Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 14s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Non-Computerised Cognitive Remediation Improves Cognitive Function And Reduces Serum Tumour Necrosis Factor Alpha (Tnf-A) Levels In Schizophrenia Patients Treated With Risperidone At Rskd Dadi Makassar In 2024

Arvita Revianty Akbar[1], A.Jayalangkara Tanra[*1,2], Kristian Liaury[1], Burhanuddin Bahar[3], Sonny Teddy Lisal[1,5], Ilhamuddin Azis[1,4], Saidah Syamsuddin[1]

[1]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

[2]Department of Psychiatry, Biological Psychiatry and Psychopharmacology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

[3]Department of Biostatics, Faculty of Public Health, Hasanuddin University, Makassar, South Sulawesi, Indonesia

[4]Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

[5]Department of Psychiatry, Psychiatry Consultation Liaison Section, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

***Corresponding Author:**

A.Jayalangkara Tanra

[1]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Jl. Perintis Kemerdekaan KM.10, Makassar, South Sulawesi, Indonesia, Postcode 90245.

Email ID:ajtanra@yahoo.com, arvitarevianti@gmail.com

Cite this paper as: Arvita Revianty Akbar, A.Jayalangkara Tanra, Kristian Liaury, Burhanuddin Bahar, Sonny Teddy Lisal, Ilhamuddin Azis, Saidah Syamsuddin, (2025) Non-Computerised Cognitive Remediation Improves Cognitive Function And Reduces Serum Tumour Necrosis Factor Alpha (Tnf-A) Levels In Schizophrenia Patients Treated With Risperidone At Rskd Dadi Makassar In 2024. *Journal of Neonatal Surgery*, 14 (14s), 558-569.

ABSTRACT

Background: Schizophrenia is a chronic mental disorder that affects millions of people worldwide. In Indonesia, its prevalence increased from 1.3 to 6.7 per 1,000 households between 2013-2018. Cognitive impairment, especially episodic memory deficits, is a major predictor of poor outcome, associated with dysfunction of brain circuits such as the dorsolateral prefrontal cortex and hippocampus. Inflammation, particularly through TNF-α, plays an important role in the pathogenesis of these cognitive impairments.

Objective: The purpose of this study was to determine the effect of cognitive remediation on the improvement of cognitive symptoms and serum TNF-a levels of schizophrenia patients who received risperidone therapy. As well as knowing the correlation between cognitive symptoms and serum TNF-a levels in schizophrenia patients in Makassar, Indonesia.

Methods: This experimental study examined 40 male schizophrenia patients at Dadi Regional Special Hospital, randomly divided into treatment (risperidon + cognitive remediation) and control (risperidon alone) groups. Conducted in September-October 2024, TNF-α levels were measured by ELISA, while cognitive function was assessed using SCORSVI.

Results: Both groups showed significant cognitive improvement, but better in the risperidone + cognitive remediation group. Serum TNF-α levels decreased significantly after 8 weeks, with a greater decrease in the treatment group. Spearman test showed a significant positive correlation between serum TNF-α and cognitive dysfunction (r=0.884; p=0.001).

Conclusion: We found that non-computerised cognitive remediation in schizophrenia patients receiving risperidone therapy can provide better improvement in cognitive dysfunction compared with no cognitive remediation. There was also a correlation between serum TNF-a levels and improvement in cognitive symptoms (SCORSVI score) in both groups, where the lower the SCORSVI score, the lower the serum TNF-a levels.

Keywords: *Schizophrenia, Risperidone, Cognitive Remediation, TNF-a , SCORSVI.*

1. INTRODUCTION

Schizophrenia is a chronic mental disorder that is complex in terms of symptoms, biological basis, and clinical course with

a debatable as well as debilitating pathogenesis, involving three clusters of positive (delusions, hallucinations), negative (flat affect, alogia, avolition), affective, and cognitive symptoms, and has major implications for public health. The prevalence of schizophrenia continues to increase globally, including in Indonesia. According to various sources, the disease affects up to 1% of the population.(Stępnicki et al., 2018) The World Health Organization (WHO) in 2022 stated that approximately 24 million people suffer from schizophrenia or 1 in 300 people (0.32%) worldwide.(Sapienza et al., 2024;World Health Organization.2022)

Schizophrenia appears in late adolescence or young adulthood, with earlier onset in males (15-25 years) and females (25-35 years).(Kahn et al., 2015) One of the symptoms of cognitive dysfunction, such as episodic memory deficits is a major symptom and has a significant impact on the patient's daily life, affecting the ability to work, learn, and socialise. About 98% of patients experience a decline in cognitive function, which makes it difficult for them to play a role in society.(Amir Nurmiati., 2021)

Cognitive impairment continues to pose significant challenges in schizophrenia as the underlying neurobiology is multifaceted, encompassing complex interactions between multiple molecules that may help explain the heterogeneity of cognitive profiles. The dopaminergic system was the first to be investigated in relation to cognition, and some evidence pointed to frontal and pre-frontal dopamine levels as one of the important determinants cognitive outcomes. Other strong findings were later reported on the relationship between N -methyl- d -aspartate (NMDA) neurotransmission and the cholinergic system and cognitive function. Indeed, it was observed that compounds that stimulate cholinergic receptors improve cognitive performance. Conversely, molecules that block NMDA receptors cause cognitive impairment. However, the glutamatergic system still remains an open issue, as glutamatergic neurotransmission improves cognitive function but at the same time high levels of glutamate can cause excitotoxicity, leading to neuronal loss and oligodendrocyte damage, thus disrupting white and grey matter (WGM). Overall, it is important to note that neuroinflammation and KP metabolites can affect cognitive function.(Sapienza et al., 2024)

In addition to neurotransmitter dysregulation affecting cognition in schizophrenia, the role of neuroinflammation in cognitive impairment is gaining attention. Several studies identified microglia activation and elevated levels of pro-inflammatory cytokines as important pathogenic mechanisms of the disease. Cytokines that play a major role in the pathophysiology of schizophrenia are Interleukin (IL)-1β, Tumour Necrosis Factor (TNF)-α, IL 6, IL-α, IL-α, IL-α, IL-α, and IL-α.

17. Systemic sub-inflammation and neuroinflammation trigger various cognitive deficits due to induction of high oxidative stress, cytotoxicity, increased synaptic pruning due to microglia activation, and white-grey matter (WGM) disruption.(Sapienza et al., 2024)

Although genetic susceptibility and environmental stresses during the early stages of life are fundamental in the development of schizophrenia, inflammation is considered a major causative/contributing/mediating factor in the onset of schizophrenia. Impaired immune system and its complex interaction with the nervous system may contribute to the pathogenesis and pathophysiology of schizophrenia.(Reale et al., 2021) Research suggests that inflammation, especially high serum TNF-α levels, may damage neurons and affect cognitive function in schizophrenia patients.(Baek et al., 2022)

Therapies to improve cognitive function are important in the treatment of schizophrenia. Schizophrenia treatment approaches include pharmacotherapy and non-pharmacotherapy. Commonly used pharmacotherapies are atypical antipsychotics (SGAs), such as risperidone, which help reduce positive and negative symptoms and improve cognitive function, although they have little effect on restoring social function. However, the effect of pharmacotherapy on cognitive function is still minimal, so the need for non-pharmacotherapeutic approaches such as cognitive remediation is important as a "co-treatment" effort focused on improving cognitive, social function and improving the quality of life of people with schizophrenia.(Azmanova et al., 2018; Kusumawardhani AAA et al., 2011; Stępnicki et al., 2018)

Cognitive Remediation Therapy (CRT) is a behavioural training-based intervention that is effective in improving and preventing cognitive decline in various cognitive domains, such as improved attention, memory, and executive function through exercises that can be performed in the stabilisation phase with persistent effects on cognition and functional outcomes even 10 years later.(Sapienza et al., 2024) This approach is effective in improving patients' daily functioning and quality of life. Research shows that inflammation, especially high levels of TNF-α , has an influence on cognitive impairment in schizophrenia patients, and treatments that target inflammation can help improve cognition.(Dawidowski et al., 2021; Patlola et al., 2023; Su et al., 2023; Bowie et al., 2020)

Research on the effect of *non-computerised* cognitive remediation on the improvement of cognitive function and its relationship with serum TNF-α levels has never been previously conducted in Indonesia, especially in Makassar. The existence of meaningful findings in this study can provide information about good non-pharmacological management in schizophrenia patients and will ultimately improve the prognosis of disorders. In addition, cognitive remediation itself is a gold standard therapy for cognitive impairment in schizophrenia that does not require a lot of money. On this basis, the researcher is interested in conducting this study.

2. RESEARCH METHODS

The samples in this study were 40 male schizophrenia patients who were the subjects of the study. The study was conducted at the Dadi Regional Special Hospital (RSKD), Makassar, South Sulawesi, from September to October 2024. All research subjects who met the inclusion and exclusion criteria were asked to agree to participate in the study through informed consent. Inclusion criteria, namely subjects diagnosed with schizophrenia according to PPDGJ, aged 20-45 years with disease onset <3 years, and have passed the acute phase with a PANSS score of 30-60, able and willing to participate in this study, and can be interviewed. Subjects in this study were patients with schizophrenia who were hospitalised, and treated with risperidone 4-6 mg/day. Exclusion criteria were set as follows, having physical comorbidities, having a history of drug consumption before being hospitalised, not willing to take part in *non-computrized* cognitive remediation sessions and using anti-inflammatory drugs and antibiotics. The *drop out* criteria were not regularly following all cognitive remediation sessions, irregular consumption of antipsychotic drugs, research subjects refused to continue research sessions, and dropped out of hospital care before 16 therapy sessions.

Measurement of the variables was done before and after the intervention. The instrument used to assess cognitive dysfunction was the *Schizophrenia Cognition Rating Scale* Indonesian version (SCORSVI). SCORSVI is an interview-based measurement scale and focuses on daily functioning, used to assess complete cognitive function, see the severity of cognitive impairment, and also to see the effect of therapeutic agents on cognitive function. The sensitivity and specificity of SCORSVI are satisfactory with a sensitivity of 92.8% and specificity of 93.7%. SCORSVI assesses a number of cognitive domains, namely attention, memory, motor skills, speech, and problem solving. Each assessment consists of 20 questions and question items are scored on a 4-point measurement scale, namely: 1-none; 2-mild; 3-moderate; 4-severe. There is also the possibility of including an N/A (*non-applicable*) scale. In addition to the 20 question items, there was also a global functioning scale assessment (1- 10), which was to be completed by the interviewer at the end of the interview. Based on interpretation, scores on the SCORSVI can be classified as; 1 being no cognitive dysfunction, and 10 being the most severe cognitive dysfunction.(Keefe & Fenton, 2007).

Serum TNF-a levels were obtained from blood serum examination, ELISA (enzyme-linked immunosorbent assay) kit namely "Human Tumour Necrosis Factora , TNF-a ELISA Kit No E0082Hu, Bioassay Technology Laboratory". Blood was then taken to the laboratory for examination of serum TNF- .a

This research is an experimental study with pre and post test measurements with randomised group selection. The Shapiro-Wilk test was used to assess the normality of the data because the sample size was <50. The minimum sample size of each group is 20 people, with the sampling technique carried out by Consecutive Sampling, namely all patients who meet the research criteria until the required sample is fulfilled. Furthermore, the data were analysed to obtain the correlation value (r). Data were analysed using SPSS 24.0 and Microsoft Excel. This study uses a systematic approach to ensure valid and reliable results.

This study has received a certificate of ethical approval from the Ethics Committee for Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University. Informed consent was obtained from participants and their families, and confidentiality was maintained.

3. RESULTS

At the beginning of the study, 44 subjects were involved who met the inclusion criteria. However, 4 subjects dropped out because they were not willing to continue research observation / subjects were discharged, experienced changes in antipsychotic therapy, and did not regularly attend cognitive remediation sessions so they were excluded from research subjects. ±Observations continued on 40 research subjects who were divided into 2 groups consisting of 20 patients in the control group who were only given risperidone 4-6mg / day and 20 patients in the treatment group who were given risperidone 4-6mg / day and non-computerised cognitive remediation therapy for 16 sessions in the morning for 45-90 minutes. Observations were conducted for 8 weeks. All of the study subjects were male and the onset of illness was

<3 years.

The demographic characteristics of the schizophrenia patients are presented in Table 1, based on the treatment and control groups. The mean age of most subjects was in the range of 31-40 years in both groups (45%). Based on marital status, the majority of subjects in both the control and treatment groups were married as many as 12 (60%). The level of education showed that the subjects in the treatment group were predominantly high school graduates (50%), while the majority of the control group were elementary school graduates (55%).

Table 1. Distribution of Demographic Characteristics of Research Subjects

Characteristics	**Treatment (n=12)**	**Control (n=12)**	**Value *p***

	Married	12 (60%)	12 (60%)	
Status	Not married	6 (30%)	8 (40%)	0.319
	Widower	2 (10%)	0	
	SD	7 (35%)	11 (55%)	
Education	SMP	3 (15%)	5 (25%)	0.138
	HIGH SCHOOL	10 (50%)	4 (20%)	
	Labour	3 (15%)	0	
	Teacher	1 (5%)	0	
	Honorary Elementary School	0	2 (5%)	
	Employees	1 (5%)	0	
	Fisherman	0	2 (5%)	
	Merchants	1 (5%)	1 (5%)	
Jobs				0.183
	RM Waiter	1 (5%)	0	
	Companion	0	1 (5%)	
	Shopkeeper	0	1 (5%)	
	Farmers	4 (20%)	1 (5%)	
	Self-employed	2 (10%)	0	
	Not working	7 (35%)	12 (60%)	
	Paranoid Schizophrenia	6 (30%)	10 (50%)	
Diagnosis				0.333
	Schizophrenia YTT	14 (70%)	10 (50%)	
	< 30 years	6 (30%)	9 (45%)	
Age	31-40 years old	9 (45%)	9 (45%)	0.390
	> 40 years	5 (25%)	2 (10%)	
	1.00	5 (25%)	7 (35%)	
Onset	2.00	9 (45%)	7 (35%)	0.747
	3.00	6 (30%)	6 (30%)	

*Data displayed with descriptive analysis, *Mann Whitney homogeneity test*

Table 2 shows the measurement of total SCORSVI scores at three observation times, namely week 0, week 4, and week 8 (after the 16th session). The results of the analysis in both the treatment and control groups showed a significant difference in the total SCORSVI score after 4 weeks of therapy with a meaning value of each group **p=0.001** ($p<0.05$) with a decrease in the mean total SCORSVI score after 8 weeks of therapy sessions greater in the treatment group (**4.60**) compared to the control group (**5.65**). It is further evidenced by the results after being compared between groups there is a significant difference in the mean total SCORSVI score which is better in the treatment group than the control group after 8 weeks of cognitive remediation sessions with a meaning value of **p=0.003**.

Table 3 shows significant differences in mean total SCORSVI scores at various time intervals; week 0 to week 4 (**p=0.001**),

week 4 to week 8 (**p=0.01**), and week 0 to week 8 (**p=0.001**), with a better reduction in mean total SCORSVI scores in the treatment group than the control group at week 8. These results show that both groups experienced a statistically significant decrease in total SCORSVI score, with a decrease seen every 4 weeks. The change in mean total SCORSVI score was greatest from week 0 to week 8, especially in the treatment group (**3.10**) compared to the control group (**1.65**). (Table 3, Graph 1)

Data Analysis of SCORSVI Scores in the Treatment and Control Groups

		Group			
VARIABLES SCORSVI	**Treatment *(Mean)***	***P-value***	**Control *(Mean)***	***P-value***	***P-value***
Week 0	7.70		7.30		0.172
Week 4	6.10	0.001	6.70	0.001	0.204
Week 8	4.60		5.65		0.003*

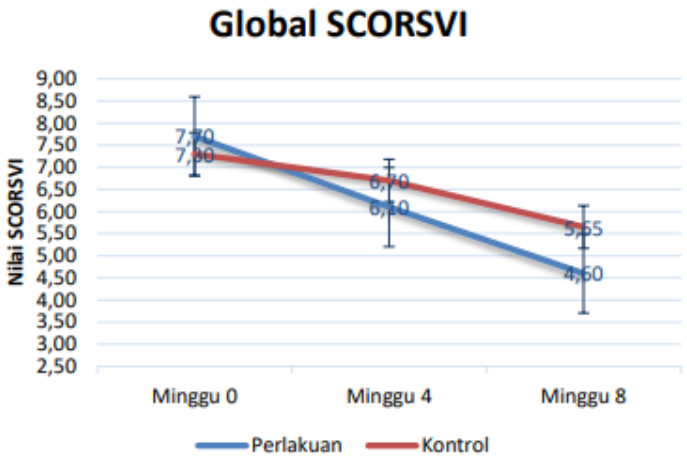
Mean± SD

**significantly significant (p<0.05)*

Table 3. Data Analysis on the Decrease of SCORSVI Score in the Treatment and Control Groups

SCORSVI VARIABLE		**Group**			
	Treatment (*Mean*)	***P* value**	**Control (*Mean*)**	***P* value**	***P* value**
D **(week 0 - week 4)**	1.60		0.60		0.001*
D **(week 4 - week 8)**	1.50	0.001	1.05	0.001	0.010*
D **(week 0 - week 8)**	3.10		1.65		0.001*

*Mean± SD *significantly significant (p<0.05)*



Comparison of SCORSVI Score Decrease in Both Groups at Week 0, 4, and 8.

Table 4 regarding the measurement of serum TNF-a levels between research subjects (individuals with schizophrenia) and healthy individuals, which shows the results that serum TNF-a levels in individuals with schizophrenia have increased significantly compared to healthy individuals with a meaning value of **p = 0.003**. From these results it can be concluded that

increased serum TNF-a levels play an important role in schizophrenia psychopathology.

Table 4. Data Analysis Regarding Serum TNF-a Levels between Schizophrenia Patients and Healthy Controls.

	Group		
TNF- VARIABLEa	**Schizophrenia Patients**	**Healthy Control**	***P* value**
	(*Mean*± SD)	**(*Mean*± SD)**	
Week 0	173.72± 71.41	90.11± 37.18	0.003*

Kruskal Wallis Test

**significantly significant (p<0.05)*

Table 5 shows the measurement of serum TNF-a levels at week 0 and week 8 (after the 16th session). The analysis showed that the cognitive remediation intervention in the treatment group not only had an impact on improving cognitive symptoms but also contributed to a more significant decrease in serum TNF-a levels compared to the control group who only received risperidone therapy. The Mann-Whitney test showed a significant decrease in serum TNF-a levels in both groups from week 0 and week 8 with a meaning value of **p=0.001**. However, after comparison, the results showed no significant difference in week 0 serum TNF-a levels between the two groups **(p>0.05)**. However, there was a significant difference at week 8 with a significance value of **p=0.033** with a decrease in the mean serum TNF-a level after 8 weeks more

large in the treatment group (**95.81pg/ml**) compared to the control group **(123.98pg/ml**).

Table 6 shows the delta/ difference in the decrease in serum TNF-a levels in both groups. These results show that both groups experienced a decrease in TNF- levels.

a There was a significant decrease in serum TNF- levels in the time interval from week 0 to week 8 with a significance value of **p=0.001**. There was a significant difference in the mean decrease in serum TNF-a levels after 8 weeks where the treatment group experienced a greater decrease of **79.09pg/ml** compared to the control group which was **48.57pg/ml**.(Table 6, graph 2).

Table 5. Data Analysis on Serum TNF-a Levels in the Treatment and Control Groups

TNF-VARIABLEa		**Group**			
	Treatment (*Mean*± SD)	***P-value***	**Control (*Mean*± SD)**	***P-value***	***P-value***
Week 0	174.90± 91.34	0 .001*	172.55± 80.69	0.001*	0.957
Week 8	95.81± 76.45		123.98± 78.67		0.033*

Mean± SD

**significantly significant (p<0.05)*

Table 6. Data Analysis on the Decrease of Serum TNF-a Levels in the Treatment and Control Groups

TNF-α VARIABLE	Group				*P-value*
	Treatment *n* (*Mean*± SD)	Value	Control *n* (*Mean*± SD)	Value	
Δ week 0-week 8	79.09± 47.63		48.57± 42.28		0.001*

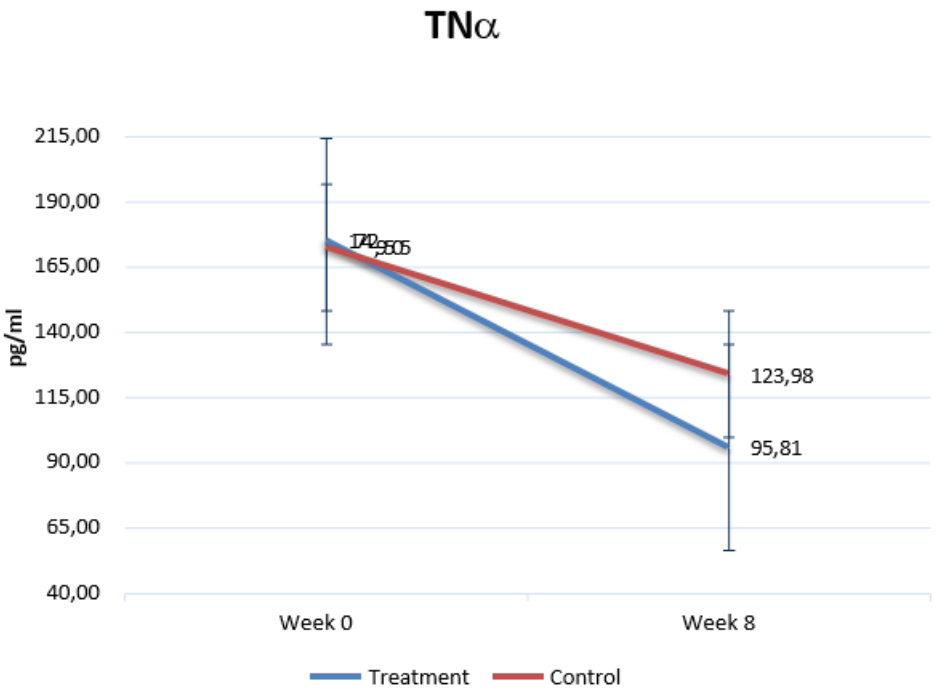
**significantly significant (p<0.05)*

Based on the results of the Spearman correlation test in Table 7, serum TNF-a levels and total SCORSVI values obtained a **p** value **<0.05** in delta / difference week 0 to week 8 in both groups (**p=0.001**) and showed that there was a correlation between serum TNF-a levels and total SCORSVI values with a correlation strength of **0.884** indicating a positive correlation with a strong correlation strength (r=0.7-<0.9). From these results it can be concluded that the decrease in total SCORSVI value was also followed by a decrease in serum TNF-a levels in both groups.

4. DISCUSSION

Characteristics of Research Subjects

This study included all male subjects, in accordance with the results of research that men have a higher risk of suffering from schizophrenia than women. This is related to men's role as household support, which increases the likelihood of greater life stress, as well as a prognosis that tends to be more poor in men than women due to lower treatment response.(Siti Zahnia & Dyah Wulan Sumekar, 2016)



Comparison of Mean Decrease in Serum TNF-a Levels in Both Groups at Week 0 and 8

Table 7. Correlation Analysis of Changes in SCORSVI Score and Serum TNF-a Levels in the Treatment and Control Group

SCORSVI - TNF-a	Value of r	*P* value
Week 0	0.409	0.095
Week 8	0.181	0.264
D **week 0 to week 8**	0.884	0.001

Spearman Correlation Test

r= strength of correlation. 0.1-0.3 weak; 0.4-0.6 medium; 0.7-0.9 strong.

D= *drop*

Based on marital status, the majority of subjects in the control and treatment groups were married (60%), according to Kaplan and Saddock, 2022 that in people with schizophrenia, spousal support is considered to improve prognosis even though there is no statistically significant relationship.(Kaplan & Saddock's, 2022).

Based on the last level of education, in the treatment group, the highest level of education was found to be high school (50%) while in the control group the most was elementary school (55%). According to the results of research by Eka Putri, et al in 2019 in Banjarmasin, a higher level of education provides a greater opportunity for treatment.

better. Where education is one of the factors responsible for the good prognosis of schizophrenia patients (Eka Putri Widyarti et al., 2019).

Based on occupational data, the majority of the treatment group worked (65%), mainly as farmers, while the majority of the control group did not work (60%). Lesmanawati mentioned that patients who work tend to have better health quality because they are more motivated and more economically stable (Jiwa et al., 2016).

Based on diagnosis, the study subjects were divided into Unspecified Schizophrenia (YTT) and Paranoid Schizophrenia. The treatment group was mostly diagnosed with YTT Schizophrenia (70%), while the control group had a balanced diagnosis distribution (50%) with disease onset generally 1-3 years. Homogeneity test analysis showed all study variables were homogeneous ($p>0.05$), making them suitable for further analysis.

The Effect of Cognitive Remediation on the Improvement of Cognitive Symptoms of Schizophrenia Patients

In Table 2 and Table 3 each study subject in both groups received risperidone at a dose of 4-6mg/day causing a significant decrease in total SCORSVI scores indicating improvement in cognitive dysfunction. The treatment group showed a greater reduction than the control group. Although **risperidone** may improve cognitive function through the mechanism of **5HT2A** receptor blockade, several studies have shown that this improvement is limited and minimal. Elevated levels of inflammatory biomarkers such as **TNF**-a are associated with little cognitive improvement after antipsychotic administration.

The administration of antipsychotics in schizophrenia patients cannot fully restore cognitive function, which is important to support daily activities. In this case, psychosocial interventions such as cognitive remediation show more promising results compared to pharmacological treatment alone. Cognitive remediation aims to improve brain neuroplasticity through various forms of exercises that improve cognitive function.(Putra & Marianto, 2023)

Kaneko's (2012) study found that the combination of the antipsychotic risperidone with cognitive remediation exercises can provide better cognitive improvement compared to antipsychotic administration alone, indicating the importance of psychosocial rehabilitation programmes. The results also showed that the group undergoing cognitive remediation therapy showed a greater reduction in cognitive symptoms than the control group, with significant improvements in SCORSVI scores, reflecting the effectiveness of this therapy.(Kaneko Y & Keshavan M, 2012)

Cognitive remediation activates brain neuroplasticity, improves basic and complex cognitive skills, and increases neural connectivity and brain neurotrophic factors such as BDNF, which contribute to cognitive improvement.(Putra & Marianto, 2023) This therapy is carried out with a duration of 60-90 minutes per session, twice a week, for 8 weeks, with the aim of improving cognitive function.

(Barlati et al., 2013) In addition, neuroimaging studies have shown that cognitive remediation can increase brain activation in frontal and parietal regions, and improve brain structure and connectivity, which is associated with cognitive improvement in schizophrenia patients.(Fernández-Sotos et al., 2019; Grynszpan et al., 2011; Trapp et al., 2022).

Effect of Cognitive Remediation on Serum TNF-a Levels of Schizophrenia Patients

Table 4 shows the comparison of serum TNF-a levels between the group with schizophrenia and healthy individuals. The mean serum TNF-a level in the group with schizophrenia was 173.72pg/ml and 90.11 pg/ml for healthy individuals, with a significance value of 0.003 ($p<0.05$). These results indicate that serum TNF-a levels in schizophrenia patients are higher compared to healthy individuals, which is in line with Elmeida Effendy's (2019) study in Medan, which also noted that serum TNF-a levels in schizophrenia patients higher compared to healthy controls, and this increase in serum TNF-a levels plays a role in schizophrenia psychopathology.(Efffendy et al., 2021).

Research by Al-Asmari and Khan in Riyadh, Saudi Arabia, also found that serum TNF-a levels in schizophrenia patients (27.04+/-4.11) were significantly higher compared to healthy controls (17.25+/-3.30). They suggested that an imbalance between pro-inflammatory and anti-inflammatory cytokines may be involved in the pathophysiology of schizophrenia. TNF-a plays a role in central nervous system homeostasis and pathophysiology. In healthy individuals, TNF-a function supports various physiological processes, such as synaptic plasticity, learning and memory, sleep, food and water intake, and

astrocyte-mediated synapse strengthening.(Effendy et al., 2021)

Changes in cytokine levels, including serum TNF-a levels, may have significant clinical implications in the diagnosis and monitoring of schizophrenia. Currently, the diagnosis of schizophrenia is based on clinical symptoms, yet there are no standardised diagnostic biomarkers that allow early recognition of disease. Cytokines such as IL-6, TNF-a , IL-1b , and IL-1RA may serve as potential biomarkers for early detection in a subset of schizophrenia patients. In addition, higher serum TNF-a levels have been reported in patients with schizophrenia, both those in the acute phase and those experiencing disease relapse, including patients taking antipsychotics. These higher serum TNF-a levels were also found in chronic patients taking atypical antipsychotic drugs, although in the absence of major inflammation.

In the results of the study in Table 5 and Table 6, serum TNF-a levels in the treatment group receiving risperidone showed a significant decrease from 174.90pg/ml at week 0 to 95.81pg/ml at week 8. Whereas in the control group, the decrease in serum TNF-a levels was smaller, from 172.55pg/ml to 123.98pg/ml. This decrease shows the effect of risperidone as a neuroprotector that can be used as a neuroprotector.

reduced microglia activation and decreased proinflammatory cytokines, including TNF-

a(Caruso et al., 2020)

Research by Momtazmanesh (2019, Iran) showed that risperidone can cause changes in serum TNF-a levels after more than three months of use, although the effect may be influenced by metabolic syndrome. *Non-computerised* cognitive remediation adjunct therapy in the treatment group showed a reduced rate of TNF- levels.

a (46%) compared to the control group (28.15%) with a p value of <0.05. Inflammation, especially neuroinflammation that induces an increase in proinflammatory cytokines such as TNF-a , can disrupt neurotransmitter systems, including dopamine, which contributes to cognitive impairment in schizophrenia patients.(Cha & Yang, 2020; Zhuo et al., 2023)

(Zhao et al., 2022) Cognitive remediation was shown to improve brain connectivity and neuroplasticity, which in turn can decrease serum TNF-a levels.(Cella et al., 2015; Tripathi et al., 2018) Neuroinflammatory theory reveals that inflammation, particularly that occurring during the maternal period, increases the risk of schizophrenia in adulthood, with an association between increased proinflammatory cytokines and changes in brain structure that affect cognitive function.(de Bartolomeis et al., 2022; Kroken et al., 2014; Miller & Goldsmith, 2019)

Relationship between Serum TNF-a Levels and Improvement in Cognitive Symptoms of Schizophrenia Patients on Risperidone Therapy and Cognitive Remediation

The results of the data analysis shown in Table 7 showed a significant correlation between the reduction of total SCORSVI score and the reduction of serum TNF-a levels exhibited by both groups between week 0 and week 8 with a significance value of $p = 0.001$ ($p < 0.05$), indicating a significant positive relationship. This correlation showed a strong positive association between cognitive function and serum TNF-a levels, with a correlation strength (r= of 0.884. These results are consistent with research conducted by Elmeida Effendy et al in Medan in 2019, which found a positive correlation between serum TNF-a levels and cognitive function with moderate correlation strength. Research by Sara Momtazmanesh in 2019 in Iran also found a positive correlation between serum TNF-a levels and the severity of cognitive symptoms in schizophrenia patients.(Efffendy et al., 2021; Momtazmanesh et al., 2019).

An imbalance between pro-inflammatory and anti-inflammatory cytokines may play a role in the pathophysiology of schizophrenia, as cytokines can disrupt the neuroendocrine system and neurotransmitter system (dopamine, serotonin, and glutamine). Cytokines can also cross the blood-brain barrier (BBB), which allows immune or neurotoxic cytokines to invade the central nervous system and cause psychopathological changes. (Efffendy et al., 2021) Neuroinflammation also triggers various cognitive deficits due to the induction of high oxidative stress, cytotoxicity,

increased synaptic pruning due to microglia activation, and disruption of white and grey matter (WM-GM).(Sapienza et al., 2024)

Based on the literature reviewed by I Putu Risdianto Eka Putra et al, there is no pharmacological management that can specifically improve cognitive function in schizophrenia. In addition to psychopharmacological treatment, non-psychopharmacological treatments, such as cognitive remediation, have been shown to be effective for cognitive impairment. Cognitive remediation can stimulate brain neuroplasticity, which is related to NMDA dysfunction that causes a decrease in BDNF. This decrease in BDNF is associated with impaired neuroplasticity, which is also associated with increased levels of immunological markers, such as TNF-a , which plays a role in brain microglia activation and cognitive impairment in schizophrenia patients.(Putra & Marianto, 2023)

5. LIMITATIONS

This study has several limitations, namely the measurement of serum TNF-a levels was only carried out at week 0 and week 8, thus not providing a more detailed picture of serial changes to determine when the adjuvant shows its effectiveness; the limited duration of observation for 8 weeks is not enough to identify long-term trends in changes in SCORSVI values and

serum TNF-a levels; as well as external factors such as smoking habits that were not controlled in this study, even though previous studies have shown thatlevels.

a serum and impair cognitive function.

6. CONCLUSION

The conclusions of this study are: (1) both in the group that received risperidone therapy and *non-computerised* cognitive remediation and the group that was only given risperidone therapy after 8 weeks, both experienced significant improvement in cognitive symptoms; (2) risperidone therapy combined with *non-computerised* cognitive remediation provided better improvement in cognitive symptoms compared to risperidone therapy alone; (3) serum TNF-a levels increased in the group with schizophrenia compared to the healthy group; (4) both the group receiving risperidone therapy and *non-computerised* cognitive remediation and the group receiving risperidone therapy only, both experienced a decrease in serum TNF-a levels after 8 weeks; (5) the decrease in serum TNF-a levels was more significant in the group receiving the combination of therapy than the group with risperidone therapy alone; and (6) there was a positive correlation between serum TNF-a levels and improvement in cognitive dysfunction through a decrease in total SCORSVI scores from week 0 to week 8, which means that improvement in the severity of cognitive dysfunction was also followed by a decrease in serum TNF-a levels in both groups.

Suggestions for future research

Clinicians should consider the use of non-computerised cognitive remediation as a nonpsychopharmacological adjunctive therapy in schizophrenia patients taking risperidone to improve cognitive symptom improvement.

Further studies with a longer duration of observation and serial measurement of serum TNF-a levels are needed to evaluate the correlation between improvement in cognitive symptoms of schizophrenia and serum TNF-a levels.

Further research is also needed to explore the effectiveness of other treatments that can improve cognitive function, such as repetitive transcranial magnetic stimulation (rTMS).

Acknowledgements

This study was supported by the Psychiatry Section of the Faculty of Medicine, Hasanuddin University, and we would also like to thank Dadi Makassar Regional Special Hospital for granting permission for this study. All errors and omissions are our own responsibility.

Funding

This research did not receive funding from any organisation for the submitted work.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Committee Approval

This study was approved by the Human Biomedical Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. Based on the recommendation letter number: 756/UN4.6.4.5.31/PP36/2024 with protocol number: UH24080644.

List of Contributors

Arvita R. Akbar: conceptualisation, formal analysis, investigation, methodology, data curation, and manuscript writing; Kristian Liaury: conceptualisation, formal analysis, investigation, methodology, and writing; A. Jayalangkara tanra: conceptualisation, manuscript writing; All authors read and approved the final version of the manuscript.

REFERENCES

[1] Amir Nurmiati. (2021). Textbook of Psychiatry-FKUI (H. G. Elvira D.S., Ed.; Third Edition). FKUI Publishing Board.

[2] Azmanova, M., Pitto-Barry, A., & Barry, N. P. E. (2018). Schizophrenia: synthetic strategies and recent advances in drug design. MedChemComm, 9(5), 759-782. https://doi.org/10.1039/C7MD00448F

[3] Baek, S. H., Kim, H., Kim, J. W., Ryu, S., Lee, J. Y., Kim, J. M., Shin, I. S., & Kim, S. W. (2022).

[4] Association between Peripheral Inflammatory Cytokines and Cognitive Function in Patients with First-Episode Schizophrenia. Journal of Personalised Medicine, 12(7). https://doi.org/10.3390/jpm12071137

[5] Barlati, S., Deste, G., De Peri, L., Ariu, C., & Vita, A. (2013). Cognitive Remediation in Schizophrenia: Current Status and Future Perspectives. Schizophrenia Research and Treatment, 2013, 1-12. https://doi.org/10.1155/2013/156084

[6] Bowie, C. R., Bell, M. D., Fiszdon, J. M., Johannesen, J. K., Lindenmayer, J. P., McGurk, S. R., Medalia, A. A., Penadés, R., Saperstein, A. M., Twamley, E. W., Ueland, T., & Wykes, T. (2020). Cognitive remediation for schizophrenia: An expert working group white paper on core techniques. In Schizophrenia Research (Vol. 215, pp. 49-53). Elsevier B.V. https://doi.org/10.1016/j.schres.2019.10.047

[7] Caruso, G., Grasso, M., Fidilio, A., Tascedda, F., Drago, F., & Caraci, F. (2020). Antioxidant Properties of Second-Generation Antipsychotics: Focus on Microglia. Pharmaceuticals, 13(12),

[8] 457. https://doi.org/10.3390/ph13120457

[9] Cella, M., Reeder, C., & Wykes, T. (2015). Cognitive remediation in schizophrenia-now it's really getting personal. Current Opinion in Behavioural Sciences, 4, 147-151. https://doi.org/10.1016/j.cobeha.2015.05.005

[10] Cha, H. Y., & Yang, S. J. (2020). Anti-Inflammatory Diets and Schizophrenia. Clinical Nutrition Research, 9(4), 241. https://doi.org/10.7762/cnr.2020.9.4.241

[11] Dawidowski, B., Górniak, A., Podwalski, P., Lebiecka, Z., Misiak, B., & Samochowiec, J. (2021). The Role of Cytokines in the Pathogenesis of Schizophrenia. Journal of Clinical Medicine, 10(17), 3849. https://doi.org/10.3390/jcm10173849

[12] de Bartolomeis, A., Barone, A., Vellucci, L., Mazza, B., Austin, M. C., Iasevoli, F., & Ciccarelli, M. (2022). Linking Inflammation, Aberrant Glutamate-Dopamine Interaction, and Post-synaptic Changes: Translational Relevance for Schizophrenia and Antipsychotic Treatment: a Systematic Review. Molecular Neurobiology, 59(10), 6460-6501. https://doi.org/10.1007/s12035-022-

[13] 02976-3

[14] Efffendy, E., Amin, M. M., & Utami, N. (2021). Role of Tumour Necrosis Factor-Alpha in Schizophrenia and Cognitive Impairment. Open Access Macedonian Journal of Medical Sciences, 9(T3), 160-163. https://doi.org/10.3889/oamjms.2021.6289

[15] Eka Putri Widyarti, Sherly Limantara, & Husnul Khatimah. (2019). Overview of Prognosis Factors in Schizophrenia Patients at Rumah Sakita Jiwa Sambang Lihum. Homeostatis, 2, 509-518.

[16] Fernández-Sotos, P., Torio, I., Fernández-Caballero, A., Navarro, E., González, P., Dompablo, M., & Rodriguez-Jimenez, R. (2019). Social cognition remediation interventions: A systematic mapping review. PLOS ONE, 14(6), e0218720. https://doi.org/10.1371/journal.pone.0218720

[17] Grynszpan, O., Perbal, S., Pelissolo, A., Fossati, P., Jouvent, R., Dubal, S., & Perez-Diaz, F. (2011). Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: A meta-...

[18] analytical study. Psychological Medicine, 41(1), 163-173. https://doi.org/10.1017/S0033291710000607

[19] Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., O'Donovan, M., Correll, C. U., Kane, J. M., van Os, J., & Insel, T. R. (2015). Schizophrenia.

[20] Nature Reviews Disease Primers, 1(1), 15067. https://doi.org/10.1038/nrdp.2015.67

[21] Kaneko Y, & Keshavan M. (2012). Cognitive Remediation in Schizophrenia. Clinical Psychopharmacology and Neuroscience, 125-135.

[22] Kaplan, & Saddock's. (2022). KAPLAN & SADOCK'S SYNOPSIS OF PSYCHIATRY TWELFTH EDITION

[23] EDITION (B. J. R. MD, V. L. M. MD, & Md. Ruiz Pedro, Eds.; 12th ed.). Wolters Kluwer.

[24] Kroken, R. A., Løberg, E.-M., Drønen, T., Grüner, R., Hugdahl, K., Kompus, K., Skrede, S., & Johnsen, E. (2014). A Critical Review of Pro-Cognitive Drug Targets in Psychosis: Convergence on Myelination and Inflammation. Frontiers in Psychiatry, 5. https://doi.org/10.3389/fpsyt.2014.00011

[25] Kusumawardhani AAA, Dharmono S, & Diatri H. (2011). Schizophrenia Consensus. Association of Mental Medicine Specialists (PDSKJI).

[26] Miller, B. J., & Goldsmith, D. R. (2019). Inflammatory biomarkers in schizophrenia: Implications for heterogeneity and neurobiology. Biomarkers in Neuropsychiatry, 1, 100006. https://doi.org/10.1016/j.bionps.2019.100006

[27] Momtazmanesh, S., Zare-Shahabadi, A., & Rezaei, N. (2019). Cytokine Alterations in Schizophrenia: An Updated Review. Frontiers in Psychiatry, 10. https://doi.org/10.3389/fpsyt.2019.00892

[28] Patlola, S. R., Donohoe, G., & McKernan, D. P. (2023). The relationship between inflammatory biomarkers and cognitive dysfunction in patients with schizophrenia: A systematic review and meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 121, 110668. https://doi.org/10.1016/j.pnpbp.2022.110668

[29] PUTRA, I. P. R. E., & MARIANTO, M. (2023). NEUROBIOLOGY AND MANAGEMENT

[30] COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA. Journal of Research and Development Results (JHPP), 1(3), 161-170. https://doi.org/10.61116/jhpp.v1i3.155

[31] Reale, M., Costantini, E., & Greig, N. H. (2021). Cytokine Imbalance in Schizophrenia. From Research to Clinic: Potential Implications for Treatment. Frontiers in Psychiatry, 12, 536257. https://doi.org/10.3389/fpsyt.2021.536257

[32] Sapienza, J., Agostoni, G., Comai, S., Nasini, S., Dall'Acqua, S., Sut, S., Spangaro, M., Martini, F., Bechi, M., Buonocore, M., Bigai, G., Repaci, F., Nocera, D., Ave, C., Guglielmino, C., Cocchi, F., Cavallaro, R., Deste, G., & Bosia, M. (2024). Neuroinflammation and kynurenines in schizophrenia: Impact on cognition depending on cognitive functioning and modulatory properties in relation to cognitive remediation and aerobic exercise. Schizophrenia Research: Cognition, 38, 100328. https://doi.org/10.1016/j.scog.2024.100328

[33] Siti Zahnia, & Dyah Wulan Sumekar. (2016). Epidemiological study of schizophrenia. . @inproceedings{Zahnia2016KajianES,Title={Epidemiological Study of Schizophrenia},Author={Siti Zahnia and Dyah Wulan

[34] Sumekar}, Year={2016}, Url={https://Api.Semanticscholar.Org/CorpusID:148831794}, 5, 161-261.

[35] Stępnicki, P., Kondej, M., & Kaczor, A. A. (2018). Current Concepts and Treatments of Schizophrenia. Molecules, 23(8), 2087. https://doi.org/10.3390/molecules23082087

[36] Su, L., Liu, X., Li, Y., Yuan, H., Li, Q., & Li, C. (2023). Comparison of olfactory function, cognitive function and serum tumour necrosis factor-α between bipolar and schizophrenic patients in the remission stage. BMC Psychiatry, 23(1). https://doi.org/10.1186/s12888-023-05330-6

[37] Trapp, W., Heid, A., Röder, S., Wimmer, F., & Hajak, G. (2022). Cognitive Remediation in Psychiatric Disorders: State of the Evidence, Future Perspectives, and Some Bold Ideas. In Brain Sciences (Vol. 12, Issue 6). MDPI. https://doi.org/10.3390/brainsci12060683

[38] Tripathi, A., Kar, S. K., & Shukla, R. (2018). Cognitive deficits in schizophrenia: Understanding the biological correlates and remediation strategies. In Clinical Psychopharmacology and Neuroscience (Vol. 16, Issue 1, pp. 7-17). Korean College of Neuropsychopharmacology. https://doi.org/10.9758/cpn.2018.16.1.7

[39] World Health Organisation. (2022).Mental health ATLAS 2022 state profile. Geneva: World Health Organisation. (2022). Mental disorders according to WHO. Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/Mental-Disorders.

[40] Wykes, T., Bowie, C. R., & Cella, M. (2024). Thinking About the Future of Cognitive Remediation Therapy Revisited: What Is Left to Solve Before Patients Have Access? Schizophrenia Bulletin, 50(5), 993-1005. https://doi.org/10.1093/schbul/sbae075

[41] Zhao, F., Li, B., Yang, W., Ge, T., & Cui, R. (2022). brain-immune interaction mechanisms: Implications for cognitive dysfunction in psychiatric disorders. Cell Proliferation,

[42] 55(10). https://doi.org/10.1111/cpr.13295

[43] Zhuo, C., Tian, H., Song, X., Jiang, D., Chen, G., Cai, Z., Ping, J., Cheng, L., Zhou, C., & Chen, C. (2023). Microglia and cognitive impairment in schizophrenia: translating scientific progress into novel therapeutic interventions. Schizophrenia, 9(1), 42. https://doi.org/10.1038/s41537-023- 00370-z

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