory. In addition, cognitive function is also described by the ratio of neurons to glia. The greater the value of the neuron-glia ratio, the more cognitive function will increase (Bahney & von Bartheld, 2018).

CONCLUSION

Before the treatment, the highest mean body weight was in the intervention group. However, after the treatment, it was in group B. Based on the results of the comparison test with the MIIT intervention, it did not show a significant difference between groups in body weight ($p=0.646$). However, if we look at body weight measurements using digital scales, changes were found between groups A, B, and C. Group C, which initially had the most significant average body weight, experienced a decrease after the MIIT intervention.

As measured by the alternation indicator, short-term memory showed no differences between groups A, B, and C before treatment ($p=0.481$) and after treatment ($p=0.646$). The variable ratio of neocortical neurons and glia was not found to be significantly different between groups A, B, and C ($p=0.370$). The histology of the neocortex shows that the cytoplasm of pyramidal cells and glia is darker in color compared with the negative control (A) and intervention (B) groups. Another variable, hippocampal pyknosis granule cells, showed no differences between groups A, B, and C ($p=0.078$).

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