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THE EFFECTS OF PHYSICAL EXERCISE IN IMPROVING COGNITIVE FUNCTION AND BRAIN-DERIVED NEUROTROPHIC FACTOR LEVELS IN PATIENTS WITH SCHIZOPHRENIA RECEIVING RISPERIDONE

Ahmad Rais Dahyar[1], Erlyn Limoa[1*], Saidah Syamsuddin[1], Arifin Seweng[2], Kristian Liaury[1], Irfan Idris[3], Sonny T Lisal[1]

[1*]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.
[2]Department of Biostatistics, Faculty of Public Health, Hasanuddin University, Makassar, Indonesia
[3]Department of Physiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

***Corresponding Authors:** Erlyn Limoa
*Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Jalan Perintis Kemerdekaan Km.10, Tamalanrea, Makassar, South Sulawesi, Indonesia, 90245
Email: elimoa.unhas@gmail.com

Abstract

Purpose: Increased BDNF levels induce neuroplasticity thus improving dopamine activity in the prefrontal cortex which is correlated with cognitive improvement. Risperidone combined with Physical Exercise is assumed to improve the aforementioned cognitive function and is associated with increased levels of (BDNF), a cognitive function marker in schizophrenia. This study aimed to determine the effect of physical exercise on improving cognitive function and BDNF levels in patients with schizophrenia receiving risperidone.

Methods: Forty (40) schizophrenic inpatients were divided into two groups, the treatment group, and the control group. Both groups received Risperidone 4 mg twice daily, and only the intervention group was given physical exercise for ten weeks. Cognitive function was assessed using SCoRS v BI at the baseline, the fifth, and the tenth weeks. The BDNF level was measured at the baseline and the tenth weeks. The difference in means between the group was assessed using the Mann-Whitney test.

Results: There was a significant improvement in cognitive function in both treatment groups (<0.01). However, in the BDNF levels in the treatment group that received a combination of 4 mg/day of risperidone and physical exercise for 10 weeks, the results were more significant (<0.00) than in the control group.

Conclusion: Physical exercise for 10 weeks accompanied by risperidone therapy of 4 mg/day could improve cognitive function and BDNF levels in patients with schizophrenia. There is a relationship between the improvement in cognitive function of patients with schizophrenia and the increased levels of BDNF they experience.

Keywords: schizophrenia, physical exercise, cognitive function, BDNF, risperidone.

1. Introduction

Schizophrenia is a severe mental disorder that affects the way a person thinks, feels and behaves (National Institute of Mental Health, 2022). Schizophrenia symptoms could differ from patient to patient, but generally fall into three main categories: positive, negative, and cognitive (National Alliance on Mental Illness, 2022; National Institute of Mental Health, 2022). According to the World Health Organization (WHO), schizophrenia sufferers worldwide are estimated to have reached around 24 million people (World Health Organization, 2022). The 2018 Basic Health Research (Riskesdas) data, the prevalence of schizophrenia in Indonesia in 2013 was 1.7% per mile, increasing to 7% per mile in 2018. South Sulawesi Province became the province with the sixth highest prevalence of schizophrenia in Indonesia. In 2013, the prevalence was around 1.8% per mile and then increased to 9% per mile in 2018 (Ministry of Health RI, 2018).

The use of first-generation antipsychotics has been known to cause negative symptoms of schizophrenia and decreasing cognitive function of schizophrenia. Therefore, it is advisable to use second generation antipsychotics (APG-2) or atypical antipsychotics such as Risperidone because they work on D2 dopamine receptors and 5 receptors. -HT2A also has a high affinity for alpha 1, alpha 2 adrenergic receptors, good for improving positive and negative symptoms and cognitive function (Rosenbaum et al., 2007; Sinaga, 2007). Comprehensive treatment of schizophrenic patients is a combination of pharmacological and nonpharmacological therapy which has shown more optimal results when compared to using only a single approach (Kusumawardhani & Dharmono, 2011).

Apart from pharmacological treatment, there are non-pharmacological approaches such as exercise therapy, which have been suggested as adjuvant treatment options. Many studies have shown the positive effects of exercise in treating schizophrenia and other mental disorders. These improvements include decreased positive and negative symptoms, improved cognitive function and increased quality of life. Studies have shown that exercise causes increased hippocampal plasticity in the brains of schizophrenic patients. This suggests that exercise could be used as part of a beneficial treatment plan for schizophrenic patients (Girdler et al., 2019). Brain-derived neurotrophic factor (BDNF) is a secretory growth factor (neurotropin) that promotes neuronal proliferation and survival, synaptic plasticity and long term potentiation in the central nervous system (CNS) (Di Carlo et al., 2020). Due to its very complex role, BDNF has been extensively researched and plays a key role in underlying the regulation of cognitive function in each individual. BDNF has been extensively investigated under the neurodevelopmental hypothesis of schizophrenia, regarding its role in the development and physiology of the central nervous system (CNS) (Di Carlo et al., 2020; Nieto et al., 2013). This study aims to provide empirical examination regarding non-pharmacological management of schizophrenic patients to improve the prognosis of the disorder. The application of exercise training as a modality of non-pharmacological therapy is quite simple and does not require a lot of money. This study was to analyze the effect of exercise training on improving cognitive function and BDNF levels in schizophrenic patients receiving risperidone therapy. The general objective of this study was to determine the effect of exercise training on improving cognitive function and BDNF levels in schizophrenic patients receiving risperidone therapy.

2. Literature Review dan Hypotheses

2.1. BDNF Level, physical exercise and lactate

Several trials have used blood lactate to monitor exercise intensity. These studies show that higher lactate concentrations are associated with increased plasma BDNF and/or serum levels. Current evidence suggests that high-intensity interval training evokes greater levels of BDNF compared to moderate and/or intense sustained exercise. For a long time, lactate was considered simply a waste product of anaerobic metabolism. Today however, it is clear that lactate is an important signaling molecule involved in several metabolic processes. The energy supply for exercise is primarily based on three pathways: ATP-creatininase, glycolysis, and oxidative phosphorylation. Lactate is produced

by oxidation of glucose when oxygen uptake is low, and could withstand acidosis. The accumulated lactate could be transported to the liver (where it is synthesized into glucose via gluconeogenesis) or it could be directly used as fuel by the muscles, heart, and brain. During acute exercise lactate accumulates depending on the intensity and duration of the exercise. Lactate threshold (also called anaerobic threshold) is defined as the highest level of physical activity that could be achieved without lactate accumulation and is a predictor of an individual's fitness level. Physical exercise could increase fitness levels and could increase lactate threshold. Lactate could cross the blood-brain barrier (BBB) to reach neurons via monocarboxylate transporters (MCTs). MCT 2 is the main transporter in neurons whereas MCT 4 is only expressed in astrocytes. Astrocytes have complex interactions with neurons. They are involved in cell volume control, energy metabolism and ionic homeostasis. Astrocytes show a glucose gradient with high glucose concentrations close to the BBB and low glucose concentrations close to neurons. This gradient allows fast glucose transfer to neurons. Astrocytes could store glycogen and support neural energy metabolism (Müller et al., 2020).

Pellerin et al. (1998) proposed astrocyte-neural lactate transport during excitatory neurotransmission. Here lactate is transported from astrocytes to neurons via the MCT where it is converted to pyruvate and enters the tricarboxylic acid cycle. Lactate in neurons could originate from astrocyte metabolism or from peripheral muscle activity. Moreover, in vitro neurons prefer lactate over glucose. Current research suggests that lactate transport from astrocytes to neurons plays an important role in memory formation and could be a link between exercise and neuroplasticity. Pharmacological inhibition of MCT 2 irreversibly impairs longterm memory. Van de Hall et al. have shown that lactate uptake in the brain increases from 8% at rest to 20% during exercise. Kempainen et al. (2005) reported higher lactate metabolism in trained healthy adults compared to controls. In rodents, a single exercise could induce MCT up-regulation. Proia et al. (2016) hypothesized that exercise could increase levels of BDNF and other growth factors such as insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) (Müller et al., 2020).

However, the interaction between lactate levels and BDNF has not been well resolved. Potential mechanisms linking the two molecules could be (i) lactate-regulated NMDA receptor activation and consequent increased intracellular calcium levels, (ii) a signalling cascade initiated by the binding of lactate to a different G-protein coupled receptor (GPCR), and (iii)) through the activation of silent information regulator 1 (SIRT1) of the PGC1α/FNDC5/BDNF pathway (Müller et al., 2020). Yang et al. (2014) reported that lactate promotes the expression of plasticity-related genes by potentiating the activity of NMDA glutamate receptors in neurons. Furthermore, lactate increases intracellular NADH and calcium levels. This could be a central mechanism for lactate-induced neuroplasticity of astrocytes. Increased intracellular calcium following lactate-induced NMDA receptor activity might be a link between exercise and BDNF expression (Müller et al., 2020).

Lactate could bind to GPCR81 (also known as hydroxycarboxylic acid receptor [HCAR1]) on neurons and at the BBB. Lauritzen et al. (2014) have shown, that HCAR1 at the BBB is essential for mediating the effects of exercise on angiogenesis in a mouse model. The binding of lactate to HCAR1 on neurons inhibits adenylate cyclase and thereby decreases cAMP, resulting in decreased neural activity and gene regulation. Here, lactate might have metabolic and regulatory functions in controlling blood flow and synaptic function. Furthermore, lactate could affect the uptake of prostaglandin E2 and thereby influence vasodilation. The potential for negative modulation of BDNF production by lactate via HCAR1 should be examined more closely in the future (Müller et al., 2020). Lactate could induce the PGC1α/FNDC5/BDNF pathway through SIRT1 activation. El Hayek et al., have shown, that voluntary exercise increases hippocampal BDNF expression and improves memory and learning in a lactate-dependent manner in rodents. They have shown that intraperitoneal infusion of lactate in rats induces SIRT1 activity and thereby enhances the PGC1α/FNDC5/BDNF pathway resulting in increased spatial learning and memory retention (Müller et al., 2020). Schiffer et al investigated

whether lactate infusion at rest could increase blood concentrations of BDNF in young adults. The lactate clamp method is a well-established method for testing the physiological (neural) effects of lactate without stimulating physical exercise. After infusion of 4 molar sodium-lactate solution, serum BDNF and lactate levels increased significantly and returned to baseline at follow-up. A potential mechanism for increased serum BDNF following lactate infusion could be lactate-driven BDNF expression or BDNF release from platelets (in the context of blood gas disturbances) (Müller et al., 2020).

2.2. BDNF level, physical exercise and schizophrenia

BDNF, which increases the expression of dopamine receptors in the brain by mimicking the effects of antipsychotic drugs, is reported to reduce manic mood. Similarly, studies in schizophrenic patients have shown that exercise improves cognitive abilities and physical health and that low levels of BDNF are associated with negative symptoms and might contribute to the psychopathology of the disease. BDNF is widely distributed throughout the central nervous system and plays a role in a variety of psychiatric disorders, disturbances in BDNF signaling are not specific for schizophrenia. However, given the effect of BDNF on the plasticity and viability of dopaminergic, serotonergic, and cholinergic neurons, and the importance of all these pathways in the pathophysiology of schizophrenia. BDNF could be a useful biological marker for clinical status and/or prognosis with this disease (Gökçe et al. al., 2019).

Increased peripheral BDNF levels and findings of enhanced cognitive performance in response to exercise support the notion that exercise could enhance neurotrophic and neuroprotective mechanisms, and thereby lead to an increase in schizophrenic symptoms. One possible way in which aerobic exercise improves schizophrenic symptoms is by increasing drug efficacy by influencing antipsychotic pharmacokinetics, for example by altering drug distribution and reducing drug excretion. BDNF is a neurotropin that is not only related to neuroprotection and development but is also effective in synaptic regulation, learning, and memory. As BDNF plays an important role in regulating synaptic plasticity, schizophrenic deficits could be understood in the context of molecular and cellular learning and memory mechanisms (Gökçe et al., 2019; Nieto et al., 2021).

Regarding the pathogenesis of schizophrenia, particularly neurodevelopmental factors and related neurotoxicity, eurotropins, such as BDNF could provide an explanatory framework at the molecular and cellular levels. Synaptic changes that occur due to BDNF expression problems could alter neurotransmitter pathways that are classically involved in the pathophysiology of schizophrenia; for example, the dopaminergic system and gammaaminobutyric acid (GABA). Abnormal BDNF and TrkB mRNA expression in the hippocampus of individuals with schizophrenia and mood disorders suggests that key features of hippocampal signal transmission and plasticity might be affected in these major mental disorders (Gökçe et al., 2019). In patients with schizophrenia, deficiency of TrkB receptormediated BDNF signaling might result in reduced GABA synthesis in the dorsolateral prefrontal cortex. This might lead to changes in the perisomatic inhibition of pyramidal neurons by reducing the activity of gamma neurons at the synchronous frequency required for working memory. Consistent with the literature, Nuechterlain et al. demonstrated that aerobic exercise increased peripheral BDNF levels in patients with schizophrenia and improved working memory findings.(Gökçe et al., 2019)

In the negative symptoms of schizophrenia, mechanisms of glutamate dysfunction are involved, and increased glutamate function has been shown to have the potential to reduce these symptoms. BDNF could directly alter glutamate signaling by altering the expression of glutamate receptor subunits and Ca2+ regulatory proteins. It might also impact glutamate signaling by inducing the production of antioxidant enzymes, energy regulatory proteins, and members of the antiapoptotic Bcl2 family. Glutamate stimulates BDNF production, which in turn influences neuronal glutamate sensitivity,

Ca2+ homeostasis, and plasticity. In early studies examining the relationship between the glutamatergic system and BDNF, mature BDNF was reported to induce rapid effects of glutamate secretion and short and long term effects of post synaptic responses to neurotransmitters. A study focusing on the acute effects of BDNF on rat hippocampal neurons found that glutamatergic synaptic transmission was increased in 30% of cells, but this increase was not seen when TrkB receptors were inhibited. These data suggest that presynaptic modification is effective in enhancing glutamatergic synaptic transmission, and BDNF is involved in this modulation. This improved clinical condition could be explained by aerobic exercise which increases the brain's use of glutamate (Gökçe et al., 2019). Decreased serum BDNF levels have been shown to correlate with poor processing speed, attention, executive function, and performance in working memory. In this context, the relationship between serum BDNF and cognitive test performance has been emphasized. In the schizophrenia studies included in this review, increasing BDNF levels through exercise accompanied by improved cognitive function appears to be consistent with the literature. Exercise might be involved in this process through exercise-induced neural activity, and it might alter cognitive performance findings. Similarly, given that the decline in physical health associated with physical inactivity in schizophrenia reduces life expectancy by an average of 10 to 15 years due to suicide, it is possible to comment that exercise also has an effect on life expectancy (Gökçe et al., 2019; Nieto et al. al., 2021)

2.3. Schizophrenia Cognitive Rating Scale (SCoRE v BI)

Schizophrenia Cognitive Rating Scale (SCoRS) is a measurement scale based on interviews and focuses on daily functioning. SCoRS consists of 20 question items that must be asked by the interviewer to the patient and the informant in a separate interview. Informants are people who have a relationship and or have a number of daily contacts or interactions with patients. Informants could be family members, friends, social workers, nurses, and others. Each question item is assessed with a 4-point measurement scale, namely: 1: none; 2: light; 3: medium; 4: severe. There is also the possibility of entering an N/A (non-applicable) scale. If due to something related to the patient's condition, this question could not be applied (Keefe et al., 2006). In addition to the 20 question items, there is also a global functional scale assessment (1-10), which the interviewer must complete at the end of the interview. This global functional scale assessment is used to assess the presence or absence of cognitive dysfunction in schizophrenic patients, where 1 is no cognitive dysfunction, and 10 is the most severe cognitive dysfunction (Keefe et al., 2006).

The Indonesian version of SCoRS (SCoRS v BI) has been validated by Herdaetha and Raharjo (2008) with the following results. In testing the validity of each question addressed to the patient, 6 questions (30%) have a high validity value and 14 questions (70%) have a very high validity value. The reliability value (Cronbach's Alpha) was 0.976, indicating that the SCoRS v BI instrument is very reliable. In testing the validity of each question addressed to the informant, 7 questions (35%) have a high validity value and 13 questions (65%) have a very high validity value. The reliability value (Cronbach's Alpha) was 0.977, indicating that the SCoRS v BI instrument is very reliable. In the sensitivity and specificity tests, high values were also obtained, namely a sensitivity of 92.8% and a specificity of 93.7%. This showed that the SCoRS v BI instrument could measure the cognitive function of schizophrenic patients correctly (Rahardjo et al., 2008).

2.4 Hypotheses

H1. Cognitive function of schizophrenic patients as measured by SCoRS v BI was better in the risperidone and exercise group than the group of schizophrenic patients who received risperidone alone.
H2. BDNF levels in schizophrenic patients who received risperidone and exercise were higher than schizophrenic patients who received risperidone alone.
H3. The change in SCoRS v BI score after 10 weeks in schizophrenic patients who received risperidone and exercise was lower than schizophrenic patients who received risperidone alone.

H4. The increase in BDNF levels after 10 weeks in schizophrenic patients who received risperidone and exercise was higher than schizophrenic patients who received risperidone alone.
H5. There was a negative correlation, namely the SCoRS v BI score was lower while the plasma BDNF level was higher in schizophrenic patients who received risperidone and exercise.

3. Method

3.1. Research Design

This research is a quasi-experimental study, by measuring pre- and post-tests with random group selection, in which variables are measured before and after treatment. This study also uses a single-blind approach. This research was conducted in August-November 2022. This research was conducted at Dadi Regional Special Hospital (RSKD) in South Sulawesi Province. In this study, research subjects were divided into 2 groups. The control group includes patients who met the inclusion criteria without getting any exercise sessions. Meanwhile, the treatment group consisted of patients who met the inclusion criteria and received physical exercises training sessions for 10 weeks (30 sessions). Instruments in this study were informed consent sheets, SCoRS v BI scale, PANS-EC scale, risperidone medication, instruments for physical exercises training (sound system, Liquid Crystal Display (LCD)), blood sampling kits and BDNF examinations. Ethical clearance was obtained from the Biomedical Research Ethics Commission on Humans, Faculty of Medicine, Hasanuddin University and asked for approval from the participants and their families. The researcher conducted informed consent before the subject participated in the study, and tried to maintain the confidentiality of the research subject's identity.
The independent variable is the type of treatment in the form of physical exercises training in the form of HIIT (High Intensity Interval Training). The dependent variable is SCoRS v BI Score. The mediating variables are increasing BDNF levels, increasing neurogenesis, promoting synaptic plasticity, improving PFC dopamine activity. Moderating variables were age, sex, education, disease onset, atypical antipsychotics, smoking, genetic history, personality.

3.2 Sampling

The sample in this study were all patients with stable phase schizophrenia who were treated at the Dadi Hospital in South Sulawesi Province who met the inclusion criteria and did not meet the exclusion criteria. The sampling technique for each group was carried out by means of consecutive sampling, namely all patients who met the selection criteria. To determine the sample size, it is determined by the sample formula, namely numerical comparative in pairs of two groups more than one measurement as follows:

$$n1 = n2 = Y\left[2\left(\frac{(Z\alpha + Z\beta)S}{x1 - x2}\right)^2\right]$$
$$= 0.5\left[2\left(\frac{(1{,}96+1{,}28)0.091924}{0.13}\right)^2\right]$$
$$= 10.498$$
$$= 11\ (\textit{rounded up})$$

* *Information*:
n1= Number of treatment subjects n2= Number of control subjects
α = Type one error, set at 5%, one-way hypothesis
Zα = The standard value of α 5% is 1.96 β = Type two error, set at 20%
Zβ = The standard β value is 10%, which is 1.282
x1-x2 = The minimum difference in the BDNF value that is considered significant is set at (1.39 – 1.26 = 0.13) (Kimhy et al., 2015)
s = Combined standard deviation of BDNF values, based on previous studies = 0.091924 (Kimhy et al., 2015)
From the above formula, the minimum sample size for each group is 11 people.

3.2 Participants

The inclusion criteria used in this study were patients diagnosed with schizophrenia, aged 20-40 years and male, disease onset <5 years. The patient had passed the acute phase (PANSS-EC < 15), was able and would ing to attend exercise therapy sessions, agreed to research informed consent, and received 4 mg/day of risperidone therapy. The exclusion criteria used were having severe organic comorbidities, and having a history of consuming Narcotics, Psychotropics and Addictive Substances (NAPZA) <1 year prior to admission to the hospital.

The criteria for Drop Out (DO) are not regularly participating in physical exercises training sessions (<80% attendance of physical exercises training sessions), the research subject's pulse rate that does not reach optimal (Zone 4: Anaerobic Zone 80-90% of the maximum pulse rate for participating in physical exercises during several sessions), not regularly taking risperidone. The research subjects refused to continue the research and died.

3.2 Objective Criteria

The ScoRS v BI consists of 20 question items that must be asked by the interviewer to the patient and the informant in a separate interview. Each question item is assessed with a 4point measurement scale, namely: 1 (none), 2 (low), 3 (medium), 4 (severe). There is also the possibility of entering an N/A (non-applicable) scale. If due to something related to the patient's condition, this question could not be applied. In addition to the 20 question items, there is also a global functional scale assessment (1-10), which the interviewer must complete at the end of the interview. This global functional scale assessment is used to assess the presence or absence of cognitive dysfunction in schizophrenic patients, where 1 is no cognitive dysfunction, and 10 is the most severe cognitive dysfunction.

3.5 Intervention

Each patient who met the criteria for schizophrenia according to the DSM-V and PPDGJ III met the inclusion criteria and was not included in the exclusion criteria in the study group and anamnesis was carried out. The researcher then found the family and research subjects regarding the aims and objectives of the research. With their agreement, the subjects would be included in the study (informed consent). The research subjects were divided into two groups, namely the control group and the treatment group.

The treatment group was given a physical exercises training session with provisions that the exercise would be carried out in the form of High Intensity Interval Training (HIIT) or interval training with the duration of each session being 25 minutes, of which the first and last 5 minutes were used for warm-up and the remaining 15 minutes were used for core. of interval training. physical exercises training sessions are carried out with moderate to severe intensity. Before exercising, a heart rate measurement is carried out first, mid-session and at the end of the session a heart rate measurement is carried out again. For the assessment, the SCoRS v BI scores were assessed for both groups at baseline week, 5th week and 10th week. BDNF blood levels were checked for both groups at baseline and 10th week. and then data analysis was carried out.

3.6 Data Analysis

Data processing was carried out after recording the research instruments using the SPSS 25.0 computer program with the Independent T-test if the data distribution was normally distributed and using the Mann Withney test if the data distribution was not normal to see the comparison of the treatment group and the control group. To see the differences in pre and post treatment in each group use the Paired T test if the data distribution is normal and the Wilcoxon test if the data distribution is not normal. To measure the correlation, Pearson's test is used if the data distribution is normal and Spearman's test if the data distribution is not normal. Statistical test results are considered significant if the p test value is <0.05. Processed data would be presented in numerical and categorical forms.

Numerical data would be presented as mean ± SD or median (minimum, maximum). Categorical data would be presented in the form of proportions.

4. Results

4.1 Description of Research Subjects

Table 1. Demographic Characteristics of Research Subjects (n=40)

Characteristics	Total (N=40) (*percentage*)	Treatment (n=20) (*percentage*)	Control (n=20) (*percentage*)	*p*
Education:				
Elementary	9 (*22.5*)	4 (*20.0*)	5 (*25.0*)	0.412
Junior High School	11 (*27.7*)	7 (*35.0*)	4 (*20.0*)	
Senior High School	29 (*50.0*)	9 (*45.0*)	11 (*55.0*)	
Profession:				
Employed	22 (*55.0*)	10 (*50.0*)	12 (*60.0*)	.379
Unemployed	18 (*45.0*)	10 (*50.0*)	8 (*40.0*)	
Marital status:				
Marry	23 (*57.5*)	12 (*60.0*)	11 (*55.0*)	0.555
Not married	17 (*42.5*)	8 (*40.0*)	9 (*45.0*)	
Disease onset:				
<1 year	23 (*57.5*)	10 (*50.0*)	13 (*65.0*)	0.179
>= 1 year	17 (*42.5*)	10 (*50.0*)	7 (*35.0*)	

Source: data analysis, 2022

In this study, initially a sample of 50 subjects was taken which was divided into 2 groups, namely the treatment group (the group that received additional physical exercise and risperidone therapy) 25 subjects and the control group (the group that only received risperidone therapy) 25 subjects where all of them met the inclusion criteria and not included in the exclusion criteria. However, over time there were several research subjects who experienced drop-outs for various reasons including patients returning home, being bored with exercise and unable to participate in exercise related to their physical condition. The last surviving until the end of the study were 40 subjects divided into 20 subjects in the treatment group and 20 subjects in the control group. This research lasted for 10 weeks with physical exercises training held 3 times a week. In the study, 3 SCoRS v BI measurements were carried out at the baseline (beginning of the study), 5th week and 10th week (end of the study), while BDNF levels were taken 2 times at the baseline and 2nd week -10th week.

Table 1 showed that the level of high school education in the treatment group was 9 people (45%) while in the control group there were 11 people (55%) for junior high school in the treatment group there were 7 people (35%) while the control group was 4 people (20%), for SD level in the treatment group was 4 people (20%) and the control group was 5 people (25%). On the characteristics of the work for the balanced treatment group between working and not working as many as 10 people (50%) each work and 10 people (50%) do not work. For the control group, there were 12 people (60%) who worked and 8 people (40%) who did not work. For marital status in the treatment group there were 12 people (60%) who were married and 8 people (40%) who were not married, while in the control group there were 11 people (55%) who were married and 9 people (45%) who were not married. Finally, for disease onset in the treatment group, it was balanced between onset less than 1 year and

more than 1 year, respectively 10 people (50%) had onset less than 1 year and 10 people (50%) had onset more than 1 year. As for the control group, there were 13 people (65%) with onset of less than 1 year and 7 people (35%) with onset of more than 1 year.

There was a different distribution of research subject data in the treatment and control groups. After the homogeneity test was carried out, the p-value for all variables was greater than 0.05 (p>0.05). This confirmed that the subjects in this study were homogeneous and feasible for further analysis tests.

Table 2. Heart Rate Monitor for the Treatment Group

Treatment	Age	Maximum Heart Rate (220-Age)	Zone 4 (80- 90% DJM (Anaerobik)	*Mean*	Min-Max
Respondent	40	180	144-162	151,8667	146-158
Respondent	28	192	154-173	154,8667	150-160
Respondent	43	177	142-159	151,6	142-156
Respondent	38	182	146-174	152,1333	146-158
Respondent	27	193	154-174	154,8667	152-158
Respondent	33	187	150-168	152,8667	150-158
Respondent	26	194	155-175	155,8	148-160
Respondent	24	196	157-176	155,2667	150-160
Respondent	28	192	154-173	155,1333	150-160
Respondent	33	187	150-168	154	150-160
Respondent	34	186	149-167	154,2667	152-160
Respondent	42	178	142-160	152	144-156
Respondent	25	195	156-175	155,4667	150-160
Respondent	38	182	146-174	153,7333	148-160
Respondent	36	184	147-166	153,8	148-158
Respondent	32	188	150-169	154,2	150-158
Respondent	39	181	149-163	154,8	150-158
Respondent	44	176	141-158	153	148-158
Respondent	45	175	140-158	151,3333	144-158
Respondent	41	179	143-161	152,4667	146-160

Table 2 showed how to monitor the treatment group who received physical exercises training in the form of High Intensity Interval Training (HIIT) where previously we had to know the maximum heart rate (DJM), namely 220 – age. After that we calculate the heart rate for each respondent's anaerobic zone, which is 85% of DJM. Each respondent has a different anaerobic zone. In the table it could be seen from the Mean values of all respondents when doing physical exercises training in the anaerobic zone range based on the count of each individual. This showed that based on the heart rate, each respondent has entered the High Intensity category when doing physical exercises training.

4.2 Comparison of Cognitive Function and BDNF by Group

Before carrying out a comparative analysis of SCoRS v BI values in each group at baseline week, 5th week, and 10th week (session 30) as well as a comparison of BDNF values at the beginning and end, a normality test was first carried out using the Shapiro- Wilk test because sample <50. From the normality test, it was found that there were data that were not normally distributed, so to see a comparison of the SCoRS v BI scale and BDNF levels by group, the Mann-Whitney test was used with the results shown in Table 3 and Figure 1.

Table 3. Comparison of Cognitive Function by Group (Mann-Whitney test)

Variable	Group	N	Median (*Min-Max*)	SD	*p*
Total SCorS v BI (Baseline)	Treatment	20	6.87 (3.75-10.00)	1.17	0.914
	Control	20	6.81 (3.50-8.37)	1.68	
Total SCorS v BI (5th week)	Treatment	20	5.12 (2.75-7.12)	0.81	0.488
	Control	20	4.87 (3.62-6.12)	1.00	
Total SCorS v BI (10th week)	Treatment	20	4.25 (2.25-5.75)	1.01	0.287
	Control	20	3.25 (2.50-5.37)	1.02	

Table 3 found comparison of cognitive function by group. The p-value is obtained in the comparison of changes in the SCoRS v BI score in the treatment group and the control group (p> 0.05). Statistically, there is no significant difference in changes in the SCoRS v BI score in the two groups.

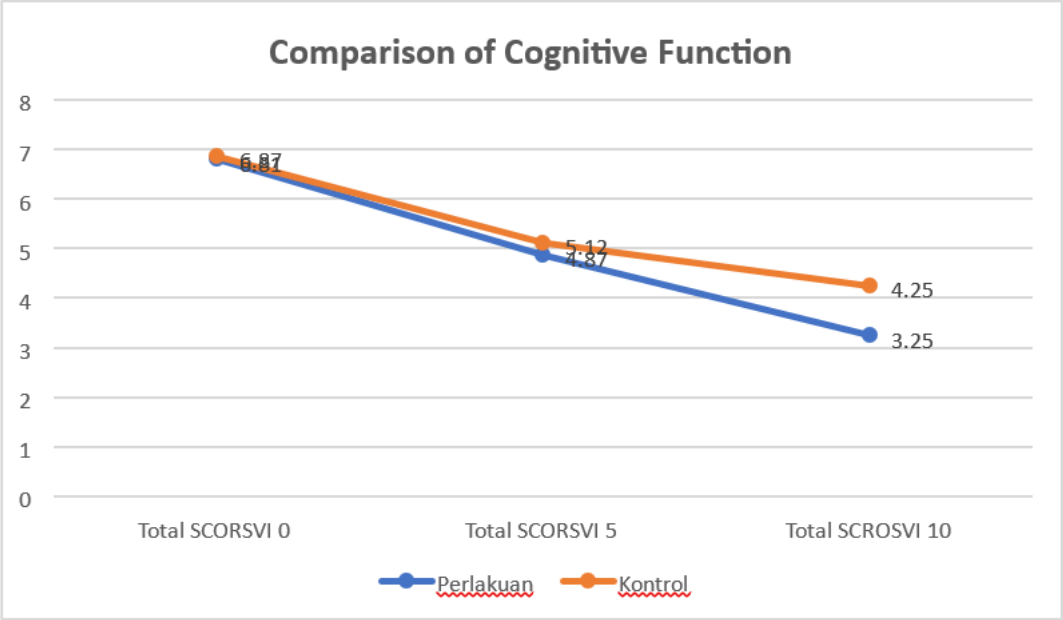

Figure 1. Comparison of Cognitive Function

Table 4. Comparison of BDNF by Group (Mann-Whitney test)

Variable	Group	N	Median (min-max)	SD	*p*
Initial BDNF	Treatment	20	0.37 (0.35-1.03)	0.25	0.016
	Control	20	0.78 (0.35-4,26)	0.955	
Final BDNF	Treatment	20	0.97 (0.37-2,84)	0.47	0.160
	Control	20	0.84 (0.71-3,74)	0.74	

Table 4 showed that the comparison of BDNF by group obtained a p-value of 0.016 (p <0.05) in initial BDNF levels between the treatment group and the control group. Thus, there is a statistically significant difference. In the final BDNF levels between the treatment group and the control group, a

p-value of 0.160 (p> 0.05) was obtained. This confirmed that there was no statistically significant difference (Figure 2).

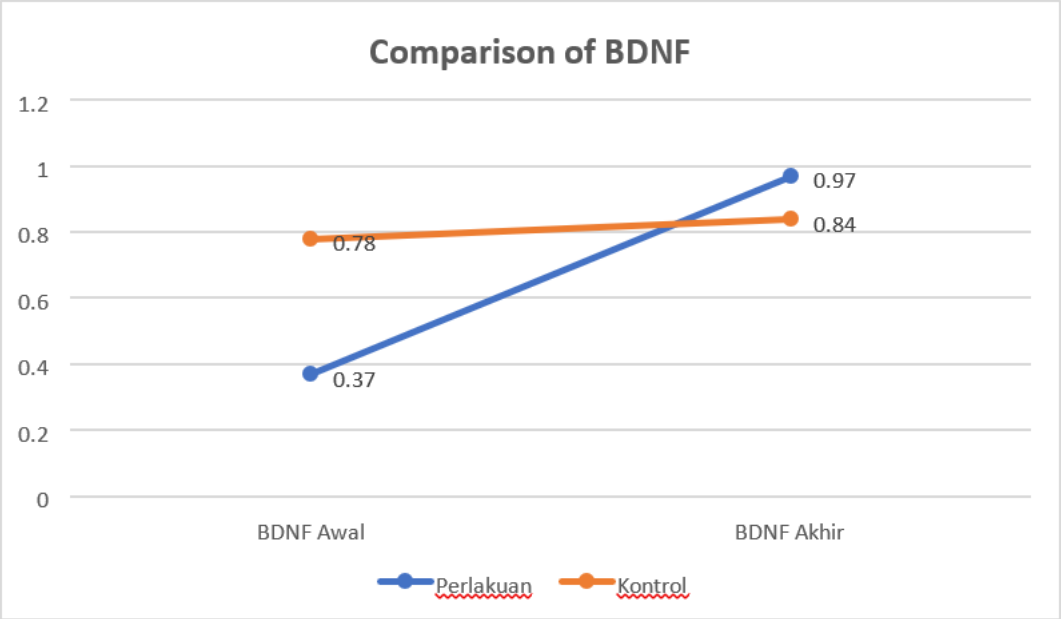

Figure 2. Comparison of BDNF

4.3 Comparison of Cognitive Function and BDNF by Time of Measurement

Before carrying out a comparative analysis of cognitive function based on the SCoRS v BI assessment and plasma BDNF levels by week, a normality test was performed using the Shapiro-Wilk test. From the normality test, it was found that there were data that were not normally distributed, so to see a comparison of the SCoRS v BI scale and plasma BDNF levels, the Wilcoxon Signed Rank test was used (Table 5).

Table 5. Cognitive Function by week (Wilcoxon Signed Rank test)

Group	Variable	N	Median (*Min-Max*)	SD	*p*
Treatment	Total SCoRS v BI (baseline)	20	6.87 (3.75-10.00)	1.17	0.000
	Total SCoRS v BI (5th week)	20	5.12 (2.75-7.12)	0.81	
	Total SCoRS v BI (baseline)	20	6.87 (3.75-10.00)	1.17	0.000
	Total SCoRS v BI (10th week)	20	4.25 (2.25-5.75)	1.01	
	Total SCoRS v BI (5th week)	20	5.12 (2.75-7.12)	0.81	0.000
	Total SCoRS v BI (10th week)	20	4.25 (2.25-5.75)	1.01	
Control	Total SCoRS v BI (baseline)	20	6.81 (3.50-8.37)	1.68	0.002
	Total SCoRS v BI (5th week)	20	4.87 (3.62-6.12)	1.00	
	Total SCoRS v BI (baseline)	20	6.81 (3.50-8.37)	1.68	0.000
	Total SCoRS v BI (10th week)	20	3.25 (2.50-5.37)	1.01	
	Total SCoRS v BI (5th week)	20	4.87 (3.62-6.12)	1.00	0.001
	Total SCoRS v BI (10th week)	20	3.25 (2.50-5.37)	1.01	

Table 5 found the comparison of cognitive function by week. In the treatment group, there were also several results, namely that there was a significant decrease in the median total SCoRS v BI (baseline - 5th week), from 6.87 to 5.12 (p <0.001). There was a significant decrease in the median total SCoRS v BI (baseline – 10th week), from 6.87 to 4.25 (<0.001). There was a significant decrease in the median total SCoRS v BI (5th week - 10th week) from 5.12 to 4.25 (<0.001). In the control group, there was a significant decrease in the median total SCoRS v BI (baseline - 5th week), from 6.81 to 4.87 (p <0.01). There was also a significant decrease in the median total SCoRS v BI (baseline – 10th week), from 6.81 to 3.25 (<0.001). A significant decrease was also found in the median total SCoRS v BI (5th week - 10th week) from 4.87 to 3.25 (<0.001).

Table 6. Comparison of Initial and Final BDNF (Wilcoxon Signed Rank test)

Group	Variable	N	Median (Min-Max)	SD	p
Treatment	Initial BDNF	20	0.37 (0.35-1.03)	0.24	0.000
	Final BDNF	20	0.97 (0.37-2,84)	0.47	
Control	Initial BDNF	20	0.78 (0.35-4,26)	0.94	0.247
	Final BDNF	20	0.84 (0.71-3,74)	0.73	

Table 6 found a comparison of early to final BDNF. In the treatment group, a median significant increase in BDNF levels was found from 0.37 to 0.97 with p-value of 0.000 (<0.001). In the control group, an increase in the median BDNF level was found from 0.78 to 0.84 with p-value of 0.247, but this increase was not statistically significant (p>0.05).

4.4. The correlation between SCoRS v BI and BDNF

Before carrying out a correlation test between changes in the SCoRS v BI score and BDNF levels, a normality test was first performed on the two domains to be correlated. It is known from previous analysis that the distribution of data in this study was not normally distributed based on the results of the normality test of the Shapiro-Wilk test. Thus, the Spearman test could be performed to determine the correlation between changes in the SCorS v BI score and plasma BDNF levels (Table 7).

Table 7. The correlation between SCoRS v BI and BDNF for all samples (Spearman's test)

Variable	Statistics	Final BDNF
Total SCorS v BI (10th week)	R	-0.324
	P	0.041
	N	40

* R= Correlation coefficient

In all samples, a significant negative correlation was found between the SCoRS v BI score and the BDNF level, where the lower the SCo RS v BI score, the higher the BDNF level (p <0.05). Based on the R value, the closeness of the correlation between the SCorS v BI scores and BDNF levels is in the Moderate category (0.250 > R < 0.500).

Table 8. Correlation between SCoRS v BI and BDNF after treatment by group

Group	Variable	Statistics	Final BDNF
Treatment	Total SCorS v BI 10th week	R	-0.492
		P	0.027
		N	20
Control	Total SCorS v BI 10th week	R	-0.284
		P	0.225
		N	20

*R= correlation coefficient

In the treatment group, a significant negative correlation was found between the SCoRS v BI score and the BDNF level, where the lower the SCorS v BI score, the higher the BDNF level ($p < 0.05$). Based on the R value, the correlation between the SCorS v BI scores and BDNF levels is in the strong category ($0.500 > R < 0.750$). In the control group, there was no significant correlation between the SCorS v BI scores and BDNF levels ($p > 0.05$).

4. Discussion

In general, most schizophrenic patients reduce their daily physical activities. They fall into the category of sedentary behavior. Many underlying factors, including fatigue, antipsychotic drug effects; metabolic and cardiorespiratory health problems; low motivation to exercise, possibly related to the negative symptoms of the disorder, and a lack of resources or encouragement from others to carry out additional activities to support daily physical activities (Viljoen & Roos, 2020). It necessary to add non-pharmacological interventions and daily pharmacological therapy. Physical exercise is one of the additional categories of adjuvant therapy. Physical exercise and training are some of the adjuvant therapies that could be used to improve the patient's cognitive function (Girdler et al., 2019; Viljoen & Roos, 2020). This is related to one part of the brain, namely the hippocampus, which plays an integral role in learning and memory. Patients with schizophrenia have been shown to have a smaller hippocampal volume compared to the general population, possibly secondary to neural atrophy. These hippocampal abnormalities have been correlated with deficits in memory, cognition and executive function in schizophrenia (Girdler et al., 2019).

Regular physical exercise has been shown to improve attention, processing speed, memory and executive function in schizophrenia. Exercise training serves to increase hippocampal volume and blood flow, stimulate neurogenesis, modulate synaptic plasticity, and increase growth factors such as BDNF which are involved in optimizing brain function. So it plays an important role in combating deficits in cognition, memory, hippocampal volume, and neural plasticity (Girdler et al., 2019).

This study used the SCoRS v BI scale which was validated in 2008 to see changes in the cognitive function of research subjects. A decrease in the SCorS v BI score it indicates an improvement in cognitive function (Rahardjo et al., 2008).The treatment subjects in this study were given additional exercise for 30 sessions with a duration of 25 minutes using the High Intensity Interval Training (HIIT) method. The method of exercising in HIIT is quite different from regular exercise which focuses on the aerobic zone with light-moderate intensity. In this study, all treatment groups first measured maximum heart rate with the 220-Age formula. After that we calculate the heart rate for each respondent's anaerobic zone, which is 80-90% of DJM. Each respondent has a different anaerobic zone due to age differences. The calculation of the anaerobic zone is in accordance with the literature which found that HIIT uses a heart rate (HR) of around 85% of maximum HR to achieve maximum lactate levels (Andrews et al., 2020; Weaver et al., 2021). This is related to several literatures regarding the impact of lactate in mediating brain plasticity. It leads to increased levels of BDNF. Several previous clinical trials have shown that high-intensity exercise could produce physiological benefits that are similar or higher than conventional light-moderate intensity exercise. HIIT could more effectively stimulate motor cortex plasticity, as evidenced by increased excitability and decreased cortex inhibition (Andrews et al., 2020; Huang et al., 2020).

The results an improvement in cognitive function as indicated by a decrease in the SCoRS v BI score in both treatment and control groups. However, there was no statistically significant difference in the decrease in the SCoRS v BI score in the two groups (Table 10), but there was a tendency to decrease the total score SCoRS v BI which is better in the treatment group than the control group. A decrease in the SCoRS v BI score also occurred in the control group which could be caused by risperidone as an atypical antipsychotic clinically proven effective in improving positive and negative clinical symptoms and preventing worsening of cognitive function in schizophrenic patients, especially

because risperidone is effective in blocking limbic D2 receptors and 5HT2A receptors in neurons cortical glutamate (Chien & Yip, 2013; Stahl, 2013; Stępnicki et al., 2018). There are other factors that influence there is no significant difference between the treatment and control groups in improving cognitive function. This is likely influenced by genetic factors from each individual. Several polymorphisms to increase the risk of schizophrenia are COMT (cathecol O methyl transferase) gene, disrupted-in-schizophrenia 1 gene (DISC1), DTNBP1 (dystrobrevin binding protein 1) gene, NRG1 SNP1 & 2 (neuregulin-1 single nucleotide polymorphism 1&2) gene (Sutrisna & Aisyah, 2010). Of the several polymorphisms, there are several genes that are expressed in brain areas such as the cerebral cortex and hippocampus (Millar et al., 2000; Owen et al., 2004). They would affect cognitive function and this was not examined in this study (Griwijoyo 2013).

The effect of exercise training on changes in BDNF levels is to induce neuroplasticity in various areas of the brain. It would trigger an increase in BDNF levels (Müller et al., 2020). This study showed a significant increase in plasma BDNF levels in the treatment group and when compared with changes in BDNF in the control group, there were statistically significant differences in changes (Table 19). This is in line with previous systematic reviews which stated that plasma/serum BDNF levels increased in schizophrenic patients after being given nonpharmacological interventions, one of which was exercise (Nieto et al., 2013; Nieto et al., 2021). Several studies have also shown that higher lactate concentrations are associated with increased plasma BDNF and/or serum levels. Current evidence suggests that high-intensity interval training increases BDNF levels to a greater extent than moderate and/or intense sustained exercise. This happens because when exercising at high intensity it would cause lactate levels in the blood to increase then lactate would cross the blood brain barrier (BBB) through monocarboxylate transporters (MCT). Furthermore, binding of lactate to the hydroxycarboxylic acid receptor (HCAR1) on the BBB could induce angiogenesis. In neurons, lactate exerts several neurotrophic and metabolic effects via transmembrane transport via MCT and direct binding to HCAR1. One of them is lactate which increases intracellular Nicotinamide Adenine Dinucleotide Hydrogen (NADH) molecules which would result in increased calcium levels and BDNF gene expression. BDNF released could then enhance neuroplasticity through different neurobiological mechanisms (eg, neurogenesis, synaptogenesis) (Huang et al., 2020; Müller et al., 2020).

The results showed that there was a significant negative correlation between the SCoRS v BI score and the BDNF level in the treatment group, where the lower the SCoRS v BI score, the higher the BDNF level compared to the control group. The same results were shown in previous studies to show improvements in cognitive function and BDNF levels in patients who received additional exercise therapy (Firth et al., 2018; Gökçe et al., 2019; Kimhy et al., 2015). This is also in line with some previous literature which found that BDNF as one of the most studied biomarkers is associated with cognitive function in schizophrenic patients because of its role in maintaining synaptic plasticity in brain areas, especially in the prefrontal cortex and hippocampus. BDNF also plays an important role in synaptic plasticity through activation of NMDA receptors in the hippocampus and prefrontal areas. In exploring the relationship between cognition and BDNF, loss of one functional copy of the BDNF gene was reported to result in cognitive impairment (Di Carlo et al., 2020; Nieto et al., 2021; Nurjono et al., 2012; Tanra et al., 2021). This showed a relationship between plasma/serum BDNF levels and cognitive function. BNDF levels increase is more likely to trigger improvements in cognitive function.

There are several limitations in this study including the diagnosis of schizophrenia based on PPDGJ III only in general, not specific to subtypes of schizophrenic disorders. It has the potential to affect the course of the disease, especially in the cognitive domain of the study subjects. In this study, genetic examination was not carried out on research subjects which might affect the cognitive function of each individual before exercising. In carrying out physical exercises training activities when

measuring heart rate is still done manually. In the future a better heart rate measurement tool is needed to support more accurate heart rate results. The relatively long research time resulted in some research subjects sometimes experiencing a feeling of boredom to take part in additional exercise therapy. A variety of exercises was needed to reduce patient saturation.

4. Conclusion

The results showed significant improvement in cognitive function in both groups who received additional exercise training with risperidone therapy (treatment group) and those who only received risperidone therapy (control group). Increased plasma BDNF levels were found in both groups who received additional physical exercises training with risperidone therapy and those who only received risperidone therapy. However, the addition of exercise in patients treated with risperidone showed a significant increase in plasma BDNF levels compared to those not given additional exercise. The findings also show a correlation between increased plasma BDNF levels and improved cognitive function.

As an implication, these results could be used as an additional alternative for nonpharmacological management of schizophrenia patients where by providing additional exercise as an adjuvant to standard therapy in patients who are still using typical antipsychotics could improve cognitive function and synaptic neuroplasticity. For further research, based on the results of this study, genetic examination could be considered in order to get rid of all variables that could be confounders and support better research results. For further research, it is hoped that the results of this study could enrich theoretical perspectives regarding exercise training both in terms of the implementation procedure and how exercise mechanisms could improve cognitive function and neuroplasticity. For psychiatric clinicians, the findings could be used as detailed educational material for families and patients themselves. They could do physical exercises as part of their lifestyle. For outpatient care, physical exercises activities could also be done to be carried out regularly.

Reference

1. Andrews, S. C., Curtin, D., Hawi, Z., Wongtrakun, J., Stout, J. C., & Coxon, J. P. (2020). Intensity matters: high-intensity interval exercise enhances motor cortex plasticity more than moderate exercise. *Cerebral Cortex*, *30*(1), 101-112.
2. Di Carlo, P., Punzi, G., & Ursini, G. (2020). Brain-derived neurotrophic factor and schizophrenia. *Psychiatric Genetics*, 200–210. https://doi.org/10.1097/YPG.0000000000000237
3. Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., & Ward, P. B. (2018). Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. *Neuroimage*, *166*, 230-238.
4. Girdler, S. J., Confino, J. E., & Woesner, M. E. (2019). Exercise as a Treatment for Schizophrenia: A Review. *Psychopharmacology Bulletin*, *49*(1), 56–69.
5. Gökçe, E., Güneş, E., & Nalçaci, E. (2019). Effect of exercise on major depressive disorder and schizophrenia: A BDNF focused approach. *Noropsikiyatri Arsivi*, *56*(4), 302–310. https://doi.org/10.29399/npa.23369
6. Griwijoyo, S., & Sidik, D. J. (2013). Ilmu Faal Olahraga (Fisiologi Olahraga): Fungsi Tubuh Manusia pada Olahraga untuk Kesehatan dan Prestasi. *Bandung: Remaja Rosdakarya*.
7. Huang, Z., Zhang, Y., Zhou, R., Yang, L., Pan, H., Müller, P., Duderstadt, Y., Lessmann, V.,
8. & Müller, N. G. (2020). Lactate as Potential Mediators for Exercise-Induced Positive Effects on Neuroplasticity and Cerebrovascular Plasticity. *Frontiers in Physiology*, *12*(4). https://doi.org/10.3390/jcm9041136
9. Keefe, R. S. E., Poe, M., Walker, T. M., Kang, J. W., & Harvey, P. D. (2006). The schizophrenia cognition rating scale: An interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. *American Journal of Psychiatry*, *163*(3), 426–432. https://doi.org/10.1176/appi.ajp.163.3.426

10. Kemenkes RI. (2018). Hasil Riset Kesehatan Dasar Tahun 2018. In *Kementrian Kesehatan RI 53* (9).
11. Kemppainen, J., Aalto, S., Fujimoto, T., Kalliokoski, K. K., Långsjö, J., Oikonen, V., ... & Knuuti, J. (2005). High intensity exercise decreases global brain glucose uptake in humans. *The Journal of physiology*, *568*(1), 323-332.
12. Kimhy, D., Vakhrusheva, J., Bartels, M. N., Armstrong, H. F., Ballon, J. S., Khan, S., Chang, R. W., Hansen, M. C., Ayanruoh, L., Lister, A., Castrén, E., Smith, E. E., & Sloan, R. P. (2015). The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: A single-blind, randomized clinical trial. *Schizophrenia Bulletin*, *41*(4), 859–868. https://doi.org/10.1093/schbul/sbv022
13. Kusumawardhani A.A.A.A, Dharmono S, D. H. (2011). *Konsensus Penatalaksanaan Gangguan Skizofrenia* (Pertama). Perhimpunan Dokter Spesialis Kedokteran Jiwa Indonesia Jakarta: (PDSKJI).
14. Lauritzen, K. H., Morland, C., Puchades, M., Holm-Hansen, S., Hagelin, E. M., Lauritzen, F., ... & Bergersen, L. H. (2014). Lactate receptor sites link neurotransmission, neurovascular coupling, and brain energy metabolism. *Cerebral cortex*, *24*(10), 27842795.
15. Millar, J. K., Wilson-annan, J. C., Anderson, S., Christie, S., Martin, S., Semple, C. A. M.,
16. Devon, R. S., Clair, D. M. S., Muir, W. J., Blackwood, D. H. R., & Porteous, D. J. (2000).
17. *Disruption of two novel genes by a translocation co-segregating with schizophrenia*. *9*(9), 1415–1424.
18. National Alliance on Mental Illness. (2022). *What is Schizophrenia? | NAMI: National Alliance on Mental Illness*. https://www.nami.org/About-Mental-Illness/Mental-HealthConditions/Schizophrenia
19. National Institute of Mental Health. (2022). *NIMH » Schizophrenia*. https://www.nimh.nih.gov/health/topics/schizophrenia
20. Nieto, R. R., Carrasco, A., Corral, S., Castillo, R., Gaspar, P. A., Bustamante, M. L., & Silva,
21. H. (2021). BDNF as a Biomarker of Cognition in Schizophrenia/Psychosis: An Updated Review. *Frontiers in Psychiatry*, *12*(June), 1–9. https://doi.org/10.3389/fpsyt.2021.662407
22. Nieto, R., Kukuljan, M., & Silva, H. (2013). BDNF and schizophrenia: From neurodevelopment to neuronal plasticity, learning, and memory. *Frontiers in Psychiatry*, *4*(JUN), 1–11. https://doi.org/10.3389/fpsyt.2013.00045
23. Nurjono, M., Lee, J., & Chong, S. A. (2012). A review of brain-derived neurotrophic factor as a candidate biomarker in schizophrenia. *Clinical Psychopharmacology and Neuroscience*, *10*(2), 61–70. https://doi.org/10.9758/cpn.2012.10.2.61
24. Owen, M. J., would iams, N. M., & Donovan, M. C. O. (2004). *The molecular genetics of schizophrenia : new findings promise new insights*. 14–27. https://doi.org/10.1038/sj.mp.4001444
25. Pellerin, L., Pellegri, G., Bittar, P. G., Charnay, Y., Bouras, C., Martin, J. L., ... & Magistretti, P. J. (1998). Evidence supporting the existence of an activity-dependent astrocyte-neuron lactate shuttle. *Developmental neuroscience*, *20*(4-5), 291-299.
26. Proia, P., Di Liegro, C. M., Schiera, G., Fricano, A., & Di Liegro, I. (2016). Lactate as a Metabolite and a Regulator in the Central Nervous System. *International journal of molecular sciences*, *17*(9), 1450.
27. Rahardjo, S., Herdaetha, A., & Sudiyanto, A. (2008). *Uji Validitas Schizophrenia Cognitive Rating Scale versi Indonesia*.
28. Rosenbaum, J. F., Arana, G. W., Hyman, S. E., Labbate, L. A., Fava, M., & would iams, M. L. (2007). Handbook of psychiatric drug therapy. *J Clin Psychiatry*, *68*(2).
29. Sinaga, B. R. (2007). *Skizofrenia dan Diagnosa Banding*. Jakarta : Balai Penerbit, Fakultas Kedokteran Universitas Indonesia, 2007.

30. Stahl, S. M. (2013). *Stahl's Essential Psychopharmacology Neuroscientific Basis and Practical Applications* (S. M. Stahl (ed.); Fourth). Cambridge University Press. Stępnicki, P., Kondej, M., & Kaczor, A. A. (2018). Current concepts and treatments of schizophrenia. *Molecules*, *23*(8). https://doi.org/10.3390/molecules23082087
31. Sutrisna, E., & Aisyah, R. (2010). *Marker Genetik dan Mekanisme Molekuler Penyakit Skizofrenia*. 33–38.
32. Tanra, A. J., Sabaruddin, H., Liaury, K., & Zainuddin, A. A. (2021). Effect of adjuvant vitamin c on brain-derived neurotrophic factor levels and improvement of negative symptoms in schizophrenic patients. *Open Access Macedonian Journal of Medical Sciences*, *9*(T3), 353–357. https://doi.org/10.3889/oamjms.2021.7086
33. Viljoen, M., & Roos, J. L. (2020). Physical exercise and the patient with schizophrenia.
34. *Australian Journal of General Practice*, *49*(12), 803–808. https://doi.org/10.31128/AJGP-04-20-5384
35. Weaver, S. R., Skinner, B. D., Furlong, R., Lucas, R. A. I., Cable, N. T., Rendeiro, C., McGettrick, H. M., & Lucas, S. J. E. (2021). Cerebral Hemodynamic and Neurotrophic
36. Factor Responses Are Dependent on the Type of Exercise. *Frontiers in Physiology*, *11*(January), 1–14. https://doi.org/10.3389/fphys.2020.609935
37. Wölfel, R., Corman, V. M., Guggemos, W., Seilmaier, M., Zange, S., Müller, M. A., ... & Wendtner, C. (2020). Virological assessment of hospitalized patients with COVID2019. *Nature*, *581*(7809), 465-469.
38. World Health Organization. (2022). *Schizophrenia*. https://www.who.int/news-room/factsheets/detail/schizophrenia
39. Yang, J., Ruchti, E., Petit, J. M., Jourdain, P., Grenningloh, G., Allaman, I., & Magistretti, P. J. (2014). Lactate promotes plasticity gene expression by potentiating NMDA signaling in neurons. *Proceedings of the National Academy of Sciences*, *111*(33), 12228-12233.